*THE DRUGS RULES, 1945[1]

[21st December, 1945]

[As amended vide G.S.R. 360(E) dated 01-07-2024 (w.e.f. 01-07-2024)]

DISCLAIMER

1. This document is a compiled version of the various amendment to the Drug Rules, 1945, as published through various gazette notifications over time.
2. Atmost care has been taken to ensure correctness of these provisions. However, in case of any discrepancy observed, it may be immediately brought to the notice of Central Drugs Standard Control Organization (CDSCO).
3. The rules governing the regulation of Ayush drugs are published by the Ministry of Ayush.. Any discrepancy regarding these rules may be reported accordingly.

*THE DRUGS RULES, 1945[1]

[21st December, 1945]

[As amended vide G.S.R. 823(E) dated 17-11-2022 (w.e.f. 01-08-2023]

In exercise of the powers conferred by [2][sections 6(2), 12, 33 and 33(N)] of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government is pleased to make the following Rules:—

PART I
PRELIMINARY

1. **Short title, extent and commencement.**—(1) These Rules may be called the Drugs [3][***] Rules, 1945.

(2) They extend to the whole of India [4][***].

[5][***]

2. Definitions.—In these Rules, unless there is anything repugnant in the subject or context—

(a) "the Act" means the Drugs and Cosmetics Act, 1940 (23 of 1940), as amended from time to time;

[6][(aa) "biopharmaceutical classification system" means a system used to classify drugs on the basis of solubility and permeability, classified as category I-high solubility and high permeability, category II-low solubility and high permeability, category III-high solubility and low permeability, and category IV-low solubility and low permeability;]

[7][(b) "Central Licence Approving Authority" means the Drugs Controller, India, or the Joint Drugs Controller (India) or the Deputy Drugs Controller (India) appointed by the Central Government;]

(c) "Director" means the Director of the Central Drugs Laboratory;

(d) "Form" means a Form set forth in Schedule A;

[8][(dd) "Homoeopathic medicines" include any drug which is recorded in Homoeopathic provings or therapeutic efficacy of which has been

established through long clinical experience as recorded in authoritative Homoeopathic literature of India and abroad and which is prepared according to the techniques of Homoeopathic pharmacy and covers combination of ingredients of such Homoeopathic medicines but does not include a medicine which is administered by parenteral route;]

(e) "Laboratory" means the Central Drugs Laboratory;

[9][(ea) "Marketer" means a person who as an agent or in any other capacityadopts any drug manufactured by another manufacturer under an agreement for marketing of such drug by labeling or affixing his name on the label of the drug with a view for its sale and distribution;]

[10][[11][(eb)] "registered Homoeopathic medical practitioner" means a person who is registered in the Central Register or a State Register of Homeopathy;]

[12][[13][(ec)] "Phytopharmaceutical drug" includes purified and standardised fraction with defined minimum four bio-active or phyto-chemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include administration by parenteral route.]

[14][(ee) "Registered medical practitioner" means a person—

(i) holding a qualification granted by an authority specified or notified under section 3 of the Indian Medical Degrees Act, 1916 (7 of 1916), or specified in the Schedules to the Indian Medical Council Act, 1956 (102 of 1956); or

(ii) registered or eligible for registration in a medical register of a State meant for the registration of persons practicing the modern scientific system of medicine [15][excluding the Homoeopathic system of medicine]; or

(iii) registered in a medical register [15][other than a register for the registration of Homoeopathic practitioners] of a State, who although not falling within sub-clause (i) or sub-clause (ii) is

declared by a general or special order made by the State Government in this behalf as a person practicing the modern scientific system of medicine for the purposes of this Act; or

(iv) registered or eligible for registration in the register of dentists for a State under the Dentists Act, 1948 (16 of 1948); or

(v) who is engaged in the practice of veterinary medicine and who possesses qualifications approved by the State Government;]

[16][(f) 'retail sale' means a sale [17][whether to a hospital, or a dispensary, or a medical, educational or research institute or to any other person] other than a sale by way of wholesale dealing;]

[18][(g) 'sale by way of wholesale dealing' means sale to a person for the purpose of selling again and includes sale to a hospital, dispensary, medical, educational or research institution;]

[19][(h) "Schedule" means a Schedule to these Rules;]

[18][(i) State Government in relation to a Union Territory means the Administrator thereof;]

[20][***]

PART II

THE CENTRAL DRUGS LABORATORY

3. Functions.—Itshall be the function of the Laboratory—

(i) to analyse or test such samples of drugs as may be sent to it under sub-section (2) of section 11, or under sub-section (4) of section 25 of the Act;

[***][21]

(iii) to carry out such other duties as may be entrusted to it by the Central Government or, with the permission of the Central Government, by a State Government after consultation with the Drugs Technical Advisory Board.

[22][3A. (1) The functions of the Laboratory in respect of the following drugs or classes of drugs shall be carried out at the Central Research Institute, Kasauli, and the functions of the Director in respect of the said drugs or classes of drugs shall be exercised by the Director of the said Institute:—

(1) Sera

(2) Solution of serum proteins intended for injection

(3) Vaccines

(4) Toxins

(5) Antigens

(6) Anti-toxins

(7) Sterilized surgical ligature and sterilized surgical suture

(8) Bacteriophages:

[23][Provided that the functions of the Director in respect of Oral Polio Vaccine shall be exercised by the Deputy Director and Head of the Polio Vaccine Testing Laboratory in case of Central Research Institute, Kasauli only.]

[24][(1A) The functions of the Laboratory in respect of Oral Polio Vaccine shall be carried out by the following Institutes and the functions of the Director in respect of the said drugs shall be exercised by the Director of the respective Institutes:—

(a) Pasteur Institute of India, Conoor.

(b) Enterovirus Research Centre (Indian Council of Medical Research), Haffkine Institute Compound, Parel, Bombay-400012.]

[25][(c) The National Institute of Biologicals, NOIDA.]

[26][(2) The functions of the Laboratory in respect of the following drugs or classes of drugs shall be carried out at the Indian Veterinary Research Institute, Izatnager or Mukteshwar and the functions of the Director in respect of the said drugs or classes of drugs shall be exercised by the Director of either of the said institutes:—

(1) Anti-sera for veterinary use.

(2) Vaccines for veterinary use.

(3) Toxoids for veterinary use.

(4) Diagnostic Antigens for veterinary use.]

[27][(3) The functions of the laboratory in respect of testing of condoms shall be carried out at the Central Drugs Testing Laboratory, Chennai, and the functions of the Director in respect of the said products shall be exercised by the Director of the said Laboratory.]

[28][[29] [(4)] The functions of the Laboratory in respect of the following drugs shall be carried out at the Laboratory of the Serologist and Chemical Examiner to the Government of India, Calcutta and the functions of the Director in respect of the said drugs shall be performed by the Serologist and Chemical Examiner of the said Laboratory:—

VDRL Antigen.]

[30][(5) The function of the Laboratory in respect of Intra-utrine Devices and Falope Rings shall be carried out at the Central Drugs Testing Laboratory, Thane, Maharashtra and the functions of the Director in respect of the said devices shall be exercised by the Director of the said Laboratory.]

[31][(6) The functions of the Laboratory in respect of human blood and human blood products including components, to test for freedom from HIV antibodies, shall be carried out by the following Institute/Hospitals and the functions of the Director in respect of the above mentioned products shall be exercised by the head of the respective institute, namely:

(a) National Institute of Communicable Disease, Department of Microbiology,Delhi.

(b) National Institute of Virology, Pune.

(c) Centre for Advanced Research in Virology, Christian Medical College, Vellore.]

[32][(7) The functions of the Laboratory in respect of Homoeopathic medicines shall becarried out at the [33][Pharmacopoeia Commission of Indian

Medicine and Homoeopathy at Ghaziabad (Uttar Pradesh)] and the functions of the Director in respect of the Homoeopathic medicines shall be exercised by the Director of the Laboratory.]

[34][(8) (a) The functions of the Laboratory in respect of the following kits or class of drugs shall be carried out at the National Institute of Biologicals, Noida and the functions of the Director in respect of the said drugs or class of drugs shall be exercised by the Director of the said institute.

(b) The kits or class of drugs referred to in clause (a) are—

(1) Blood grouping reagents.

(2) Diagnostic kits for human immunodeficiency virus, Hepatitis B Surface Antigen and Hepatitis C Virus.

(3) Blood products—

(a) Human Albumin;

(b) Human normal Immunoglobulin (intramuscular and intravenous);

(c) Human Coagulation Factor VIII;

(d) Human Coagulation Factor IX;

(e) Plasma Protein Fractionation;

(f) Fibrin Sealant Kit;

(g) Anti Inhibitor Coagulation complex.

(4) Recombinant products such as—

(a) Recombinant Insulin and Insulin analogues;

(b) r-erythropoietin (EPO);

(c) r-Granulocyte Colony Stimulating Factor (G-CSF).

(5) Biochemical kits—

(a) Glucose Test Strips;

(b) Fully automated analyzer based glucose reagents.]]

[35][(6) Enzyme and Hormones such as—

(a) Streptokinase (Natural and Recombinant);

(b) Human Chorionic Gonadotropin (hCG);

(c) Human Menopausal Gonadotropin (hMG).

(7) Bacterial vaccine such as—

(a) Bacillus Calmette-Guerin (BCG) vaccine.

(8) Viral vaccines such as—

(a) Live attenuated Measles vaccine;

(b) Live attenuated Rubella vaccine;

(c) Cell culture Rabies vaccine.]

[36][(9) The functions of the laboratory in respect of testing of the following veterinary vaccines shall be carried out at the Chaudhary Charan Singh National Institute of Animal Health, Baghpat, Uttar Pradesh and the functions of the Director in respect of the said veterinary vaccines shall be exercised by the Director of the said Institute, namely:—

(i) Haemorrhagic Septicaemia vaccine;

(ii) Ranikhet Disease vaccine.]

4. **Despatch of samples for test or analysis.**—(1) Samples for test or analysis under sub-section (4) of section 25 of the Act shall be sent by registered post in a sealed packet, enclosed, together with a memorandum in Form 1, in an outer cover addressed to the Director.

(2) The packet as well as the outer cover, shall be marked with a distinguishing number.

(3) A copy of the memorandum in Form 1 and a specimen impression of the seal used to seal the packet shall be sent separately by registered post to the Director.

5. Recording of condition of seals.—On receipt of the packet, it shall be opened by an officer authorised in writing in that behalf by the Director, who shall record the condition of the seal on the packet.

6. Report of result of test or analysis.—After test or analysis the result of the test or analysis, together with full protocols of the tests applied, shall be supplied forthwith to the sender in Form 2.

7. Fees.—The fees for test and analysis shall be those specified in Schedule B.

8. Signature of certificates.—Certificates issued under these Rules by the Laboratory shall be signed by the Director or by an officer authorised by the Central Government by notification in the Official Gazette to sign such certificates.

PART III

[Rules 9 to 20.—*Omitted by S.R.O. 2136, dated 15th June, 195/]*

PART IV

[37][IMPORT AND REGISTRATION]

21. In this Part—

[38][(a) 'import licence' means either a licence in Form 10 to import drugs [39][***], excluding those specified in Schedule X, or a licence in Form10A to import drugs specified in Schedule X;]

(b) "licensing authority" means the authority appointed by the Central Government to perform the duties of the licensing authority under these rules and includes any person to whom the powers of a licensing authority may be delegated under rule 22;

(c) "licence for examination, test or analysis" means a licence in Form 11 to import small quantities of drugs the import of which is otherwise prohibited, for the purpose of examination, test or analysis.

[40][(d) 'manufacturer", includes a manufacturer of drugs, who may be a Company or a unit or a body corporate or any other establishment in a country

other than India, having its drugs manufacturing facilities duly approved by the National Regulatory Authority of that country, and who also has a free sale approval of the drugs approved by the said authority in the concerned country, and/or in other major countries,

(e) "Registration Certificate" means a certificate issued under rule 27A by the licensing authority in Form 41 for registration of the premises and the drugs manufactured by the manufacturer meant for import into and use in India.]

22. The licensing authority may with the approval of the Central Government by an order in writing delegate the [41][power to sign licences and Registration Certificates and] such other powers as may be specified in the order to any other person under his control.

[42][**23.Import licences**.—An import licence in Form 10 shall be required for [43][import of drugs], excluding those specified in Schedule X, and an import licence in Form 10A shall be required for the import of drugs specified in Schedule X.]

[44][**24**. **Form and manner of application for import licence**.—(1) An application for an import licence shall be made to the licensing authority in Form 8 for drugs excluding those specified in Schedule X, and in Form 8A for drugs specified in Schedule X, either by the manufacturer himself having a valid wholesale licence for sale or distribution of drugs under these rules, or by the manufacturer's agent in India either having a valid licence under the rules to manufacture for sale of a drug or having a valid wholesale licence for sale or distribution of drugs under these rules, ana shall be accompanied by a licence fee of [45][ten thousand rupees for a single drug and an additional fee at the rate of one thousand rupees] for each additional drug and by an undertaking in Form 9 duly signed by or on behalf of the manufacturer:

Provided that in the case of any subsequent application made by the same importer for import licence for drugs manufactured by the same manufacturer, the fee to accompany each such application shall be [46][one thousand rupees] for each drug.

(2) Any application for import licence in Form 8 or Form 8A, as the case may be, shall be accompanied by a copy of Registration Certificate issued in Form 41 under rule *27A:*

Provided that in case of emergencies the licensing authority may, with the approval of the Central Government, issue an import licence in Form 10 or 10A, as the case may be, without the issuance of Registration Certificate under rule 27A, for reasons to be recorded in writing:

[47][Provided further that Registration Certificate shall not be required to be accompanied with an application for an import licence under the rules for the import of in-vitro diagnostic kits and regents, except for the diagnostic kits notified from time to time under sub-clause (iv) of clause (b) of section 3.]

(3) A fee of [48][one thousand five hundred rupees shall be paid for making amendment in the licence [49][***].]

[50][24A. Form and manner of application for Registration Certificate.—

(1) An application for issue of a Registration Certificate shall be made to the licensing authority in Form 40, either by the manufacturer himself, having a valid whole sale licence for sale or distribution of drugs under these rules, or by his authorised agent in India, either having a valid licence under the rules to manufacture for sale of a drug or having a valid whole sale licence for sale or distribution of drugs under these rules, and shall be accompanied by the fee specified in sub-rule (3) and the informations and undertakings specified in Schedules D-I and D-II duly signed by or on behalf of the manufacturer.

(2) The authorisation by a manufacturer to bis agent in India shall be documented by a power of attorney executed and authenticated either in India before a First-Class Magistrate, or in the country of origin before such an equivalent authority, the certificate of which is attested by the Indian Embassy of the said country, and the original of the same shall be furnished alongwith the application for Registration Certificate.

(3) (i) A fee of [51][ten thousand US dollars] [47][or its equivalent in Indian rupees] shall be paid alongwith the application in Form 40 as registration fee for his premises meant for manufacturing of drugs intended for import into and use in India.

(ii) A fee of [52][five thousand US dollars] [47][or its equivalent in Indian rupees] shall be paid alongwith the application in Form 40 for the registration of a

single drug meant for import into and use in India and an additional fee at the rate of [52][five thousand US dollars] for each additional drug:

Provided that in the case of any subsequent application for registration of additional drugs by the same manufacturer, the fee to accompany shall be [52][five thousand US dollars] [47][or its equivalent in Indian rupees] for each drug.

(4) The fees shall be paid through a Challan in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110 001 or any other branch or branches of Bank of Baroda, or any other bank, as notified, from time to time, by the Central Government, to be credited under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines":

Provided that in the case of any direct payment of fees by a manufacturer in the country of origin, the fees shall be paid through Electronic Clearance System (ECS) from any bank in the country of origin to the Bank of Baroda, Kasturba Gandhi Marg, New Delhi, through the Electronic Code of the bank in the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fee and Fines", and the original receipt of the said transfer shall be treated as an equivalent to the bank challan, subject to the approval by the Bank of Baroda that they have received the payment.

(5) The applicant shall be liable for the payment of a fee of [53][twenty five thousand US dollars] [47][or its equivalent in Indian rupees] for expenditure as may be required for inspection or visit of the manufacturing premises of drugs, by the be required for inspection or visit of the manufacturing premises of drugs, by the licensing authority or by any other persons to whom powers have been delegated in this behalf by the licensing authority under rule 22:

(6) The applicant shall be liable for the payment of testing fees directly to a testing laboratory approved by the Central Government in India or abroad, as may be required for examination, tests and analysis of drug.

(7) A fee of [54][one thousand eight hundred US dollars or its equivalent in Indian rupees shall be paid for making amendment in the registration certificate or] for a duplicate copy of the Registration Certificate, if the original is defaced, damaged or lost.

(8) No Registration Certificate shall be required under these rules in respect of an inactive bulk substance to be used for a drug formulation, with or without pharmacopeal conformity.]

25. Licences for import of drugs manufactured by one manufacturer.—(1) A single application may be made, and a single licence may be issued, in respect of the import of more than one drug or class of drugs manufactured by the same manufacturer:

[55][Provided that the drugs or classes of drugs are manufactured at one factory or more than one factory functioning conjointly as a single manufacturing unit:

Provided further that if a single manufacturer has two or more factories situated in different places manufacturing the same or different drugs a separate licence shall be required in respect of the drugs manufactured by each such factory.]

[56][***]

[57]**[25A. Conditions to be satisfied before a licence in Form 10 or Form 10A is granted.**—(1) A licence in Form 10 or in Form 10A shall be granted by the licensing authority having regard to—

(i) the premises, where the imported substances will be stocked areequipped with proper storage accommodation for preserving theproperties of the drugs to which the licence applies; and

(ii) the occupation, trade or business ordinarily carried out by the applicant:

Provided that the licensing authority may refuse to grant a licence in Form 10A in respect of any applicant where he is satisfied,—

(a) that the applicant has not complied with the provisions of the Act or these rules, or

(b) that by reasons of—

[58][(i) his conviction under the Act or these rules or the Narcotic Drugs and Psychotropic Substances Act, 1985 (61 of 1985) or the rules made thereunder;]

(ii) previous suspension or cancellation of the licence granted to him, he is not a fit person to whom licence shall be granted.

(2) Any person who is aggrieved by the order passed by the licensing authority under this rule may, within thirty days of the receipt of the order, appeal to the Central Government and the Central Government may after such enquiry into the matter as it considers necessary and after giving the appellant an opportunity for making a representation in the matter, make such orders in relation thereto as it thinks fit.]

[59]**[25B. Registration Certificate for import of drugs manufactured by one manufacturer.**—(1) A single application may be made, and a single Registration Certificate in Form 41 may be issued in respect of the import of more than one drug or class of drugs, manufactured by the same manufacturer:

Provided that the drug or classes of drugs, are manufactured at one factory or more than one factory functioning conjointly as a single manufacturing unit:

Provided further that if a single manufacturer has two or more factories situated in different places manufacturing the same or different drugs, separate Registration Certificates shall be required in respect of the drugs manufactured by each such factory.]

26. Conditions of import licence.—An import licence shall be subject to the following conditions:—

(i) the manufacturer shall at all times observe the undertaking given by him or on his behalf in Form 9;

(ii) the license shall allow any Inspector authorized by the licensing authority in that behalf to enter with or without notice any premises where the imported substance is stocked to inspect the means, if any, employed for testing the substance and to take samples;

(iii) the licensee shall on request furnish to the licensing authority from every batch of each substance or from such batch or batches at the licensing

authority may from time to time specify a sample of such amount as the licensing authority may consider adequate fur any examination required to be made, and the licensee shall, if so required, furnish full protocols of the tests, if any, which have been applied;

(iv) if the licensing authority so directs the licensee shall not sell or offer for sale any batch in respect of which a sample is or protocols are furnished under the last preceding sub-rule until a certificate authorizing the sale of the batch has been issued to him by or on behalf of the licensing authority;

(v) the licensee shall, on being informed by the licensing authority that any part of any batch of the substance has been found by the licensing authority not to conform with the standards of strength, quality and purity prescribed by Chapter III of the Act, or the Rules thereunder and on being directed so to do, withdraw the remainder of that batch from sale and, so far as may in the particular circumstances of the case be practicable, recall the issues already made from that batch;

(vi) the licensee shall maintain a record of all sales by him of substances for the import of which a license is required, showing particulars of the substance and of the person to whom sold and such further particulars, if any, as the licensing authority may specify and such record shall be open to the inspection of any Inspector authorized in that behalf by the licensing authority:

[60][Provided that in respect of the sale or distribution of drugs specified in Schedule X, the licensee shall maintain a separate record or register showing the following particulars, namely:—

1. Name of the drug,
2. Batch number,
3. Name and address of the manufacturer,
4. Date of transaction,
5. Opening stock on the business day,
6. Quantity of drug received, if any, and the source from which received,
7. Name of the purchaser, his address and licence number,
8. Balance quantity of drug at the end of the business day,

9. Signature of the person under whose supervision the drugs have been supplied;]

(vii) the licensee shall comply with such further requirements, if any, applicable to the holders of import licences, as may be specified in any rules, subsequently made under Chapter III of the Act and of which the licensing authority has given to him not less than four months' notice.

27. Grant ofimport licence.—On receipt of an application for an importlicence in the Form and manner prescribed in rule 24, the licensing authorityshall, on being satisfied that, if granted, the conditions of the licence will be observed, issue an import licence in Form 10 [60][or Form 10A, as the case may be],

[61][27A. **Grant of Registration Certificates.**—(1) On receipt for an application for Registration Certificate in the Form and manner specified in rule 24A, the licensing authority shall, on being satisfied, that, if granted, the conditions of the Registration Certificate will be observed, issue a Registration Certificate inForm 41:

Provided further that if the application is complete in all respects and informations specified in Schedules DI and DII are in order, the licensing authority shall, within nine months from the date of receipt of an application, issue such Registration Certificate, and in exceptional circumstances and for reasons to be recorded in writing, the Registration Certificate may be issued within such extended period, not exceeding three months as the licensing authority, may deem fit.

(2) If the applicant does not receive the Registration Certificate within the period as specified in proviso to sub-rule (1), he may appeal to the Central Government and the Central Government may after such enquiry into the matter, as it considers necessary, may pass such orders in relation thereto as it thinks fit.]

[62]**[28. Duration of import licence.**—**A** licence, unless, it is sooner suspended or cancelled, shall be [63][valid for a period of three years from the date of its issue]: Provided that if application for a fresh licence is made three months before the expiry of the existing licence the current licence shall be deemed to continue in force until orders are passed on the application.]

[64][**28A. Duration of Registration Certificate.—A** Registration Certificate, unless, it is sooner suspended or cancelled, shall be valid for a period of three years from the date of its issue:

Provided that if the application for a fresh Registration Certificate is made nine months before the expiry of the existing certificate, the current Registration Certificate shall be deemed to continue in force until orders are passed on the application.]

29. Suspension and cancellation of import licence.—If the manufacturer or licensee fails to comply with any of the conditions of an import licence, the licensing authority may after giving the manufacturer or licensee an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, suspend or cancel it for such period as it thinks fit either wholly or in respect of some of the substances to which it relates:

[65][Provided that a person who is aggrieved by the order passed by the licensing authority under this rule may, within thirty days of the receipt of the order, appeal to the Central Government, and the Central Government may, after such enquiry into the matter, as it considers necessary and after giving the said appellant an opportunity for representing his views, pass such orders in relation thereto as it thinks fit.]

[64][**29A. Suspension and cancellation of Registration Certificate.**—If the manufacturer fails to comply with any of the conditions of the Registration Certificate, the licensing authority may after giving him an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, suspend or cancel the Registration Certificate for such period as it thinks fit either wholly or in respect of some of the substances to which it relates:

Provided that a person, who is aggrieved by the order passed by the licensing authority under this rule may, within thirty days of the receipt of the order, appeal to the Central Government, and the Central Government may, after such enquiry into the matter as it considers necessary and after giving the appellant an opportunity for representing his views in the matter, pass such orders in relation thereto as it thinks fit.]

30. Prohibition of import after expiry of potency.—No biological or other special product specified in Schedule C or C(l) shall be imported after the date shown on the label, wrapper or container of the drug as the date up to which the drug may be expected to retain a potency not less than, or not to acquire a toxicity greater than, that required, or as the case may be, permitted by the prescribed test.

[66][***]

[67]**[30AA. Import of New Homoeopathic medicines.—(1)** No NewHomoeopathic medicine shall be imported except under and in accordance with the permission in writing of the Licensing Authority.

(2) The importer of a New Homoeopathic medicine when applying for permission shall produce before the Licensing Authority such documentary and other evidence as may be required by the Licensing Authority for assessing the therapeutic efficacy of the medicine including the minimum provings carried out with it.]

[68][*Explanation*.—For the purpose of this rule, 'New Homoeopathic medicine' means,—

(i) a Homoeopathic medicine which is not specified in the Homoeopathic Pharmacopoeia of India or the United States of America or the United Kingdom or the German Homoeopathic Pharmacopoeia; or

(ii) which is not recognized in authoritative Homoeopathic literature as efficacious under the conditions recommended; or

(iii) a combination of Homoeopathic medicines containing one or more medicines which are not specified in any of the Pharmacopoeias referred to in clause (i) as Homoeopathic medicines and also not recognized in authoritative Homoeopathic literature as efficacious, under the conditions recommended.]

[69]**[30B. Prohibition of import of certain drugs.**—No drug, the manufacture, sale or distribution of which is prohibited in the country of origin, shall be imported under the same name or under any other name except for the purpose of examination, test or analysis.]

[70][**31. Standard for certain imported drugs.**—No drug shall be imported unless it complies with the standard of strength, quality and purity, if any, and the test prescribed in the rules shall be applicable for determining whether any such imported drug complies with the said standards:

Provided that the drugs intended for veterinary use, the standards of strength, quality and purity, if any, shall be those that are specified in Schedule F(l) and the test prescribed in that Scheduled shall be applicable for determining whether any such imported drug complies with the said standards and where no standards are specified in Schedule F(l) for any veterinary drug, the standards for such drug shall be those specified in the current edition, for the time being in force, of the British Pharmacopoeia Veterinary:

Provided further that the licensing authority shall not allow the import of any drug having less than sixty per cent, residual shelf-life period as on the date of import:

Provided also that in exceptional cases the licensing authority may, for reasons to be recorded in writing, may allow, the import of any drug having lesser shelf-life period, but before the date of expiry as declared on the container of the drug.]

[71][**32. Packing and labelling of imported drugs.**—No drug shall be imported unless it is packed and labelled in conformity with the rules in Parts IX and X [72][***] and further conforms to the standards laid down in Part XII provided that in the case of drugs intended for veterinary use, the packing and labelling shall conform to the rules in Parts IX and X and Schedule F(l).]

[73][**32A.Packing and labelling of Homoeopathic medicine.**—No Homoeopathic medicine shall be imported unless it is packed and labelled in conformity with the rules in Part IXA.]

33.Import of drugs for examination, test or analysis.—Small quantities of drugs the import of which is otherwise prohibited under section 10 of the Act may be imported for the purpose of examination, test or analysis subject to the following conditions:—

(a) no drug shall be imported for such purpose except under a licence in Form 11;

(b) the licensee shall use the substances imported under the licence exclusively for purposes of examination, test or analysis and shall carry on such examination, test or analysis in the place specified in the licence, or in such other places as the licensing authority may from time to time authorize;

(c) the licensee shall allow any Inspector authorized by the licensing authority in this behalf to enter, with or without prior notice, the premises where the substances are kept, and to inspect the premises, and investigate the manner in which the substances are being used and to take samples thereof;

(d) the licensee shall keep a record of, and shall report to the licensing authority, the substances imported under the licence, together with the quantities imported, the date of importation and the name of the manufacturer;

(e) the licensee shall comply with such further requirements, if any, applicable to the holders of licences for examination, test or analysis as may be specified in any rules subsequently made under ChapterIII of the Act and of which the licensing authority has given to him not less than one month's notice.

[74][33A.Import of drugs by a Government Hospital or Autonomous Medical Institution for the treatment of patients.—Small quantities of a new drug, as defined in rule 122E, the import of which is otherwise prohibited under section 10 of the Act, may be imported for treatment of patients suffering from life threatening diseases, or diseases causing serious permanent disability, or such disease requiring therapies for unmet medical needs, by a Medical Officer of a Government Hospital or an Autonomous Medical Institution providing tertiary care, duly certified by the Medical Superintendent of the Government Hospital, or Head of the Autonomous Medical Institution, subject to the following conditions, namely:—

(a) no new drug shall be imported for the said purpose except under a licence in Form 11 A, and the said drug has been approved for marketing in the country of origin;

(b) the licencee shall use the substances or drugs imported under the licence exclusively for the purpose of treatment of patients suffering from life threatening diseases, or diseases causing serious permanent disability, or such diseases requiring therapies for unmet medical needs, under the supervision of its ow i Medical Officers at the place, specified in the licence or at such ott er places, as the licensing authority, may from time to time authorise;

(c) The licencee shall allow an Inspector authorised by the licensing authority in this behalf to enter, with or without prior notice, the premises where the substances or drugs are stocked, and to inspect the premises and relevant records and investigate the manner in which the substances or drugs are being used and to take, if necessary, samples thereof;

(d) the licencee shall keep a record of, and shall submit the said report half yearly to the licensing authority, the substances or drugs imported under the licence, together with the quantities imported and issued to the patients, the date of importation, the name of the manufacturer, the name and address of the patient for whom the drug is prescribed and the name of disease:

(e) the licencee shall comply with such other requirements, if any,applicable to the holders of import licences for import of new drugs for treatment of patients by Government Hospitals, as may be specified from time to time in any rule subsequently made under Chapter III of the Act and of which the licensing authority has given to him not less than one month's notice;

(f) the drug shall be stocked under proper storage conditions and shall be dispensed under the supervision of a registered pharmacist;

(g) the quantity of any single drug so imported shall not exceed 100average dosages per patient:

Provided that the licensing authority may, in exceptional circumstances, sanction the import of drug a larger quantity.]

34. Application for licence for examination, test or analysis.— (1) An application for a licence for examination, test or analysis shall be made in Form

12 and shall be made or countersigned by the head of the institution in which, or by a proprietor or director of the company or firm by which the examination, test or analysis will be conducted.

(2) The licensing authority may require such further particulars to be supplied as he may consider necessary.

[75][(3) Every application in Form 12 shall be accompanied by a fee of [76][five thousand rupees for a single drug and an additional fee of two thousand rupees] for each additional drug.]

(4) The fees shall be paid through a challan in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110001 or any other branch or branches of Bank of Baroda, or any other Bank, as Notified, from time to time, by the Central Government, to be certified under the Head of Account "0210—Medical and Public Health 04—Public Health, 104—Fees and Fine."]

[77]**[34A. Application for licence to import small quantities of new drugs by a Government Hospital or Autonomous Medical Institution for the treatment of patients.—(1)** An application for an import licence for small quantities of a new drug, as defined in rule 122E for the purpose of treatment of patients suffering from life threatening diseases, or diseases causing serious permanent disability, or such diseases requiring therapies for unmet medical needs, shall be made in Form 12 AA, by a Medical Officer of the Government Hospital or Autonomous Medical Institution, which shall be certified by the Medical Superintendent of the Government Hospital or Head of the Autonomous Medical Institution, as the case may be.

(2) The licensing authority may require such further particulars to be supplied, as he may consider necessary.

(3) Every application in Form 12AA shall be accompanied by a fee of [78][six hundred rupees for a single drug and an additional fee of three hundred rupees] for each additional drug.

(4) The fees shall be paid through a challan in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110001 or any other branch or branches of Bank of Baroda, or any other Bank, as Notified, from time to time, by the

Central Government, to be certified under the Head of Account "0210—Medical and Public Health, 04—Public Health, 104—Fees and Fine".]

35. Cancellation of licence for examination, test or analysis.—(1) A licence for examination, test or analysis may be cancelled by the licensing authority for breach of any of the conditions subject to which the licence was issued.

(2) A licensee whose licence has been cancelled may appeal to the Central Government within three months of the date of the order.

[79][**35A. Cancellation of licence for import of small quantities of new drugs.**—(1) A licence for import of small quantities of a new drug, defined in rule 122E, for the purpose of the treatment of patients suffering from life threatening diseases, or diseases causing serious permanent disability, or such diseases requiring therapies for unmet medical needs, by a Government Hospital or an Autonomous Medical Institution may be cancelled by the licensing authority for breach of any of the conditions subject to which the licence was issued or for contravention of any of the provisions of the Act and rules made thereunder.

(2) A licencee whose licence has been cancelled may appeal to the Central Government within three months from the date of the receipt of the order, and the Central Government may after such enquiry into the matter, as it considers necessary and after giving the appellant an opportunity for representing his views, may pass such orders in relation thereto, as it thinks fit.]

36. Import of drugs for personal use.—Small quantities of drugs, the imports of which is otherwise prohibited under section 10 of the Act, may be imported for personal use subject to the following conditions:—

(i) the drugs shall form part of a passenger's *bona fide* baggage and shall be the property of, and be intended for, the exclusive personal use of the passenger;

(ii) the drugs shall be declared to the Customs authorities if they so direct;

(iii) the quantity of any single drug so imported shall not exceed onehundred average doses:

Provided that the licensing authority may in an exceptional case in any individual case sanction the imports of a larger quantity:

[80][Provided further that any drug, imported for personal use but not forming part of *bona fide* personal baggage, may be allowed to be imported subject to the following conditions, namely:—

(i) the licensing authority, on an application made to it in Form 12A issatisfied that the drug is for *bona fide* personal use;

(ii) the quantity to be imported is reasonable in the opinion of thelicensing authority and is covered by prescription from a registered medical practitioner; and

(iii) the licensing authority grants a permit in respect of the said drug in Form 12B [81][requiring the permit holder to give details of drugs imported and utilised on yearly basis].]

[82][**36A.Import of drugs by charitable hospital free of cost.**—(1) Small quantity of drugs received in donation by a charitable hospital for the purpose of treatment of the patients in the said hospital may be imported provided the drugs are given or administered to the patients free of cost.

(2) The drugs shall not be prohibited for import and permitted to be marketed in the country with residual shelf life of one year or more.]

[83][**37. Packing of patent or proprietary medicines**.—Patent or proprietary medicine shall be imported in containers intended for retail sale:

[84][Provided that such medicine may be imported in bulk containers by any person who holds a licence to manufacture, if such person has obtained permission in writing to import such medicines from the licensing authority at least three months prior to the date of import and the imports are made within a period of twelve months from the date of issue of such permission].]

38. Statement to accompany imported drugs.—All consignments of drugs sought to be imported shall be accompanied by an invoice or other statement showing the name and address of the manufacturer and the names and quantities of the drugs.

39. Documents to be supplied to the Customs Collector.—Before drugs for the import of which a licence is not required are imported a declaration signed by or on behalf of the manufacturer or by or on behalf of the importer that the drugs comply with the provisions of Chapter III of the Drugs and Cosmetics Act, 1940 and the rules thereunder shall be supplied to the Customs Collector.

[85]**[40. Procedure for the import of drugs.—(**1) If the Customs Collector has reason to doubt whether any drugs comply with the provisions of Chapter III of the Act and rules thereunder he may, and if requested by any officer appointed for this purpose by the Central Government shall, take samples of any drugs in the consignment and forward them to the director of the laboratory appointed for this purpose by the Central Government and may detain the drugs in the consignment of which samples have been taken until the report of the director of the said laboratory or any other officer empowered by him on this behalf, subject to the approval of the Central Government on such samples is received: Provided that if the importer gives an undertaking in writing not to dispose of the drugs without the consent of the Customs Collector and to return the consignment or such portion thereof as may be required, the Customs Collector shall make over the consignment to the importer.

(2) If an importer who has given an undertaking under the proviso to subrule (1) is required by the Customs Collector to return the consignment or any portion thereof he shall return the consignment or portion thereof within ten days of receipt of the notice.]

[86]**[41.** (1) If the Director of the laboratory appointed for the purpose by the Central Government or any other officer empowered by him on this behalfsubject to the approval of the Central Government reports to the Customs Collector that the samples of any drug in a consignment are not of standard quality, or that the drug contravenes in any other respect the provisions of Chapter III of the Act or the rules thereunder and that the contravention is such that it cannot be remedied by the importer, the Customs Collector shall communicate the report forthwith to the importer who shall, within two months of his receiving the communication either export all the drugs of that description in the consignment, to the country in which they were manufactured or forfeit them to the Central Government which shall cause them to be destroyed:]

Provided that the importer may within fifteen days of receipt of the report make a representation against the report to the Customs Collector, and the Customs Collector shall forward the representation with a further sample to the licensing authority, who after obtaining, if necessary, the report of the Director of the Central Drugs Laboratory, shall pass orders thereon which shall be final.

[87][(2) If the Director of the laboratory appointed for the purpose by the Central Government or any other officer empowered by him on this behalf, subject to the approval of the Central Government reports to the Customs Collector that the samples of any drug contravene in any respect the provisions of Chapter III of the Act or the rules thereunder and that the contravention is such that it can be remedied by the importer, the Customs Collector shall communicate the report forthwith to the importer and permit him to import the drug on his giving an undertaking in writing not to dispose of the drug without the permission of the office authorised in this behalf by the Central Government.]

[88][***]

43. The drugs specified in Schedule D shall be exempt from the provisions of Chapter III of the Act and of the Rules made thereunder to the extent, and subject to the conditions specified in that Schedule.

[89]**[43A**. NOdrug shall be imported into India except through one of the following places, namely:—

Firozepur Cantonment and Amritsar Railway Stations:

In respect of drugs imported bv rail across the frontier with Pakistan; Ranaghat, Bongaon and Mohiassan Railway Stations:

In respect of drugs imported by rail across the frontier with Bangladesh;

[90][Petrapole Road in West Bengal, Sutarkandi in Assam, old Raghna Bazar and Agartala in Tripura:

In respect of drugs imported by road from Bangladesh;]

[91][Raxaul:

In respect of drugs imported by road and railway lines connecting Raxaul in India and Birganj in Nepal;]

[92][[93][Chennai, Kolkata, Mumbai, Cochin, Nhava Sheva, Kandla, Inland Container Depots at Tuglakabad and Patparganj in Delhi, [94][Tuticorin and Kamrajar Port] in Tamil Nadu, Marmugao port in Goa, Visakhapatnam and [1340]["Krishnapatnam and Gangavaram ports"] in Andhra Pradesh and Haziia port and Inland Container Depot Khohdiyar, [95][Gandhinagar and Mundra Port] in Gujarat [96][and [97][lnland Container Depot at Dhannad and Tihi], Indore in Madhya Pradesh]: in respect of drugs imported by sea into India;]

Chennai, Kolkata, Mumbai, Delhi, Ahmedabad, Hyderabad, Goa, Bengaluru and Visakhapatnam:

in respect of drugs imported by air into India.]

[98]**[43B.** Drugs, consignments of which are intransit through India to foreigncountries and which shall not be sold or distributed in India shall be exempted from the requirements of Chapter III of the Drugs and Cosmetics Act, 1940 (23 of 1940) and rules made thereunder:

Provided that if the Government of the countries to which the drugs are consigned regulate their import by the grant of import licences, the importer shall at the time of import into India, produce such import licences.]

PART V

[99][GOVERNMENT ANALYSTS, INSPECTORS, LICENSING AUTHORITIES AND CONTROLLING AUTHORITIES]

[100]**[44. Qualifications of Government Analyst.**—A person appointed as a Government Analyst under the Act shall be a person who—

(a) is a graduate in Medicine or Science or Pharmacy or Pharmaceutical Chemistry of a [101][University established in India by the law or has an equivalent qualification recognised and notified by the CentralGovernment for such purpose] and has had not less than five years' post-graduate experience in the testing of drugs in a laboratory under the control of (i) a Government Analyst appointed under the Act, or (ii) the head of an Institution or testing laboratory approved for the purpose by the appointing authority [102][or has

completed two years' training on testing of drugs, including items stated in Schedule C, in Central Drugs Laboratory], or

(b) possesses a post-graduate degree in Medicine or Science or Pharmacy or Pharmaceutical Chemistry of a [101][University established in India by the law or has an equivalent qualification recognised and notified by the Central Government for such purpose] or possesses theAssociateship Diploma of the Institution of Chemists (India) obtained by passing the said examination with 'Analysis of Drugs and Pharmaceuticals' as one of the subjects and has had after obtaining the said post-graduate degree or diploma not less than three Years' experience in the testing of drugs in a laboratory under the control of (i) a Government Analyst appointed under the Act, or (ii) the head of an Institution or testing laboratory approved for the purpose by the appointing authority [103][or has completed two years' training on testing of drugs, including items stated in Schedule C, in Central Drugs Laboratory]:

Provided that—

[104][(i) for the purpose of examination of items in Schedule C,—

(ia) the persons appointed under clause (a) or (b) and having degree in Medicine, Physiology, Pharmacology, Microbiology, Pharmacy should have experience or training in testing of said items in an institution or laboratory approved by the appointing authority for a period of not less than six months;

(ib) the person appointed under clause (a) or (b) but not having degree in the above subjects should have experience or training in testing of the said Schedule C drugs for a period of not less than three years in an institution or laboratory approved by the appointing authority or have completed two years training on testing of drugs including item stated in Schedule C in Central Drugs Laboratory;]

(ii) for a period of four years from the date on which Chapter IV of the Act takes effect in the States, persons, whose training and experience are regarded by the appointing authority as affording, subject to such further training, if any, as may be considered necessary, a reasonable guarantee of adequate knowledge and competence may be appointed as Government

Analysts. The persons so appointed may, if the appointing authority so desires, continue in service after the expiry of the said period of four years;

(iii) no person who is engaged directly or indirectly in any trade or business connected with the manufacture of drugs shall be appointed as a Government Analyst for any area:

Provided further that for the purpose of examination of Antisera, Toxoid and Vaccines and Diagnostic Antigens for Veterinary use, the person appointed shall be a person who is a graduate in Veterinary Science, or general science, or medicine or pharmacy and has had not less than five years' experience in the standardization of biological products or a person holding a post-graduate degree in Veterinary Science, or General Science, or medicine or Pharmacy or Pharmaceutical Chemistry with an experience of not less than three years in the standardisation of biological products:

Provided also that persons, already appointed as Government Analysts may continue to remain in service, if the appointing authority so desires, notwithstanding the fact that they do not fulfil the qualifications as laid down in clause (a), clause (b) or the preceding proviso.]

45. Duties of Government Analysts.—(1) The Government Analyst shall cause to be analysed or tested such samples of drugs [105][***] as may be sent to him by Inspector or other persons under the provisions of Chapter IV of the Act and shall furnish reports of the results of test or analysis in accordance with these rules [106][within a period of sixty days of the receipt of the sample:

Provided that where it is not possible to test or analyse the sample within the specified period, the Government Analyst shall seek extension of time from the Government giving specific reasons for delay in such testing or analysis.]

(2) A Government Analyst shall from time to time forward to the Government reports giving the result of analytical work and research with a view to their publication at the discretion of Government.

46. Procedure on receipt of sample.—On receipt of a package from an Inspector containing a sample for test or analysis, the Government Analyst shall compare the seals on the packet [107][or on portion of sample or container] with the specimen impression received separately and shall note the condition of the

seals on the [108][packet or on portion of sample or container]. After the test or analysis has been completed, he shall forthwith supply to the Inspector a report in triplicate in Form 13 of the result of the test or analysis, together with full protocols of the tests or analysis applied.

[109][*Explanation*.—It shall be deemed to be full and sufficient compliance with the requirement of the rule in respect of the supply of "protocols of the tests or analysis applied", if—

(1) for pharmacopoeial drug, where the tests or methods of analysis prescribed in the official pharmacopoeia are followed, references to the specific tests or analysis in the pharmacopoeias are given in the report;

(2) for patent or proprietary medicines for which the tests and methods prescribed in any of the official pharmacopoeias are applicable and are followed, references to the specific tests or analysis in the pharmacopoeias are given in the report;

(3) for patent or proprietary medicines containing pharmacopoeial drugs for which the official tests or analysis or methods of assays are modified and applied, a description of the actual tests or, as the case may be, analysis or methods of assays so applied is given in the report;

(4) for patent or proprietary medicines for which no pharmacopoeial tests or methods of analysis are available or can be applied but for which tests or methods of analysis given in standard books or journals are followed, a description of such tests or methods of analysis applied together with the reference to the relevant books or journals from which the tests or methods of analysis have been adopted, is given the report;

(5) for those drugs for which methods of test are not available and have been evolved by the Government Analyst, a description of tests applied is given in the report.]

47. Report of result of test or analysis.—An application from a purchaser for test or analysis of a drug under section 26 of the Act shall be made in Form 14A and the report of test or analysis of the drug made on such application shall be supplied to the applicant in Form 14B.

48. Fees.—The fees to be paid by a person submitting to the Government Analyst under section 26 of the Act for test or analysis of a drug [110][***] purchased by him shall be those specified in. Schedule B.

[111]**[49. Qualifications of Inspectors.**—A person who is appointed an Inspector under the Act shall be a person who has a degree in Pharmacy or Pharmaceutical Sciences or Medicine with specialisation in Clinical Pharmacology or Microbiology from a University established in India by law:

Provided that only those Inspectors—

(i) who have not less than 18 months' experience in the manufacture of at least one of the substances specified in Schedule C, or

(ii) who have not less than 18 months' experience in testing of at least one of the substances in Schedule C in a laboratory approved for this purpose by the licensing authority, or

(iii) who have gained experience of not less than three years in the inspection of firm manufacturing any of the substances specified in Schedule C during the tenure of their services as Drugs Inspectors;

shall be authorised to inspect the manufacture of the substances mentioned in Schedule C:]

[112][Provided further that the requirement as to the academic qualification shall not apply to persons appointed as Inspectors on or before the 18th day of October, 1993.]

[113]**[49A. Qualification of a Licensing Authority.**—No person shall be qualified to be a Licensing Authority under the Act unless—

(i) he is a graduate in Pharmacy or Pharmaceutical Chemistry or in Medicine with specialisation in Clinical Pharmacology or Microbiology from a University established in India by law; and

(ii) he has experience in the manufacture or testing of drugs or enforcement of the provisions of the Act for a minimum period of five years:

[114][Provided that the requirements as to the academic qualification shall not apply to those Inspectors and the Government Analysts who were holding those positions on the 12th day of April, 1989.]]

[115]**[50. Controlling Authority.—(1)** All Inspectors appointed by the Central Government shall be under the control of an officer appointed in this behalf by the Central Government.

(2) All Inspectors appointed by the State Government shall be under the control of an officer appointed in this behalf by the State Government.

(3) For the purposes of these rules an officer appointed by the Central Government under sub-rule (1), or as the case may be, an officer appointed by the State Government under sub-rule (2) shall be a controlling authority.]

[116]**[50A.Qualification of a Controlling Authority.**—(1) No person shall be qualified to be a Controlling Authority under the Act unless—

(i) he is a graduate in Pharmacy or Pharmaceutical Chemistry or in Medicine with specialisation in Clinical Pharmacology or Microbiology from a University established in India by law; and

(ii) he has experience in the manufacture or testing of drugs or enforcement of the provisions of the Act for a minimum period of five years:

[117][Provided that the requirements as to the academic qualification shall not apply to those Inspectors and the Government Analysts who were holding those positions on the 12th day of April, 1989.]]

51. Duties of Inspectors of premises licensed for sale.—Subject to the instructions of the controlling authority, it shall be the duty of an Inspector authorized to inspect premises licensed for the sale of drugs—

(1) to inspect [118][not less than once a year] all establishments licensed for the sale of drugs within the area assigned to him;

(2) to satisfy himself that the conditions of the licences are being observed;

(3) to procure and send for test or analysis, if necessary, imported packages which he has reason to suspect contain drugs being sold or stocked or exhibited for sale in contravention of the provisions of the Act or rules thereunder;

(4) to investigate any complaint in writing which may be made to him;

(5) to institute prosecutions in respect of breaches of the Act and rules thereunder;

(6) to maintain a record of all inspections made and action taken by him in the performance of his duties, including the taking of samples and the seizure of stocks, and to submit copies of such record to the controlling authority;

(7) to make such enquiries and inspections as may be necessary to detect the sale of drugs in contravention of the Act;

(8) when so authorized by the State Government, to detain imported packages which he has reason to suspect contain drugs, the import of which is prohibited.

52. Duties of inspectors specially authorised to inspect the manufacture of [119][drugs [120][***]].—Subject to the instructions of the controlling authority it shall be the duty of an Inspector authorized to inspect the manufacture of [119][drugs [120][***]]

(1) to inspect [121][not less than once a year], all premises licensed for manufacture of [119][drugs [120][***]] within the area allotted to him to satisfy himself that the conditions of the licence and provisions of the Act and Rules thereunder are being observed;

(2) in the case of establishments licensed to manufacture products specified in Schedules C and C (1) to inspect the plant and the process of manufacture, the means employed for standardizing and testing the drug, the methods and place of storage, the technical qualifications of the staff employed and all details of location, construction and administration of the establishment likely to affect the potency or purity of the product;

(3) to send forthwith to the controlling authority after each inspection a detailed report indicating the conditions of the licence and provisions of the Act and rules thereunder which are being observed and the conditions and provisions, if any, which are not being observed;

(4) to take samples of the [1][drugs [2][***]] manufactured on the premises and send them for test or analysis in accordance with these Rules;

(5) to institute prosecutions in respect of breaches of the Act and rules thereunder.

53. Prohibition of disclosure of information.—Except for the purposes of official business or when required by a Court of law, an Inspector shall not, without the sanction in writing of his official superior, disclose to any person any information acquired by him in the course of his official duties.

54. Form of order not to dispose of stock.—An order in writing by an Inspector under clause (c) of section 22 of the Act requiring a person not to dispose of any stock in his possession shall be in Form 15.

[122]**[54A. Prohibition of sale.**—No person in possession of a drug [35][***] in respect of which an Inspector has made an order under clause (c) of sub-section(i) of section 22 of the Act shall in contravention of that order sell or otherwise dispose of any stock of such drug [123][***].]

[124]**[55. Form of receipts for seized drugs, [125][***], record, register, documents or any other material objects.**—A receipt by an Inspector for the stock of any drug [126][***] or for any record, register, document or any other material object seized by him under clause (c) or clause (cc) of sub-section (1) of section 22 ofthe Act shall be in Form 16.]

[127]**[55A.Manner of certifying copies of seized documents.**—The Drugs Inspector shall return the documents, seized by him under clause (cc), or produced before him under clause (cca) of sub-section (1) of section 22 of the Act, within a period of twenty days of the date of such seizure or production, to the person from whom they were seized or, as the case may be, the person who produced them, after copies thereof of extracts therefrom have been signed by

the concerned Drugs Inspector and the person from whom they were seized, or as the case may be, who produced such records.]

56. Form of intimation of purpose of taking samples.—When an Inspector takes a sample of a drug for the purpose of test or analysis, he shall intimate such purpose in writing in Form 17 to the person from whom he takes it.

[128]**[56A. Form of receipt for samples of drugs where fair price tendered is refused.**—Where the fair price, for the samples of drugs taken for the purpose of test or analysis, tendered under sub-section (1) of section 23 has been refused, the Inspector shall tender a receipt therefor to the person from whom the said samples have been taken as specified in Form 17A.]

57. Procedure for despatch of sample to Government Analyst.—(1) The portion of sample or the container sent by an Inspector to the Government Analyst for test or analysis under sub-section (4) of section 23 of the Act shall be sent by registered post or by hand in a sealed packet, enclosed together with a memorandum in Form 18, in an outer cover addressed to the Government Analyst.

(2) A copy of the memorandum and a specimen impression of the seal used to seal the packet shall be sent to the Government Analyst separately by registered post or by hand.

[129]**[58. Confiscation of drugs, implements, machinery, etc.**—(1) Where any person has been convicted for contravening any of the provisions of Chapter IV of the Act or any rule made thereunder, the stock of the drug in respect of which the contravention has been made shall be liable to confiscation.

(2) Where any person has been convicted for the manufacture, of any drug deemed to be misbranded under clause (a), clause (b), clause (c), clause (d), clause (f) or clause (g) of section 17 of the Act, or adulterated drug under section 17B of the Act, or for manufacture for sale, or stocking or exhibiting for sale or distribution of any drug without a valid licence as required under clause (c) of section 18 of the Act, any implements or machinery used in such manufacture, sale or distribution and any receptacle, packages, or coverings in which such drug is contained and the animals, vehicles, vessels or other conveyances used in carrying such drug shall also be liable to confiscation.]

[130]**[58A.Procedure for disposal of confiscated drugs.**—(1) The Court shall refer the confiscated drugs to the Inspector concerned for report as to whether they are of standard quality or contravene the provisions of the Act or the rulesin any respect.

(2) If the Inspector, on the basis of Government Analyst's report finds the confiscated drugs to be not of standard quality or to contravene any of the provisions of the Act or the rules made thereunder, he shall report to the Court accordingly. The Court shall thereupon order the destruction of the drugs. The destruction shall take place under the supervision of the Inspector in the presence of such authority, if any, as may be specified by the Court.

(3) If the Inspector finds that the confiscated drugs are of standard quality and do not contravene the provisions of the Act or the rules made thereunder, he shall report to the Court accordingly. [131][The Court may then order the Inspector to give the stocks of confiscated drugs to hospital or dispensary maintained or supported by the Government or by Charitable Institutions.]]

PART VI

SALE OF DRUGS OTHER THAN HOMEOPATHIC MEDICINES

59. (1) The State Government shall appoint licensing authorities for the purpose of this Part for such areas as may be specified.

[132][(2) Application for the grant [133][***] of a licence [134][to sell, stock, exhibit or offer for sale or distribute] drugs, other than those included in Schedule X, [135][shall be made in Form 19 accompanied by a fee of rupees one thousand and five hundred or in Form 19A accompanied by a fee of rupees five hundred, as the case may be, or in the case of drugs included in Schedule X shall be made in Form 19C accompanied by a fee of rupees five hundred, to the licensing authority:]

Provided that in the case of an itinerant vendor or an applicant who desires to establish a shop in a village or town having population of 5,000 or less, the application in Form 19A shall be accompanied by a fee of rupees ten.

(3) [135][A fee of rupees one hundred and fifty] shall be paid for a duplicate copy of a licence [134][to sell, stock, exhibit or offer for sale or distribute] drugs, other than those included in Schedule X, or for a licence to sell, stock, exhibit

for sale or distribute drugs included in Schedule X, if the original is defaced, damaged or lost:

Provided that in the case of itinerant vendor or an applicant who desires to establish a shop in a village or town having a population of 5,000 or less, the fee for a duplicate copy of a licence if the original is defaced, damaged or lost, shall be rupees two.

[136][***]

[137]**[60.** A licensing authority may with the approval of the State Government by an order in writing delegate the power to sign licences and such other powers as may be specified in the order to any other person under his control.]

[138]**[61.Forms of licences to sell drugs.**—(1) A licence [139][to sell, stock, exhibit or offer for sale or distribute] drugs other than those specified in Schedules C, C (1) and X and by retail on restricted licence or by wholesale, shall be issued in Form 20, Form 20A or Form 20B, as the case may be:

Provided that a licence in Form 20A shall be valid for only such drugs as are specified in the licence.

(2) A licence [139][to sell, stock, exhibit or offer for sale or distribute] drugs specified in Schedules C and C (1) excluding those specified in Schedule X, by retail on restricted licence or by wholesale shall be issued in Form 21, Form 21A or Form 21B, as the case may be:

[140][Provided that a licence in Form 21A shall not be granted for drugs specified in Schedule C and shall be valid for only such Schedule C (i) drugs as are specified in the licence.]

(3) A licence [139][to sell, stock, exhibit or offer for sale or distribute] drugs specified in Schedule X by retail or by wholesale shall be issued in Form 20F or Form 20G as the case may be]

62. Sale at more than one place.—If drugs are sold or stocked for sale at more than one place, separate application shall be made, and a separate licence shall be issued, in respect of each such place:

[141][Provided that this shall not apply to itinerant vendors who have no specified place of business and who will be licensed to conduct business in a particular area within the jurisdiction of the licensing authority.]

[142]**[62A. Restricted licences in Forms 20A and 21A**—(a) Restricted licences in Forms 20A and 21A shall be issued subject to the discretion of the licensing authority to dealers or persons in respect of drugs whose sale does not require the supervision of a qualified person.

(b) Licences to itinerant vendors shall be issued only in exceptional circumstances for *bona fide* travelling agents of firms dealing in drugs or for a vendor who purchases drugs from a licensed dealer for distribution in sparsely populated rural areas where other channels of distribution of drugs are not available.

(c) The licensing authority may issue a licence in Form 21A to a travelling agent of a firm but to no other class of itinerant vendors for the specific purpose of distribution to medical practitioners or dealers samples of biological and other special products specified in Schedule C:

Provided that travelling agents of licensed manufacturers, agents of such manufacturers and of importers of drugs shall be exempted from taking out licence for the free distribution of samples of medicines among members of the medical profession, hospitals, dispensaries and the medical institutions or research institutions.

[143]**[62B. Conditions to be satisfied before a licence in Form 20A or Form 21A is granted.**—(1) A licence in Form 20A or Form 21A shall not be granted to any person unless the authority empowered to grant the licence is satisfied that the premises in respect of which the licence is to be granted are adequate and equipped with proper storage accommodation for preserving the properties of drugs to which the licence applies:

Provided that this condition shall not apply in the case of licence granted to itinerant vendors.

(2) In granting a licence under rule 62A the authority empowered to grant to it shall have regard to—

(i) the number of licences granted in the locality during one year immediately preceding; and

(ii) the occupation, trade or business carried on by such applicant:

Provided that the licensing authority may refuse to grant [144][***] a licence toany applicant or licensee in respect of whom it is satisfied that by reason of his conviction of an offence under the Act or these rules or the previous cancellation or suspension of any licence granted thereunder, he is not a fit person to whom a licence should be granted under this rule.

(3) Any person who is aggrieved by the order passed by the licensing authority in sub-rule (1) may, within 30 days from the date of the receipt of such order appeal to the State Government and the State Government may, after such enquiry into the matter as it considers necessary and after giving the appellant an opportunity for representing his views in the matter, make such order in relation thereto as it thinks fit.]

[145]**[62C. Application for licence to sell drugs by wholesale or to distribute the same from a motor vehicle.**—(1) Application for the grant [146][***] of a licence to sell by wholesale or to distribute from a motor vehicle shall be made to the licensing authority in Form 19AA and shall be accompanied by [147][a fee of rupees five hundred]:

[148][***]

(2) A fee of rupees [149][one hundred and fifty] shall be paid for a duplicate copy of a licence issued under this rule, if the original is defaced, damaged or lost.

62D. Form of licences to sell drugs by wholesale or distribute drugs from a motor vehicle.—A licence shall be issued for sale by wholesale or for distribution from a motor vehicle of drugs other than those specified in Schedule C and Schedule C (1) in Form 20BB and of drugs specified in Schedule C and Schedule C (1) in Form 21BB:

Provided that such a licence shall not be required in a case where a public carrier or a hired vehicle is used for transportation or distribution of drugs.]

[150]**[63. Duration of licence.—(1)** A licence issued in Forms 20, 20A, 20B, 20BB, 20F, 20G, 21, 21A, 21B or Form 21BB shall remain valid, if licencee deposits a licence retention fee referred to in sub-rule (2) before the expiry of a period of every succeeding five years from the date of its issue, unless, it is suspended or cancelled by the licensing authority.

(2) The licence retention fee referred to in sub-rule (1) shall be equivalent to the respective fee required for the grant of such licence.

(3) If the licencee fails to pay licence retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay licence retention fee along with a late fee calculated at the rate of two per cent, of the licence fee for every month or part thereof up to six months, and in the event of non-payment of such fee, the licence shall be deemed to have been cancelled.]

63A. [151]**[***]**

63B. [152]**[***]**

[153]**[64. Conditions to be satisfied before a licence in** [154]**[Form 20, 20B, 20F, 20G, 21 or 21B] is granted** [155]**[***]** —(i) A licence in [154][Form 20, 20B, 20F, 20G, 21 or 21B] [156][to sell, stock, exhibit or offer for sale or distribute] drugs shall not be granted [155][***] to any person unless the authority empowered to grant the licence is satisfied that the premises in respect of which the licence is to be granted [155][***] are adequate, equipped with proper storage accommodation for preserving the properties of the drugs to which the licence applies and are in charge of a person competent in the opinion of the licensing authority to supervise and control the sale, distribution and preservation of drugs:

Provided that in the case of a pharmacy a licence in Form 20 or 21 shall not be granted [155][***] unless the licensing authority is satisfied that the requirements prescribed for a pharmacy in Schedule N have been complied with:

[157][Provided further that licence in Form 20F shall be granted [155][***] only to a pharmacy and in areas where a pharmacy is not operating, such licence may be granted [155][***] to a chemist and druggist.]

Explanation.—For the purpose of this rule the term 'pharmacy' shall be held to mean and include every store or shop or other place—(1) where drugs are dispensed, that is, measured or weighed or made up and supplied; or (2) where prescriptions are compounded; or (3) where drugs are prepared; or **(4)** which has upon it or displayed within it, or affixed to or used in connection with it, a sign bearing the word or words "Pharmacy", "Pharmacist", "Dispensing Chemist", or "Pharmaceutical Chemist", or (5) which, by sign, symbol or indication within or upon it gives the impression that the operations mentioned at (1), (2) and(3) are carried out in the premises; or (6) which is advertised in terms referred to in (4) above.

(2) In granting [158][***] a licence under sub-rule (1) the authority empowered to grant it shall have regard—

[159][(i) to the average number of licences granted [155][***] during the period of 3 years immediately preceding, and]

(ii) to the occupation, trade or business ordinarily carried on by such applicant during the period aforesaid:

Provided that the licensing authority may refuse to grant if [160][***] a licence to any applicant or licensee in respect of whom it is satisfied that by reason of his conviction of an offence under the Act or these rules, or the previous cancellation or suspension of any licence granted [161][***] thereunder, he is not a fit person to whom a licence should be granted [161][***] under this rule. Every such order shall be communicated to the licensee as soon as possible:

[162][Provided further that in respect of an application for the grant of a licence in Form 20B or Form 21B or both, the licensing authority shall satisfy himself that the premises in respect of which a wholesale licence is to be granted [161][***] are—

(i) of an area of not less than ten square metres; and

[163][(ii) in the charge of a competent person, who—

(a) is a Registered Pharmacist, or;

(b) has passed the matriculation examination or its equivalentexamination from a recognised Board with the four years'experience in dealing with sale of drugs, or;

(c) holds a degree of a recognised University with one year's experience in dealing with drugs:]

[164][Provided also that—

(i) in respect of an application for the grant of a licence in Form 20 orForm 21 or both, the licensing authority shall satisfy itself that thepremises are on an area of not less than 10 square metres, and

(ii) in respect of an application for the grant of a licence—

(a) in Form 20 or Form 21 or both, and

(b) in Form 20B or Form 21B or both,

the licensing authority shall satisfy itself that the premises are of an area not less than 15 square metres:

Provided also that the provisions of the preceding proviso shall not apply to the premises for which licences have been issued by the licensing authority before the commencement of the Drugs and Cosmetics (1st Amendment) Rules, 1997.]

[165][(3) Any person who is aggrieved by the order passed by the licensing authority in sub-rule (1) may, within 30 days from the date of the receipt ofsuch order, appeal to the State Government and the State Government may, after such enquiry into the matter as it considers necessary and after giving the appellant an opportunity for representing his views in the matter, make such order in relation thereto as it thinks fit.]

65. Condition of licences.—Licences in [166][Forms 20, 20A, 20B, 20F, 20G, 21 and 21B] shall be subject to the conditions stated therein and to the following general conditions:—

[166][(1) Any drug shall, if compounded or made on the licensee's premises, be compounded or made by or under the direction and personal supervision of a [167][registered pharmacist],

(2) The supply, otherwise than by way of wholesale dealing [168][***] of any drug supplied on the prescription of a Registered Medical Practitioner shall be effected only by or under the personal supervision of a [167][registered pharmacist].

[169][(3) (1) The supply of any drug [166][other than those specified in Schedule X] on a prescription of a Registered Medical Practitioner shall be recorded at the time of supply in a prescription register specially maintained for the purpose and the serial number of entry in the register shall be entered on the prescription. The following particulars shall be entered in the register:—

(a) serial number of the entry,

(b) the date of supply,

(c) the name and address of the prescribes

[170][(d) the name and address of the patient, or the name and address of the owner of the animal if the drug supplied is for veterinary use,]

(e) the name of the drug or preparation and the quantity or in the case of a medicine made up by the licensee, the ingredients and quantities thereof,

(f) in the case of a drug specified in [166][Schedule C or [171][Schedule H and Schedule H1]] the name of manufacturer of the drug, its batch number and the date of expiry of potency, if any,

(g) the signature of the [167][Registered Pharmacist] by or under whose supervision the medicine was made up or supplied:

Provided that in the case of drugs which are not compounded in the premises and which are supplied from or in the original containers the particulars specified in items (a) to (g) above may be entered in a case

or credit memo books, serially numbered and specially maintained for this purpose:

Provided further that if the medicine is supplied on a prescription on which the medicine has been supplied on previous occasion and entries made in the prescription register it shall be sufficient if the new entry in the register includes a serial number, the date of supply, the quantity supplied and asufficient reference to an entry in the register recording the dispensing of the medicine on the previous occasion:

Provided further that it shall not be necessary to record the above details in the register or in the cash or credit memo particulars in respect of—

(i) any drugs supplied against prescription under the Employees State Insurance Scheme if all the above particulars are given in that prescription, and

(ii) any drugs other than that specified in [172][Schedule C or [173][Schedule H and Schedule H1]] if it is supplied in the original unopened container of the manufacturer and if the prescription is duly stamped at the time of supply with the name of the supplier and the date on which the supply was made and on condition that the provisions of sub-rule (4) (3) of this rule are complied with.

[174][(h) the supply of a drug specified in Schedule HI shall be recorded in a separate register at the time of the supply giving the name and address of the prescriber, the name of the patient, the name of the drug and the quantity supplied and such records shall be maintained for three years and be open for inspection.]

(2) The option to maintain a prescription register or a cash or credi memo book in respect of drugs and medicines which are supplied from or in the original container, shall be made in writing to the Licensing Authority at the time of application for the grant [175][***] of the licence to sell by retail:

Provided that the Licensing Authority may require records to be maintained only in prescription register if it is satisfied that the entries in the carbon copy of the cash or credit memo book are not legible.]

[176][(4) (1) The supply by retail, otherwise than on a prescription of a drug specified in Schedule C [177][***] shall be recorded at the time of supply either—

(i) in a register specially maintained for the purpose in which the following particulars shall be entered:—

(a) serial number of the entry,
(b) the date of supply,
(c) the name and address of the purchaser,
(d) the name of the drug and the quantity thereof,
(e) in the case of a drug specified in Schedule C, the name of the manufacturer, the batch number and the date of expiry of potency,
(f) the signature of the person under whose supervision the sale was effected, or

(ii) in a cash or credit memo book, serially numbered containing all the particulars specified in items (b) to (f) of sub-clause(i) above.

Note.—The entries in the carbon copy of the cash or credit memo which is retained by the licensee shall be maintained in a legible manner.

(2) The option to maintain a register or cash or credit memo book shall be made in writing to the Licensing Authority at the time of application for the grant [178][***] of a licence to sell by retail:

Provided that the Licensing Authority may require records to be maintained in a register if it is satisfied that the entries in the carbon copy of the cash or credit memo book are not legible.

(3) (i) The supply by retail of any drug shall be made against a cash or credit memo which shall contain the following particulars: —

(a) name, address and sale licence number of the dealer,
[179][(b) serial number of the cash or credit memo,]
[180][(c)] the name and quantity of the drug supplied.

(ii) Carbon copies of cash or credit memos shall be maintained by the licensee as record.

[181][(4) (i) Records of purchase of a drug intended for sale or sold by retail shall be maintained by the licensee and such records shall show the following particulars, namely:—

(a) the date of purchase,

(b) the name and address of the person from whom purchased and the number of the relevant licence held by him,

(c) the name of the drug, the quantity and the batch number, and

(d) the name of the manufacturer of the drug.

(ii) Purchase bills including cash or credit memos shall be serially numbered by the licensee and maintained by him in a chronological order.]]

[182][(5) (1) Subject to the other provisions of these rules the supply of a drug by wholesale shall be made against a cash or credit memo bearing the name and address of the licensee and his licence number under the Drugs and Cosmetics Act in which the following particulars shall be entered:—

(a) the date of sale,

(b) the name, address of the licensee to whom sold and his sale licence number. In case of sale to an authority purchasing on behalf of Government, or to a hospital, medical, educational or research institution or to a Registered Medical Practitioner for the purpose of supply to his patients the name arid address of the authority, institution or the Registered Medical Practitioner, as the case may be,

(c) the name of the drug, the quantity and the batch number,

(d) the name of the manufacturer,

[183][(e) the signature of the competent person under whose supervision the sale was effected.]

(2) Carbon copies of cash or credit memos specified in clause (1) shall be preserved as records for a period of three years from the date of the sale of the drug.

[184][(3) (i) Records of purchase of a drug intended for resale or sold by wholesale shall be maintained by the licensee and such records shall show the following particulars, namely—

(a) the date of purchase,

(b) the name, address and the number of relevant licence held by the person from whom purchased,

(c) the name of the drug, the quantity and the batch number, and

(d) the name of the manufacturer of the drug.

(ii) Purchase bills including cash or credit memos shall be serially numbered by the licensee and maintained by him in a chronological order.]]

(6) The licensee shall produce for inspection by an Inspector appointed under the Act on demand all registers and records maintained under these rules, and shall supply to the Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and rules thereunder have been observed.

(7) Except where otherwise provided in these rules, all registers and records maintained under these rules shall be preserved for a period of not less than two years from the date of the last entry therein.

(8) Notwithstanding anything contained in this rule it shall not be necessary to record any particulars in a register specially maintained for the purpose if the particulars are recorded in any other register specially maintained under any other law for the time being in force.

[185][(9) (a) Substances specified in [186][Schedule H and Schedule H1] or Schedule X shall not be sold by retail except on and in accordance with the prescription of a Registered Medical Practitioner and in the case of substances specified in Schedule X, the prescriptions shall be in duplicate, one copy of which shall be retained by the licensee for a period of two years.

(b) The supply of drugs specified in [186][Schedule H and Schedule HI] or Schedule X to Registered Medical Practitioners, Hospitals, Dispensaries and Nursing Homes shall be made only against the signed order in writing which shall be preserved by the licensee for a period of two years.]

(10) For the purposes of clause (9) a prescription shall—

(a) be in writing and be signed by the person giving it with his usual signature and be dated by him;

[187][(b) specify the name and address of the person for whose treatment it is given, or the name and address of the owner of the animal if the drug is meant for veterinary use;]

(c) indicate the total amount of the medicine to the supplied and the dose to be taken.

(11) The person dispensing a prescription containing a drug specified in [186][Schedule H and Schedule H1] [188][and Schedule X] shall comply with the following requirements in addition to other requirements of these rules:—

(a) the prescription must not be dispensed more than once unless the prescriber has stated thereon that it may be dispensed more than once;

(b) if the prescription contains a direction that it may be dispensed a stated number of times or at stated intervals it must riot be dispensed otherwise than in accordance with the directions;

(c) at the time of dispensing there must be noted on the prescription above the signature of the prescriber the name and address of the seller and the date on which the prescription is dispensed.

[189][(11A) No person dispensing a prescription containing substances specified in [185][[186][Schedule H and Schedule HI] or X] may supply any other preparation, whether containing the same substances or not in lieu thereof.]

[185][(12) Substances specified in Schedule X kept in retail shop or premises used in connection therewith shall be stored—

(a) under lock and key in cupboard or drawer reserved solely for the storage of these substances; or

(b) in a part of the premises separated from the remainder of the premises and to which only responsible persons have access.]

[190][***]

[191][(15) (a) The description "Drugstore" shall be displayed by such licensees who do not require the services of a [192][Registered Pharmacist].

(b) The description "Chemists and Druggists" shall be displayed by such licensees who employ the services of a [192][Registered Pharmacist] but who do not maintain a "Pharmacy" for compounding against prescriptions.

(c) The description "Pharmacy", "Pharmacist", "Dispensing Chemist" or "Pharmaceutical Chemist" shall be displayed by such licensees who employ the services of a [192][Registered Pharmacist] and maintain a "Pharmacy" for compounding against prescriptions.

[192]*[Explanation*.—For the purpose of this rule—

(i) 'Registered Pharmacist' means a person who is a registered pharmacist as defined in clause (i) of section 2 of the Pharmacy Act, 1948 (8 of 1948):

Provided that the provisions of sub-section (i) shall not apply to those persons who are already approved as "qualified person" by the Licensing authority on or before the 31st December, 1969.

(ii) "Date of Expiry of Potency" means the date that is recorded on the container label or wrapper as the date upto which the substance may be expected to retain a potency nor less than or not to acquire a toxicity greater than that required or permitted by the prescribed test.]]

[193][(16) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and the defects noticed.]

[194][(17) No drug shall be sold or stocked by the licensee after the date of expiration of potency recorded on its container, label or wrapper, or in violation of any statement or direction recorded on such container, label or wrapper:

Provided that any such drugs in respect of which the licensee has taken steps with the manufacturer or his representative for the withdrawal, reimbursement or disposal of the same, may be stocked after the date of expiration of potency pending such withdrawal, reimbursement or disposal, as the case may be, subject to the condition that the same shall be stored separately from the tradestocks [195][and all such drugs shall be kept in packages or cartons, the top of which shall display prominently, the words "Not for sale"].]

[196][(18) No drug intended for distribution to the medical profession as free sample which bears a label on the container as specified in clause [197][(ix)] of sub-rule (1) of rule 96, and no drug meant for consumption by the Employees' State Insurance Corporation, the Central Government Health Scheme, the Government Medical Stores Depots, the Armed Forces Medical Stores or other Government institutions, which bears a distinguishing mark or any inscription on the drug or on the label affixed to the container thereof indicating this purpose shall be sold or stocked by the licensee on his premises:]

[198][Provided that this sub-rule shall not be applicable to licensees who have been appointed as approved chemists, by the State Government in writing, under the Employee's State Insurance Scheme, or have been appointed as authorised agent or distributor, by the manufacturer in writing, for drugs meant for consumption under the Central Government Health Scheme, the Government Medical Stores Depots, the Armed Forces Medical Stores or other Government Institutions for drugs meant for consumption under those schemes [199][or have been appointed as authorised Depots or Carrying and Forwarding agent by the manufacturer in writing, for storing free samples meant for distribution to medical profession] subject to the conditions that the stock shall be stored separately from the trade stocks and shall maintain separate records of the stocks received and distributed by them.]

[200][(19) The supply by retail of any drug in a container other than the one in which the manufacturer has marketed the drug, shall be made only by dealers who employ the services of a [201][Registered Pharmacist] and such supply shall be made under the direct supervision of the [201][Registered Pharmacist] in an envelope or other suitable wrapper or container showing the following particulars on the label:—

(a) name of the drug,

(b) the quantity supplied,

(c) the name and address of the dealer.]

[202] [(20) The medicines for treatment of animals kept in a retail shop or premises shall be labelled with the words "Not for human use—for treatment of animals only" and shall be stored—

(a) in a cupboard or drawer reserved solely for the storage of veterinary drug, or

(b) in a part of the premises separated from the remainder of the premises to which customers are not permitted to have access.]

[203][(21) (a) The supply of drugs specified in Schedule X shall be recorded at the time of supply in a register (bound and serially page numbered specially maintained for the purpose and separate pages shall be allotted for each drug.

(b) The following particulars shall be entered in the said register, namely:—

(i) Date of transaction;
(ii) Quantity received, if any, the name and address of the supplier and the number of the relevant licence held by thesupplier;
(iii) Name of the drug;
(iv) Quantity supplied;
(v) Manufacturer's name;
(vi) Batch No. or Lot No.;
(vii) Name and address of the patient/purchaser;
(viii) Reference Number of the prescription against which supplies were made;
(ix) Bill No. and date in respect of purchases and supplies made by him;
(x) Signature of the person under whose supervision the drugs have been supplied.]

[204][**65A.Additional information to be furnished by an applicant for licence or a licensee to the licensing authority.—**The applicant for the grant of a licence or any person granted a licence under this Part shall, on demand, furnish to the licensing authority, before the grant of the licence or during the period the licence is in force, as the case may be, documentary evidence in respect of the ownership or occupation on rental or other basis of the premises, specified in the application for licence or in the licence granted, constitution of the firm, or any other relevant matter which may be required for the purpose of verifying the correctness of the statements made by the applicant or the licensee which applying for or after obtaining the licence, as the case may be.]

[205][**65B. Inspection for verification of compliance. —**The licensing authority shall cause inspection, by the Inspector appointed under the Act, of

each premises licensed under this Part, to verify the compliance with the conditions of licence and the provisions of the Act and these rules, not less than once in three years or as needed as per risk based approach.]

66. Cancellation and suspension of licences.—(1) The licensing authority may, after giving the licensee an opportunity to show cause why such an order should not be passed by an order in writing stating the reasons therefore, cancel a licence issued under this Part or suspend it for such period as he thinks fit, either wholly or in respect of some of the substances to which it relates, if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act or rules thereunder:

[209][Provided that, where such failure or contravention is the consequence of an Act or omission on the part of an agent or employee, the licence shall not be cancelled or suspended if the licensee proves to the satisfaction of the licensing authority—

(a) that the act or omission was not instigated or connived at by him or, if the licensee is a firm or company, by a partner of the firm or a director of the company, or

(b) that he or his agent or employee had not been guilty of any similar act or omission within twelve months before the date on which the act or omission in question took place, or where his agent or employee had been guilty of any such act or omission, the licensee had not or could not reasonably have had, knowledge of that previous act or omission, or

(c) if the act or omission was a continuing act or omission, he had not or could not reasonably have had knowledge of that previous act or omission, or

(d) that he had used due diligence to ensure that the conditions of the licence or the provisions of the Act or the rules thereunder were observed.]

[210][(2) A licensee whose licence has been suspended or cancelled may, within three months of the date of order under sub-rule (1), prefer an appeal against that order to the State Government, which shall decide the same.]

[211][**66A. Procedure for disposal of drugs in the event of cancellation oflicence.** — (1) In case a licensee, whose license has been cancelled, desires to dispose of the drugs he has in his possession in the premises in respect of which tine licence has been cancelled, he shall apply in writing to the licensing authority for this purpose, giving the following particulars, namely: —

(a) the name and address of the person to whom the drugs are proposed to be sold or supplied together with the number of the licence for sale or manufacture, as the case may be, held by him,

(b) the names of drugs together with their quantities, batch numbers, the names and addresses of their manufacturers and the dates of their expiry, if any, proposed to be sold to the person mentioned in clause (a).

(2) The licensing authority may, after examination of the particulars referred to in sub-rule (1) and, if necessary, after inspection by an Inspector of the premises where the drugs are stocked, grant the necessary permission for their disposal.]

[212] [***]

[213][PART VIA

SALE OF HOMOEOPATHIC MEDICINES

67A. (1) The State Government shall appoint licensing authorities for the purpose of this Part for such areas as may be specified.

(2) Application for the grant or renewal of a licence [214][to sell, stock, exhibit or offer for sale or distribute] Homoeopathic medicines shall be made in Form 19B to the licensing authority and shall be accompanied by [215][a fee of rupees two hundred and fifty]:

[216][Provided that if the applicant applied for renewal of licence after its expiry but within six months of such expiry the fee payable for renewal of such licence shall be [4][rupees two hundred and fifty plus an additional fee at the rate of rupees fifty per month or part thereof].]

[217][(3) If the original licence is either defaced, damaged or lost, a duplicate copy thereof may be issued on payment of [218][a fee of rupees fifty].]

67B. A licensing authority may, with the approval of the State Government, by an order in writing, delegate the power to sign licences and such other powers, as may be specified, to any other person under this control.

67C.Form of licences to sell drugs.—(1) A licence [214][to sell, stock, exhibit or offer for sale or distribute] Homoeopathic medicines by retail or by wholesale shall be issued in Form 20C or Form 20D as the case may be:

[219][Provided that no licence shall be required for exhibiting the drugs for promotional activities in any fair.]

67D. **Sale at more than one place.**—If drugs are sold or stocked for sale at more than one place, a separate application shall be made and a separate licence shall be obtained in respect of each place.

67E.Duration of licences.—An original licence or a renewed licence unless it is sooner suspended or cancelled shall be [218][valid for a period of five years on and from the date on which] it is granted or renewed:

[216][Provided that if the application for renewal of a licence in force is made before its expiry or if the application is made within six months of its expiry, after payment of additional fee, the licence shall continue to be in force until orders are passed on the application and the licence shall be deemed to have expired if application for its renewal is not made within six months after its expiry]

[220]**[67EE. Certificate of renewal.**—The certificate of renewal of a sale licence in Forms 20C and 20D shall be issued in Form 20E.]

67F. Conditions to be satisfied before a licence in Form 20C or Form 20D is granted.—(1) A licence in Form 20C or Form 20D [221][to sell, stock exhibit or offer for sale or distribute] Homoeopathic medicines shall not be granted to any person unless the authority empowered to grant the licence is satisfied that the premises in respect of which the licence is to be granted are clean and in the case of a licence in form 20C the sale premises is in charge of a person who is or has been dealing in Homoeopathic medicines and

[222][who is having,—

(a) degree in Homoeopathy from a recognised University; or

(b) degree in Pharmacy from a recognised University; or

(c) Bachelor's degree from a recognised University with one year experience of dealing in Homoeopathic medicines in the clinic of a registered Homoeopathic Medical Practitioner or with the holder of licence in Form 20C or Form 20D; or

(d) diploma in Homeopathic Pharmacy; or

(e) diploma in Homeopathy Medicine and Surgery:]

[223][Provided that the person already registered with the State Licensing Authority as competent person for the purposes of grant of license in Form 20C or Form 20D or both prior to the coming into force of the Drugs and Cosmetics (11th Amendment) Rules, 2017, shall continue to be considered as a competent person for the said purposes:

Provided further that no registered Homeopathic medical practitioner who is practising Homeopathy in the premises where Homeopathic medicines are sold shall deal in Homeopathic medicines.]

(2) Any person who is aggrieved by the order passed by the licensing authority under sub-rule (1) may within 30 days from the date of the receipt of such order appeal to the State Government and the State Government may, after such enquiry into the matter as it considers necessary and after giving the appellant an opportunity for representing his case, make such order in relation thereto as it thinks fit.

67G. Conditions of licence.—Licence in Form 20C or 20D shall be subject to the conditions stated therein and to the following further conditions, namely:—

(1) The premises where the Homoeopathic medicines are stocked for sale or sold are maintained in a clean condition.

[224][(2) In the case of licence in Form 20C the Homeopathic medicines shall be sold,—

(i) under the supervision of a person having qualifications referred to in sub-rule (1) of rule 67F; and

(ii) in manufacturer's sealed packing only except dispensing of medicines in globules, water or milk sugar or as per prescription of a Homoeopathic Medical Practitioner.]

(3) The licensee shall permit an Inspector to inspect the premises and furnish such information as he may require for ascertaining whether the provisions of the Act and the rules made thereunder have been observed.

(4) The licensee in Form 20D shall maintain records of purchase and sale of Homoeopathic medicines containing alcohol together with names and addresses of parties to whom sold.

[225][(5) The licensee in Form 20C shall maintain records of purchase and sale of Homoeopathic medicines containing alcohol. No records of sale in respect of Homoeopathic potentised preparations in containers of 30 ml. or lower capacity and in respect of mother tinctures made up in quantities up to 60 ml. need be maintained.]

[226][(6) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and the defects noticed.]

[227]**[67GG. Additional information to be furnished by an applicant for licence or a licensee to the licensing authority.**—The applicant for the grant of a licence or any person granted a licence under this part shall, on demand furnish to the licensing authority, before the grant of the licence or during the period the licence is in force, as the case may be, documentary evidence in respect of the ownership or occupation on rental or other basis of the premises specified in the application for licence or in the licence granted, constitution of the firm, or any other relevant matter which may be required for the purpose or verifying the correctness of the statements made by the applicant or the licensee, while applying for or after obtaining the licence, as the case may be.]

67H. Cancellation and suspension of licences.—**(**1)The licensing authority may, after giving the licensee an opportunity to show cause why such an ordershouldnot be passed, by an order in writing stating the reasons therefore, cancela licence issued under this Part or suspend it for such period as he thinks fit, if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act or rules made thereunder:

[228][Provided that, where such failure or contravention is the consequence of an act or omission on the part of an agent or employee, the licence shall not be cancelled or suspended if the licensee proves to the satisfaction of the licensing authority—

(a) that the act or omission was not instigated or connived at by him or, if the licensee is a firm or company, by a partner of the firm or a director of the company, or

(b) that he or his agent or employee had not been guilty of any similar act or omission within twelve months before the date on which the act or omission in question took place or where his agent or employee had been guilty of any such act or omission the licensee had not or could not reasonably have had knowledge of that previous act or omission, or

(c) if the act or omission was a continuing act or omission, that he had not or could not reasonably have had knowledge of that previous act or omission, or

(d) that he had used due diligence to ensure that the conditions of the licence or the provisions of the Act or the rules thereunder were observed.]

[229][(2) A licensee whose licence has been suspended or cancelled may, within three months of the date of the order under sub-rule (1), prefer an appeal against that order to the State Government, which shall decide the same.]]

PART VII

[230][MANUFACTURE FOR SALE OR FOR DISTRIBUTION] OF DRUGS OTHER THAN HOMOEOPATHIC MEDICINES

68. Manufacture on more than one set of premises. —If drugs are manufactured on more than one set of premises a separate application shall be made and a separate licence shall be issued in respect of each such set of premises.

[231][**68A. Grant** [232][***] **of Licences by the Central Licence Approving** Authority. —(1) Notwithstanding anything contained in this Part, on and from the commencement of the Drugs and Cosmetics (9th Amendment) Rules, *[vide* G.S.R 923 (E), dated 14th December, 1992], a licence for the manufacture for

sale or distribution of drugs as specified from time to time by the Central Government by notification in the Official Gazette, for the purpose of this rule, shall be granted [233][***] by the Central Licence Approving Authority (appointedby the Central Government):]

Provided that the application for the grant [234][***] of such licence shall be made to the licensing authority.

(2) On receipt of the application for grant [234][***] of a licence, the licensing authority shall—

(i) verify the statement made in the application form;

(ii) cause the manufacturing the testing establishment to be inspected in accordance with the provisions of rule 79; and

[235][***]

(3) If the licensing authority is satisfied that the applicant is in a position to fulfil the requirements laid down as in these rules, he shall prepare a report to that effect and forward it alongwith the application [236][and the licence (in triplicate) to be granted [237][***], duly completed] to the Central Licence Approving Authority:

Provided that if the licensing authority is of the opinion that the applicant is not in a position to fulfil the requirements laid down in these rules, he may, by order, for reasons to be recorded in writing, refuse to grant the licence as the case may be.

(4) If on receipt of the application and the report of the licensing authority referred to in sub-rule (3) and after taking such measures including inspection of the premises by the Inspector, appointed by the Central Government under section 21 of the Act, with or without an expert in the concerned field if deemed necessary, the Central Licence Approving Authority, is satisfied that the applicant is in a position to fulfil the requirements laid down in these rules, he may grant [238][***] the licence, as the case may be:

Provided that if the Central Licence Approving Authority is of the opinion that the applicant is not in a position to fulfil the requirements laid down in these rules, he may, notwithstanding the report of the licensing authority, by

order, for reasons to be recorded in writing, reject the application for grant [234][***] of licence as the case may be.]

[239]**[68B. Delegation of Powers by the Central Licence Approving Authority.—**The Central Licence Approving Authority may with the approval of the Central Government, by notification delegate his powers of signing licences and any other power under the rules to any person under his control having same qualifications as prescribed for controlling authority under rule 50A for such areas and for such periods as may be specified.]

[240]**[69. Application for licence to manufacture drugs other than those specified in Schedules C and C (1) to the Drugs and Cosmetics Rules.—** [241]**[(1)** Application for grant [242][***] of [243][licence to manufacture for sale or for distribution] of drugs, other than those specified in Schedules C and C(l) shall be made to the licensing authority appointed by the State Government for the purpose of this Part (hereinafter in this Part referred to as the licensing authority) and shall be made—

(a) in the case of repacking of drugs excluding those specified in Schedule X for sale or distribution in Form 24B;

(b) in the case of manufacture of drugs included in Schedule X in Form 24F;

(c) in any other case, in Form 24.

(2) [244][(a) Every application in Form 24B shall be made up to ten items for each category of drugs categorised in Schedule M and shall be accompanied by a licence fee of rupees five hundred plus and an inspection fee of rupees two hundred for every inspection [245][***].

(b) Every application in Form 24F shall be made up to ten items for each category of drugs categorised in Schedule M and shall be accompanied by a licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred for every subsequent inspection [245][***].

(c) Every application in Form 24 shall be made upto ten items for each category of drugs [246][referred to in Schedule M relating to Pharmaceuticals products and Schedule M-III relating to medical devices and *in-vitro*

diagnostics] and shall be accompanied by a licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred for every inspection [245][***].]

[247][***]

(4) A fee of [248][rupees one hundred shall be paid] for a duplicate copy of the licence issued under clause (a), clause (b) or clause (c) of sub-rule (1) if the original is defaced, damaged or lost.

[249][(5) Applications for manufacture of more than ten items of each category of drugs as [250][referred to in Schedule M relating to pharmaceuticals products and Schedule M-III relating to medical devices and *in-vitro* diagnostics] or for manufacture of additional items of drugs by licensees in Form 24 or Form 24F shall be accompanied by an additional fee at the rate of rupees three hundred for each additional item of drug. Applications in Form 24B for licence to manufacture for sale and distribution for repacking for more than 10 items of each category or for manufacture of additional item of drug shall be accompanied by additional fee of rupees one hundred for each additional item of drugs as categorized in Schedule M and M-III.]

[251][(6) Where an application under this rule is for the manufacture of drug formulations falling under the purview of new drug as defined in rule 122E, such application shall also be accompanied with approval, in writing, in favour of the applicant, from the licensing authority as defined in clause (b) of rule 21.]

[252]**[69A. Loan licences.**—[1][(1) Application for the grant [253][***] of loan licences to manufacture for sale or for distribution of drugs other than those specified in Schedule C, Schedule C(l) and Schedule X shall be made up to ten items for each category of drugs [250][referred to in Schedule M relating to pharmaceulicals products and Schedule M-III relating to medical devices and *in-vitro* diagnostics] and shall be made in Form 24A accompanied by a licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred to the licensing authority:

[254][***]

[255]*[Explanation*.—For the purpose of this rule a loan licence means a licence which a licensing authority may issue to an applicant who intends to avail the manufacturing facilities owned by a licensee in Form 25.]

(2) The licensing authority shall, before the grant of a loan licence, satisfy himself that the manufacturing unit has adequate equipment, staff, capacity for manufacture, and facilities for testing, to undertake the manufacture on behalf of the applicant for a loan licence.

[256][(3) subject to the provisions of sub-rule (2), application for manufacture of more than ten items for each category of drug on a loan licence shall be accompanied by an additional fee of rupees three hundred per additional item [257][referred to in Schedule M relating to pharmaceuticals products and Schedule M-III relating to "medical devices and *in-vitro* diagnostics].]

[258][(4) If the licensing authority is satisfied that a loan licence is defaced damaged or lost or otherwise rendered useless, he may, on payment of [259][a fee of rupees one thousand] issue a duplicate licence.]]

[260][***]

[261]**[70. Form of licence to repack or manufacture drugs other than those specified in Schedules C and C(l).**—Licences for repacking of drugs against application in Form 24B shall be granted in Form 25B, licences for manufacture of drugs included in Schedule X against application in Form 24F shall be granted in Form 25F and licences for manufacture of drugs against application in Form24 shall be granted in Form 25.]

[262]**[70A. Form of loan licence to manufacture for sale [263][or for distribution] of drugs other than those [261][specified in Schedules C, C(l) and X].—**A loan [263][licence to manufacture for sale or for distribution] of drugs other than those specified in [263][Schedules C, C(l) and X] shall be issued in Form 25A.]

[264]**[71. Conditions for the grant [265][***] of a licence in Form 25 [261][or Form 25F.]**—Before a licence in Form 25 [261][or Form 25F] is granted [266][***] the following conditions shall be complied with by the applicant:—

(1) the manufacture shall be conducted under the active direction and personal supervision of competent technical staff consisting at least of one person who is a whole time employee and who is—

(a) a graduate in Pharmacy or Pharmaceutical Chemistry of [267][a University established in India by law or has an equivalent qualification recognized and notified by the Central Government for such purpose] and has had at least eighteen months' practical experience after the graduation in the manufacture of drugs. This period of experience may, however, be reduced by six months if the person has undergone training in manufacture of drugs for a period of six months during his University course; or

(b) a graduate in Science of [267][a University established in India by law or has an equivalent qualification recognised and notified by the Central Government for such purpose] who for the purpose of his degree has studied Chemistry as a principal subject and has had at least three years' practical experience in the manufacture of drugs after his graduation; or

(c) a graduate in Chemical Engineering or Chemical Technology or Medicine of [267][a University established in India by law or has an equivalent qualification recognised and notified by the Central Government for such purpose] with general training and practical experience, extending over a period of not less than three years in the manufacture of drugs, after his graduation; or

[268][(d) holding any foreign qualification the quality and content of training of which are comparable with those prescribed in clause(a), clause (b) or clause (c) and is permitted to work as competent technical staff under this rule by the Central Government:]

Provided that any person who was immediately before the 29th June, 1957, actively directing and personally supervising the manufacture of drugs and whose name was accordingly entered in any licence granted in Form 25 [269][or Form 25F] as it existed before that date shall be deemed to be qualified for the purposes of this rule:

[270][Provided further that for drugs other than those specified in Schedules C, C(l), and X and meant for veterinary use, the wholetime employee under whose supervision the manufacture is conducted shall be a graduate in Veterinary

Science or Pharmacy or General Science or Medicine of a University recognized by the Central Government and who has had atleast three years' practical experience in the manufacture of drugs excluding graduate in Pharmacy who shall have at least eighteen months' practical experience in the manufacture of drugs:]

[271][Provided [272][also] that the licensing authority may, in the matter of manufacture of disinfectant fluid insecticides, liquid paraffin, medicinal gases, non-chemical contraceptives, plaster of paris and surgical dressings, for the manufacture of which the knowledge of Pharmaceutical Chemistry or Pharmacy is not essential, permit the manufacture of the substance under the active direction and personal supervision of the competent technical staff, who, although not having any of the qualifications included in clause (a), (b) or (c) of this rule, has, in the opinion of the licensing authority, adequate experience in the manufacture of such substance.]

(2) The factory premises shall comply with the conditions prescribed in Schedule M.

(3) The applicant shall provide adequate space, plant and equipment for the manufacturing operations; the space, plant and equipment recommended for various operations are given in Schedule M.

[273][(4) The applicant shall provide and maintain adequate staff, premises and laboratory equipment for carrying out tests of the strength, quality and purity of the substances at the testing unit which shall be separate from the manufacturing unit and head of the testing unit shall be independent of the head of the manufacturing unit:

Provided that the manufacturing units, which, before the commencement of the Drugs and Cosmetics (Amendment) Rules, 1977[274], were making arrangements with institutions approved by the licensing authority for such tests to be carried out on their behalf may continue such arrangements up to the 30th June, 1977:

Provided further that for tests requiring sophisticated instrumentation techniques or biological or microbiological methods other than sterility the licensing authority may permit such tests to be conducted by institutions approved by it [275][under Part XV (A) of these rules] for this purpose.]

[276][(4A) The head of the testing unit referred to in condition (4) shall possess a degree in Medicine or Science or Pharmacy or Pharmaceutical Chemistry of a University recognised for this purpose and shall have experience in the testing of drugs, which in the opinion of the licensing authority is considered adequate.]

(5) The applicant shall make adequate arrangements for the storage of drugs manufactured by him.]

[277][(6) The applicant shall, while applying for a licence to manufacture [278][drugs], furnish to the licensing authority evidence and date justifying that the [278][drugs]—

(i) contain the constituent ingredients in therapeutic/prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful;

(ii) are safe for use in the context of the vehicles, excipients additives and pharmaceutical aids used in the formulation and under the conditions in which the formulations for administration and use are recommended;

(iii) are stable under the conditions of storage recommended; and

(iv) contain such ingredients and in such quantities for which there is therapeutic justification.]

[279][(v) have the approval, in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drug as defined in rule 122E, from the licensing authority as defined in clause (b) of rule 21.]

[280][(7) The licensee shall comply with the requirements of 'Good Manufacturing Practices' as laid down in Schedule M.]]

[281][(8) The applicant shall make application for grant of licence for a drug formulation containing single active ingredient only in proper name.]

[282][(9) In case the applicant intends to market the drug under a brand name or trade name, the applicant shall furnish an undertaking in Form 51 to the licensing authority to the effect that to the best of his knowledge based on search in trade marks registry, central data base for brand name or trade name of

drugs maintained by Central Drugs Standard Control Organisation, literature and reference books on details of drug formulations in India, and internet, such or similar brand name or trade name is not already in existence with respect to any drug in the country and the proposed brand name or trade name shall not lead to any confusion or deception in the market.]

[283][**71A. Conditions for the grant** [284][***] **of a licence in Form 25B.**—Before a licence in Form 25B is granted [285][***] the following conditions shall be complied with by the applicant—

(1) the repacking operation shall be carried out under hygienic conditions under the supervision of a competent person;

[286][(2) the factory premises shall comply with the conditions prescribed in Schedule M; and]

[287][(3) the applicant shall have adequate arrangements in his own premises for carrying out tests for the strength, quality and purity of the drugs at a testing unit which shall be separate from the repacking unit;

[281][(4) The application for grant of licence for a drug formulation containing single active ingredient shall be made only in proper name:]

[282][(5) In case the applicant intends to market the drug under a brand name or trade name, the applicant shall furnish an undertaking in Form 51 to the licensing authority to the effect that to the best ofhis knowledge based on search in trademarks registry, central data base for brand name or trade name of drugs maintained by Central Drugs Standard Control Organisation, literature and reference books on details of drug formulations in India, and internet, such or similar brand name or trade name is not already in existence with respect to any drug in the country and the proposed brand name or trade name shall not lead to any confusion or deception in the market:]

Provided that the repacking units, which, before the commencement of the Drugs and Cosmetics (Second Amendment) Rules, 1977[288], were making arrangement with institutions approved by the licensing authority for such tests to be carried out on their behalf, may continue such arrangement up to the 31st July, 1977:

Provided further that for tests requiring sophisticated instrumentation techniques or biological or microbiological methods the licensing authority may permit such test to be conducted by institutions approved by it [289][under Part XV(A) of these rules] for this purpose.]

Explanation.—A person who satisfies the following minimum qualifications shall be deemed to be a "competent person" for the purposes of rule 71A or 74A of these rules, namely:—

(a) a person who holds the Diploma in Pharmacy approved by the Pharmacy Council of India under the Pharmacy Act, 1948 (8 of 1948) or a person who is registered under the said Act, or

(b) a person who has passed the Intermediate examination with Chemistry as one of the principal subjects or an examination equivalent to it or an examination recognised by the licensing authority as equivalent to it, or

(c) a person who has passed the Matriculation examination or an examination recognised by the licensing authority as equivalent to it and has had not less than four years' practical experience in the manufacture, dispensing or repacking of drugs.]

[290]**[71B. Conditions for the grant** [291][***] **of a licence in Form 25A.**—Before a licence in Form 25A is granted [292][***], the applicant shall, while applying for a licence to manufacture [293][drugs], furnish to the licensing authority evidence and date justifying that the [293][drugs]—

(i) contain the constituent ingredients in therapeutic/prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful;

(ii) are safe for use in the context of the vehicles, excipients, additives and pharmaceutical aids used in the formulations and under conditions in which the formulations for administration and use are recommended;

(iii) are stable under the conditions of storage recommended; and

(iv) contain such ingredients and in such quantities for which there is therapeutic justification:]

[294][(v) in case the applicant intends to market the drug under a brand name or trade name, the applicant shall furnish an undertaking in Form 51 to the licensing authority to the effect that to the best of his knowledge based on search in trade marks registry, central data base for brand name or trade name of drugs maintained by Central Drugs Standard Control Organisation, literature and reference books on details of drug formulations in India, and internet, such or similar brand name or trade name is not already in existence with respect to any drug in the country and the proposed brand name or trade name shall not lead to any confusion or deception in the market:]

[295][Provided that the application for grant of a licence for a drug formulation containing single active ingredient shall be made only in proper name.]

[296]**[72.Duration of licence.**—(1) A licence issued in Form 25, Form 25B and Form 25F shall remain valid if the licencee deposits a licence retention fee referred to in sub-rule (2) before the expiry of a period of every succeeding five years from the date of its issue, unless, it is suspended or cancelled by the licensing authority.

(2) The licence retention fee referred to in sub-rule (1) shall be equivalent to the respective fee required for the grant of such licence excluding inspection fee paid for grant of licence.

(3) If the licencee fails to pay licence retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay licence retention fee along with a late fee calculated at the rate of two per cent, of the licence fee for every month or part thereof up to six months, and in the event of non-payment of such fee, the licence shall be deemed to have been cancelled.]

73.[297][***]

73A.[298][***]

[299]**[73AA.Duration of loan licence.**—(1) A licence issued in Form 25A shall remain valid if licencee deposits a licence retention fee referred to in sub-rule (2) before the expiry of a period of every succeeding five years from the date of its issue, unless, it is suspended or cancelled by the licensing authority.

(2) The licence retention fee referred to in sub-rule (1) shall be equivalent to the respective fee required for the grant of such licence excluding inspection fee paid for grant of licence.

(3) If the licencee fails to pay licence retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay licence retention fee along with a late fee calculated at the rate of two per cent, of the licence fee for every month or part there of up to six months, and in the event of non-payment of such fee, the licence shall be deemed to have been cancelled.]

[300]**[73AB. Inspection for grant of licence and verification of compliance.—** (1)Before a licence in Form 25 or Form 25A or Form 25B or Form 25F is granted, the licensing authority shall cause the establishment in which the manufacture of drugs is proposed to be conducted or being conducted to be inspected jointly by the Drugs Inspectors appointed by the Central Government and the State Government under this Act who shall examine the establishment intended to be used or being used for the manufacture of drugs.

(2) The premises licensed under sub-rule (1) shall be inspected jointly by Inspector appointed by the Central Government and State Government to verify the compliance with the conditions of licence and the provisions of the Act and these rules not less than once in three years or as needed as per risk based approach.]

73B. [301]**[***]**

[302]**[74. Conditions of licence in** [303]**[Form 25 and Form 25F].**—A licence in [303][Form25 and Form 25F] shall be subject to the conditions stated therein and to the following further conditions, namely:—

(a) the licensee shall provide and maintain staff, premises and the equipment as specified in rule 71;

(b) the licensee shall comply with the provisions of the Act and of these rules and with such further requirements, if any, as may be specified in any rules subsequently made under Chapter IV of the Act, provided that where such further requirements are specified in the rules, these would come into force, four months after publication in the Official Gazette;

(c) the licensee shall either in his own laboratory or in any other laboratory approved by the licensing authority [304][under Part XV (A) of these rules] test each batch or lot of the raw material used by him for the manufacture of his products and also each batch of the finalproduct and shall maintain records or registers showing the particulars in respect of such tests as specified in Schedule U. The records or registers shall be retained for a period of five years from the date of manufacture;

(d) the licensee shall keep records of the details of manufacture as per particulars given in Schedule U of each batch of the drugs manufactured by him and such records shall be retained for a period of five years;

(e) the licensee shall allow an [305][Inspector appointed under the Act] to enter, with or without prior notice, any premises and to inspect the plant and the process of manufacture and the means employed in standardising and testing the drugs;

(f) the licensee shall allow an [305][Inspector appointed under the Act] to inspect all registers and records maintained under these rules and to take samples of the manufactured drugs and shall supply to such Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and the rules thereunder have been observed;

(g) the licensee shall, from time to time, report to the licensing authority any changes in the expert staff responsible for the manufacture or testing of the drugs and any material alterations in the premises or plant used for the purpose which have been made since the date of the last inspection made on behalf of the licensing authority;

[306][(h) the licensee shall, on request, furnish to the licensing authority, the controlling authority or to such authorities as the licensing authority or the controlling authority may direct, from every batch or batches of drugs as the licensing authority or the controlling authority may from time to time specify, a sample of such quantity as may be considered adequate by such authority for any examination and, if so required, also furnish full protocols of tests which have been applied;]

(i) if the licensing authority [307][or the controlling authority] so directs and if requested by the licensee who had also furnished *prima facie* reasons for

such directions, the licensee shall not sell or offer for sale any batch in respect of which a sample is or protocols are furnished under clause (h) until a certificate authorising the sale of the batch has been issued to him by or on behalf of the licensing authority [307][or the controlling authority];

(j) the licensee shall on being informed by the licensing authority [307][or the controlling authority] that any part of any batch of the drug has been found by the licensing authority [307][or the controlling authority] not to conform with the standards of strength, quality or purity specified in these rules and on being directed so to do, withdraw the remainder of the batch from sale, and, so far as may in the particular circumstances of the case be practicable, recall all issues already made from that batch;

(k) the licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and the defects noticed;

[308][(1) the licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing an expiry date on the label, the reference samples shall be maintained for a period of three months beyond the date of expiry of potency. In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture;]

[309][(m) the licensee, who has been granted a licence in Form 25F, shall—

(i) forward to the licensing authority of the concerned States of manufacture and supply of the drug a statement of the sales effected to the manufacturers, wholesalers, retailers, hospitals, dispensaries and nursing homes and Registered Medical Practitioners every three months;

(ii) maintain accounts of all transactions giving details as indicated below in a register bound and serially page numbered and such records shall be retained for a period of five years or one year after the expiry of potency, whichever is later—

A. Accounts of the drugs specified in Schedule X used for themanufacture—

1. Date of issue
2. Name of the drug.
3. Opening balance of stock on the production day.
4. Quantity received, if any, and source from where received.
5. Quantity used in manufacture.
6. Balance quantity on hand at the end of the production day.
7. Signature of the person in charge.

B. Accounts of production—

1. Date of manufacture.
2. Name of the drug.
3. Batch Number.
4. Quantity of raw material used in manufacture.
5. Anticipated yield.
6. Actual yield.
7. Wastage.
8. Quantity of the manufactured goods transferred.

C. Accounts of the manufactured drugs—

1. Date of manufacture.
2. Name of the drug.
3. Batch Number.
4. Opening Balance.
5. Quantity manufactured.
6. Quantity sold.
7. Name of the purchaser and his address.
8. Balance quantity at the end of the day.
9. Signature of the person in charge.

(n) The licensee shall store drugs specified in Schedule X in bulk form and when any of such drug is required for manufacture in a place other than its place of storage it shall be kept in a separate place under the direct custody of a responsible person.]]

[310][(o) The licensee shall comply, with the requirements of [311]["Good Laboratory Practices" as laid down in Schedule L-I and] [1191]["Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products"] as laid down in Schedule M.]

[312][(p) No advertisement of the drugs specified in Schedule H, Schedule HI and Schedule X shall be made except with the previous sanction of the Central Government.]

[313][(q) the applicant shall submit the result of bioequivalence study referred to in Schedule Y, along with the application for grant of a licence of oral dosage form of drugs specified under category II and category IV of the biopharmaceutical classification system.]

[314]**[74A.Conditions for licence in Form 25B.**—A licence in Form 25B shall be subject to conditions stated therein and to the following conditions:—

(a) the repacking of drugs shall at all times be conducted under the personal supervision of at least one person who is approved as a competent person by the licensing authority;

(b) the licensee shall either provide and maintain adequate arrangements in his own premises for carrying out tests of the strength, quality and purity of the drugs repacked or make arrangements with some institution approved by the licensing authority [315][under Part XV (A) ofthese rules] for such tests to be regularly carried out on his behalf by the institution;

(c) the licensee shall make adequate arrangements for the storage of drugs;

[316][(d) the licensee shall comply with the provisions of the Act and of these rules and with such further requirements, if any, as may be specified in any rules subsequently made under Chapter IV of the Act: Provided that where such further requirements are specified in the rules, these would come into force four months after publication in the Official Gazette;]

(e) the licensee shall allow any [317][Inspector appointed under the Act] to enter with or without notice, any premises where the packing of drugs in respect of which the licence is issued is carried on, to inspect the premises and to take samples of repacked drugs;

[318][(f) the licensee shall, either in his own laboratory or, in any other laboratory approved by the licensing authority, test each batch or lot of raw material used by him for repacking and also each batch of the product thus repacked and shall maintain records or registers showing the particulars in respect of such tests as specified in Schedule U. The records or register shall be retained for a period of five years from the date of repacking. The licensee shall allow the Inspector to inspect all registers and records maintained under these rules and shall supply to the Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and these rules have been observed;]

[319][(g) the licensee shall maintain an Inspection Book, in Form 35, to enable an Inspector to record his impressions and the defects noticed;]

[320][(h) the licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing an expiry date on the label, the reference samples shall be maintained for a period of three months beyond the date of expiry of potency. In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture.]

[321][(i) No advertisement of the drugs specified in Schedule H, Schedule HI or Schedule X shall be made except with the previous sanction of the Central Government.]

[322]**[74B. Conditions of licence in Form 25A.**—(1) The licence in Form 25A shall be deemed to be cancelled or suspended, if the licence owned by the licensee in Form 25 whose manufacturing facilities have been availed of by the licensee is cancelled or suspended as the case may be, under these rules.

(2) The licensee shall comply with the provisions of the Act and of these rules and with such further requirements if any, as may be specified in any rules subsequently made under Chapter IV of the Act; provided that where such further requirements are specified in the rules, these would come into force four months after publication in the Official Gazette.

(3) The licensee shall test each batch or lot of the raw material used by him for the manufacture of his products and also each batch of the final product and shall maintain records or registers showing the particulars in respect of such tests as specified in Schedule U. The records or registers shall be retained for a period of five years from the date of manufacture. The licensee shall allow an Inspector to inspect all registers and records maintained under these rules and shall supply to the Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and these rules have been observed.

(4) The licensee shall either—

(i) provide and maintain to the satisfaction of the licensing authority adequate staff and adequate laboratory facilities for carrying out tests of strength, quality and purity of the substances manufactured by him; or

(ii) make arrangements with some institution approved by the licensing authority [323][under Part XV(A) of these rules] for such tests to be regularly carried out on his behalf by the institution.]

[324][(5) The licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing an expiry date on the label the reference samples shall be maintained for a period of three months beyond the date of expiry of potency. In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture.]

[325][(6) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and the defects noticed.]

[326][(7) No advertisement of the drugs specified in Schedule H, Schedule HI or Schedule X shall be made except with the previous sanction of the Central Government.]

[327][(8) the applicant shall submit the result of bioequivalence study referred to in Schedule Y, along with the application for grant of a licence of oral dosage

form of drugs specified under category II and category IV of the biopharmaceutical classification system.]

[328]**[75.Forms of application for licence to manufacture for sale or distribution of** drugs **specified in Schedules C and C (1)** [329]**[excluding those specified in Part XB and Schedule X].**—(1) Applications for the grant [330][***] of licence to manufacture for sale or distribution of drugs specified in Schedules C and C(1) [329][excluding those specified in Part XB and Schedule X], shall be made to the licensing authority in Form 27, and [331][shall be made upto ten items for each category of drugs [332][referred to in Schedule M relating to pharmaceuticals products and Schedule M-III relating to medical devices and *in-vitro* diagnostics] and shall be accompanied by a licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred for every inspection.

[333][***]

[334][***]

(2) Application for grant [330][***] of licence to manufacture for sale or distribution of drugs specified in Schedules C, C(1) and X shall be made to the licensing authority in Form 27B, and [331][shall be made upto ten items for each category of drugs [332][referred to in Schedule M relating to pharmaceuticals products and Schedule M-III relating to medical devices and *in-vitro* diagnostics] and shall be accompanied by a licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred for every inspection

[333][***]

Provided that the applicant shall possess a licence in Form 28 to manufacture such drugs:

[334][***]

[335][(3) The application for grant [330][***] of licenses to manufacture for sale or for distribution of drugs in [336][Large Volume Parenterals, Sera and Vaccine and Recombinant DNA (r-DNA) derived drugs,] shall be made to the licensing authority appointed under this Part in Form 27D and [337][shall be made upto ten

items for each category of drugs categorised in Schedule M and shall be accompanied by a licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred for every inspection [338][***]]:

[339][***]

[1338][(3A) The application referred to in sub-rule (3) of rule 75 of these rules, and the application for grant of permission to manufacture new drug for sale or distribution under rule 80 of the New Drugs and Clinical Trials Rules, 2019 or rule 122B of these rules, as the case may be, shall be made simultaneously.]

[340][(4) A fee of rupees one thousand shall be paid for duplicate copy of the licence issued under sub-rule (1), sub-rule (2) or sub rule (3), as the case may be, if the original licence is detected, damaged or lost.

(5) If the licensee applies for manufacture of more than ten items of each category of drugs, the application shall be accompanied by an additional fee at the rate of rupees three hundred for each additional item of drugs [341][referred to in Schedule M relating to pharmaceuticals products and Schedule M-III relating to medical devices and *in-vitro* diagnostics].]

[342][(6) Where an application under this rule is for the manufacture of drug formulations falling under the purview of new drug under rule 80 of the New Drugs and Clinical Trials Rules, 2019 or rule 122B, the licence to manufacture for sale or distribution of the drugs shall be granted after approval of the drug as new drug.]

[343]**[75A. Loan licences.**—(1) Applications for the grant [344][***] of loan [345][licences for the manufacture for sale or for distribution] of drugs specified in Schedules Cand C(l) [346][excluding those specified in Part XB and Schedule X] shall be made in Form 27 A to the licensing authority and [337][shall be made upto ten items foreach category of drugs [341][referred to in Schedule M relating to pharmaceuticals products and Schedule M-III relating to medical devices and *in-vitro* diagnostics]and shall be accompanied by a licence fee of rupees six thousand and aninspection fee of rupees one thousand and five hundred for every inspection

[338][***].

[347][***].

[348]*[Explanation*.—For the purpose of this rule a loan licence means a licence which a licensing authority may issue to an applicant who intends to avail the manufacturing facilities owned by a licensee in Form 28.]

[349][(1A) The application for grant [350][***] of loan licence to manufacture for sale or distribution of drugs in 'Large Volume Parenterals', 'Sera and Vaccine' and 'Recombinant DNA (r-DNA) derived drugs' shall be made to the licensing authority appointed under this Part, in Form 27DA and be made upto ten items for each category of drugs categorized in Schedule M and accompanied by a licence fee of six thousand rupees and an inspection fee of one thousand five hundred rupees for every inspection [351][***]:

[352][***].

(2) The licensing authority, shall, before the grant of a loan licence, satisfy himself that the manufacturing unit has adequate equipment, staff, capacity for manufacture and facilities for testing, to undertake the manufacture on behalf of the applicant for a loan licence.

[353][***].

[354][(3) Subject to the provisions of sub rule (2), the application for manufacture of more than ten items of each category of drugs on a loan licence, shall be accompanied by an additional fee at the rate of rupees three hundred for each additional item of drugs.

(4) If the licensing authority is satisfied that a loan licence is defaced, damaged or lost, he may, on payment of a fee of rupees one thousand, issue a duplicate copy of loan licence.]

75B.[355][***].

[356]**[76. Form of licences to manufacture drugs specified in Schedules C and C(l), excluding those specified in [357][Part XB and] Schedule X, or drugs specified in Schedules C, C(l) and X and the conditions for the grant [358][***] of such licences.**- [359][A licence to manufacture for sale or for distribution of drugs specified in Schedules C and C(l) other than [360][Large Volume Parenterals, Sera and Vaccines and Recombinant DNA (r-DNA)

derived drugs,], drugs specified in Part XB and Schedule X shall be issued in Form 28 and a licence to manufacture for sale or distribution of drugs specified under Schedule C and C(l) (other than [360][Large Volume Parenterals, Sera and Vaccines and Recombinant DNA (r-DNA) derived drugs,], drugs specified in Part XB) and Schedule X shall be issued in Form 28B. A licence to manufacture for sale or for distribution of [360][Large Volume Parenterals, Sera and Vaccine and Recombinant DNA (r-DNA) derived drugs] shall be issued in Form 28D. Before a licence in Form 28 or Form 28B or Form 28D is granted [361][***], the following conditions shall be complied with by the applicant:—]]

(1) The manufacture will be conducted under the active direction and personal supervision of competent technical staff consisting at least of one person who is a whole-time employee and who is—

(a) a graduate in Pharmacy or Pharmaceutical Chemistry of [362][a University established in India by law or has an equivalent qualification recognised and notified by the Central Government for such purpose] and has had at least eighteen months' practical experience after the graduation in the manufacture of drugs to which this licence applies, this period of experience may, however, be reduced by six months if the person has undergone training in manufacture of drugs to which the licence applies for a period of six months during his University course; or

(b) a graduate in Science of [362][a University established in India by law or has an equivalent qualification recognised and notified by theCentral Government for such purpose] who for the purpose of his degree has studied Chemistry [363][or Microbiology] as a principal subject and has had at least three years' practical experience in the manufacture of drugs to which this licence applies after his graduation; or

(c) a graduate in Medicine of [364][a University established in India by law or has an equivalent qualification recognised and notified by the Central Government for such purpose] with at least three years' experience in the manufacture and pharmacological testing of biological products after his graduation; or

[365][(d) a graduate in Chemical Engineering of a University recognised by the Central Government with at least three years' practical

experience in the manufacture of drugs to which this licence applies after his graduation; or

(e) holding any foreign qualification the quality and content of training of which are comparable with those prescribed in clause (a), clause (b), clause (c) or clause (d) and is permitted to work as competent technical staff under this rule by the Central Government:]

Provided that any person who was approved by the licensing authority as an expert responsible for the manufacture of drugs for the purpose of rule 76 read with rule 78 as these rules were in force immediately before the 29th June, 1957, shall be deemed to be qualified for the purposes of this rule:

[366][Provided further that for the drugs specified in Schedules C and C (1) meant for veterinary use, the whole time employee under whose supervision the manufacture is conducted may be a graduate in Veterinary Science or General Science or Medicine or Pharmacy of a University recognised by the Central Government and who has had at least three years' experience in the manufacture of biological products:]

[367][Provided also that for medical devices, the whole time employee under whose supervision the manufacture or testing is conducted shall be—

(i) a graduate in Pharmacy or Engineering (in appropriate branch) from a University recognised by the CentralGovernment for such purposes and has had at least eighteen months practical experience in the manufacturing or testing of devices to which this licence applies after his graduation; or

(ii) a graduate in science, from a University recognised by the Central Government for such purposes, with Physics or Chemistry or Microbiology as one of the subject and has had at least three years practical experience in the manufacturing or testing of devices to which this licence applies after his graduation; or

(iii) a diploma in Pharmacy or Engineering (in appropriate branch) from a Board or Institute recognised by the Central Government or the

State Government, as the case may be, for such purposes and has had at least four years practical experience in the manufacturing or testing of devices towhich this licence applies after his diploma; or

(iv) having a foreign qualification, the quality and content of training of which are comparable with those specified in clause (i), clause (ii) and clause (iii) and is permitted to work as competent technical staff under this rule by the Central Government.]

[368][(2) The applicant proposing to manufacture pharmaceutical products shall comply with the provisions referred to in Schedule M.]

[368][(2A) The applicant proposing to manufacture medical devices and *in-vitro* diagnostics shall comply with the quality management system as referred to in Schedule M-III.]

[368][(3) The applicant shall provide adequate space, plant and equipment for pharmaceutical products as referred to in Schedule M and for Medical devices and *in-vitro* diagnostics as referred to in Schedule M-III.]

[369][(4) The applicant shall provide and maintain adequate staff, premises and laboratory equipment for carrying out such tests of the strength, quality and purity of the substances as may be required to be carried out by him under the provisions of Part X of these rules including proper housing for animals used for the purposes of such tests, the testing unit being separate from the manufacturing unit and the head of the testing unit being independent of the head of the manufacturing unit:]

Provided that the manufacturing units which before the commencement of the Drugs and Cosmetics (Amendment) Rules, 1977,[370] were making arrangements with institutions approved by the licensing authority for such tests to be carried out on their behalf may continue such arrangement up to the 30th June, 1977:

Provided further that for tests requiring sophisticated instrumentation techniques or biological or microbiological methods other than sterility the licensing authority may permit such tests to be conducted by institutions approved by it [371][under Part XV (A) of these rules] for this purpose.]

[372][(4A) The head of the testing unit referred to in condition (4) shall possess a degree in Medicine or Science or Pharmacy or Pharmaceutical Chemistry of a University recognised for this purpose and shall have experience in the testing of drugs, which in the opinion of the licensing authority is considered adequate.]

(5) The applicant shall make adequate arrangements for the storage of drugs manufactured by him.

[373][(6) The applicant shall furnish to the licensing authority, if required to do so, data on the stability of drugs which are likely to deteriorate for fixing the date of expiry which shall be printed on the labels of such drugs on the basis of the date so furnished.]

[374][(7) The applicant shall, while applying for a licence to manufacture [375][drugs], furnish to the licensing authority evidence and data justifying that the [375][drugs]—

(i) contain the constituent ingredients in therapeutic/prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful;

(ii) are safe for use in the context of the vehicles, excipients, additives and pharmaceutical aids used in formulations, and under the conditions in which the formulations for administration and use are commended;

(iii) are stable under the conditions of storage recommended; and

(iv) contain such ingredients and in such quantities for which there is therapeutic justification.]

[376][(v) have the approval, in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drug as defined in rule 122E, from the licensing authority as defined in clause (b) of rule 21.]

[377][(8) The licensee of pharmaceutical products shall comply with therequirements of [1191]["Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products"] as laid down in Schedule M and the licensee of Medical Devices and *in-vitro* diagnostics shall

comply with the requirements of "Quality Management System" as laid down in Schedule M-III.]

[378][(9) The applicant shall make application for grant of licence for a drug formulation containing single active ingredient only in proper name.]

[379]*[Explanation*.—For the purpose of this rule, [380]["Large Volume Parenterals" sera and Vaccines and Recombinant DNA (r-DNA) derived drugs;] shall mean the sterile solutions intended for parenteral administration with a volume of 100 ml. or more (and shall include anti-coagulant solutions) in one container of the finished dosage form intended for single use.]

[381][(10) the applicant shall submit the result of bioequivalence study referred to in Schedule Y, along with the application for grant of a licence of oral dosage form of drugs specified under category II and category IV of the biopharmaceutical classification system.]

[382][(11) In case the applicant intends to market the drug under a brand name or trade name, the applicant shall furnish an undertaking in Form 51 to the licensing authority to the effect that to the best of his knowledge based on search in trade marks registry, central data base for brand name or trade name of drugs maintained by Central Drugs Standard Control Organisation, literature and reference books on details of drug formulations in India, and internet, such or similar brand name or trade name is not already in existence with respect to any drug in the country and the proposed brand name or trade name shall not lead to any confusion or deception in the market.]

[383]**[76A, Forms of loan licences to manufacture for sale or for distribution drug specified in Schedules C and Cl excluding drugs specified in Schedule X or of Large Volume Parenterals, Sera and Vaccine and recombinant DNA(r-DNA) derived drugs, and conditions for the grant** [384][***] **of such licences.**—A loan to licence to manufacture for sale or for distribution of drugs specified in Schedules C and C(l), excluding drugs specified in Schedule X, and large Volume Parenterals, Sera and Vaccine and Recombinant DNA (r-DNA) derived drug specified in Part XB shall be issued in Form 28A and a loan licence to manufacture for sale or for distribution of Large Volume Parenterals, Sera and Vaccine and Recombinant DNA (r-DNA) derived drugs shall be issued in Form 28DA, and the] applicant shall, while applying for a licence to

manufacture [385][drugs] furnish to the Licensing Authority evidence and data justifying that the [385][drugs]—

(i) contain the constituent ingredients in therapeutic/prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful;

(ii) are safe for use in the context of the vehicles, excipients, additives and pharmaceutical aids used in the formulations and under the conditions in which the formulations for administration and use are recommended;

(iii) are stable under the conditions of storage recommended; and

(iv) contain such ingredients and in such quantities for which there is therapeutic justification.]

[386][(v) in case the applicant intends to market the drug under a brand name or trade name, the applicant shall furnish an undertaking inForm 51 to the licensing authority to the effect that to the best ofhis knowledge based on search in trade marks registry, central data base for brand name or trade name of drugs maintained by Central Drugs Standard Control Organisation, literature and reference books on details of drug formulations in India, and internet, such or similar brand name or trade name is not already in existence with respect to any drug in the country and the proposed brand name or trade name shall not lead to any confusion or deception in the market:]

[387][Provided that the application for grant of a licence for a drug formulation containing single active ingredient shall be made only in proper name.]

[388]**[77.Duration of licence.**—(1) A licence issued in Form 28, Form 28B and Form 28D shall remain valid, if the licencee deposits a licence retention fee referred to in sub-rule (2) before the expiry of period of every succeeding five years from the date of its issue, unless it is suspended or cancelled by the licensing authority.

(2) The licence retention fee referred to in sub-rule (1) shall be equivalentto the respective fee required for the grant of such licence excluding inspection fee paid for grant of licence.

(3) If the licencee fails to pay licence retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay licence retention fee along with a late fee calculated at the rate of two per cent, of the licence fee for every month or part thereof up to six months, and in the event of non-payment of such fee, the licence shall be deemed to have been cancelled.]

[389][**78. Conditions of licence.**—A licence in [390][Form 28, Form 28B or Form 28D] shall be subject to the special conditions, if any, set out in Schedule F or Schedule F(l), as the case may be, which relate to the substance in the respect of which the licence is granted and to the following general conditions:—

(a) (i) The licensee shall provide and maintain an adequate staff and adequate premises and plant for the proper manufacture and storage of the substances in respect of which the licence is issued;

(ii) without prejudice to the generality of the foregoing requirement, every holder of a licence who for any purpose engaged in the culture or manipulation of pathogenic spore-bearing micro-organisms shall be provided to the satisfaction of the Licensing Authority separate laboratories and utensils and apparatus required for the culture or manipulation of such micro-organisms, the laboratories, utensils and apparatus so provided not being used for the manufacture of any other substance;

[391][(b) The licensee shall provide and maintain staff, premises and equipment as specified in rule 76;]

[392][(c) (i) The licensee shall maintain records of manufacture as per particulars given in Schedule U.

(ii) The licensee shall either in his own laboratory or in any laboratory approved by the licensing authority [393][under Part XV (A) to these rules] test each batch or lot of the raw material used by him for the manufacture of his product and also each batch of the final product and shall maintain records or registers showing the particulars in respect of such tests as specified in

Schedule U. The records or registers shall be retained in the case of a substance for which a potency date if fixed for a period of two years from the expiry of such date, and in the case of other substances for a period of five years from the date of manufacture;]

(d) The licensee shall allow an [394][Inspector appointed under the Act], to enter, with or without prior notice, any premises where the manufacture is carried on and to inspect the premises, and in the case of substances specified in Schedules C and C (1), to inspect the plant and the process of manufacture and the means employed for standardizing and testing the substance;]

(e) The licensee shall allow an [394][Inspector, appointed under the Act], to inspect all registers and records maintained under these rules and to take samples of the manufactured product and shall supply to such Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and rules thereunder have been observed;]

(f) The licensee shall from time to time report to the licensing authority any changes in the expert staff responsible for the manufacture or testing of the substance and any material alterations in the premises or plant used for that purpose which have been made since the date of the last inspection made on behalf of the licensing authority before the issue of the licence;

[395][(g) The licensee shall on request furnish to the licensing authority, controlling authority or to such authorities as the licensing authority or the controlling authority may direct, from every batch of drugs as the licensing authority or the controlling Authority may from time to time specify, a sample of such quantity as may be considered adequate by such authority for any examination and, if so required, also furnish full protocols of the tests which have been applied.]

[396][(h) If the licensing authority or the controlling authority so directs, the licensee shall not sell or offer for sale any batch in respect of which a sample is, or protocols are furnished under the last preceding sub-paragraph until a certificate authorizing the sale of the batch has been issued to him by or on behalf of the licensing authority or the controlling authority;]

[397][(i) The licensee shall on being informed by the licensing authority or the controlling authority that any part of any batch of the substance has been found

by the licensing authority or the controlling authority not to conform with the standard of strength, quality or purity specified in these rules and on being directed so to do, withdraw the remainder of that batch from sale and so far as may in the particular circumstances of the case be practicable recall all issues already made from that batch;]

(j) No drug manufactured under the licence shall be sold unless the precautions necessary for preserving its properties have been observed throughout the period after manufacture;

[398][(k) The licensee shall comply with the provisions of the Act and of these rules and with such further requirements, if any, as may be specified in any rules subsequently made under Chapter IV of the Act, provided that where such further requirements are specified in the rules, these would come into force four months after publication in the Official Gazette;]

[398][(l) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and defects noticed;]

[399][(m) The licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing and expiry date on the label the reference samples shall be maintained for a period of three months beyond the date of expiry of potency. In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture;]

[400][(n) The licence, who has been granted a licence in Form 28B shall—

(i) forward to the licensing authority of the concerned States of manufacture and supply of drug a statement of the sales effected to the manufacturers, wholesalers, retailers, hospitals, dispensaries, Nursing Homes and Registered Medical Practitioners every three months;

(ii) maintain accounts of all transactions giving details as indicated below in a register bound and serially page numbered, and such records shall be retained for a period of five years or one year after the date of expiry of potency, whichever is later.

A. Accounts of the drugs specified in Schedule X used for themanufacture—

1. Date of issue.
2. Name of the drug.
3. Opening balance of stock on the production day.
4. Quantity received, if any, and source from where received.
5. Quantity used in manufacture.
6. Balance quantity on hand at the end of the production day.
7. Signature of the person in charge.

B. Accounts of Production—

1. Date of manufacture.
2. Name of the drug.
3. Batch number.
4. Quantity of raw material used in manufacture.
5. Anticipated yield.
6. Actual yield.
7. Wastage.
8. Quantity of the manufactured goods transferred to stock.

C. Accounts of manufactured drugs—

1. Date of manufacture.
2. Name of the drug.
3. Batch Number.
4. Opening Balance.
5. Quantity manufactured.
6. Quantity sold.
7. Name of purchaser and his address.
8. Balance quantity at the end of the day;

(o) The licensee shall store drugs specified in Schedule X in bulk form and when any such drug is required for manufacture it shall be kept in a separate place under direct custody of a responsible person;]

[401][(p) The licensee shall comply with the requirements of [402]["Good Laboratory Practices" as laid down in Schedule L-I and] [1191]["Good Manufacturing

Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products"] as laid down in Schedule M.]

[403][(q) No advertisement of the drugs specified in Schedule H, Schedule HIor Schedule X shall be made except with the previous sanction ofthe Central Government.]

[404][(r) the applicant shall submit the result of bioequivalence study referred to in Schedule Y, along with the application for grant of a licence of oral dosage form of drugs specified under category II and categoryIV of the biopharmaceutical classification system.]

[405]**[78A.Conditions of licence in [405][Form 28A or Form 28DA].—**(1) The licence in [406][Form 28A or Form 28DA] shall be deemed to be cancelled or suspended, if the licence owned by the licensee in [407][[408][Form 28 or Form 28D] whose manufacturing facilities have been availed of by the licensee is cancelled or suspended, as the case may be, under these rules.

(2) The licensee shall comply with the provisions of the Act, and of these rules and with such further requirements if any, as may be specified in any rules subsequently made under Chapter IV of the Act, provided that where such further requirements are specified in the rules, those would come into force four months after publication in the Official Gazette.

(3) The licensee shall test each batch or lot of the raw material used by him for the manufacture of his products and also each batch of the final product and shall maintain records or registers showing the particulars in respect of such tests as specified in Schedule U. Records or registers shall be retained, in the case of a substance for which a potency date is fixed, for a period of two years from the expiry of such date and in the case of other substances, for a period of five years from the date of manufacture. The licensee shall allow an Inspector to inspect all registers and records maintained under these rules and shall supply to the Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and these rules have been observed.

(4) The licensee shall either (i) provide and maintain to the satisfaction of the licensing authority adequate staff and adequate laboratory facilities for carrying out tests of the strength, quality and purity of the substances manufactured by him. or (ii) make arrangements with some institution approved

by the licensing authority for such tests to be regularly carried out on his behalf by the institution.]

[409][(5) The licensee shall furnish to the licensing authority, if required to do so, data on the stability of drugs which are likely to deteriorate for fixing the date of expiry which would be printed on the labels of such drugs on the basis of the date so furnished.]

[410][(6) The licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing an expiry date on the labels, the reference samples shall be maintained for a period of three months beyond the date of expiry of potency.] In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture.]

[411][(7) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and the defects noticed.]

[412][(8) No advertisement of the drugs specified in Schedule H, Schedule HI or Schedule X shall be made except with the previous sanction of the Central Government.]

[413][(9) the applicant shall submit the result of bioequivalence study referred to in Schedule Y, along with the application for grant of a licence of oral dosage form of drugs specified under category II and category TV of the biopharmaceutical classification system.]

[414]**[79.Inspection before grant** [415]**[***l of licence.**—Before a licence under this part is granted [416][***] the licensing authority or Central Licence Approving Authority, as the case may be, shall cause the establishment in which the manufacture is proposed to be conducted or being conducted to be inspected by one or more Inspectors appointed under the Act with or without an expert in the field concerned. The Inspector or Inspectors shall examine all portions of the premises, plant and appliances and also inspect the process of manufacture intended to be employed or being employed along with the means to be employed or being employed for standardising and testing the drugs to be manufactured or being manufactured and enquire into the professional

qualifications of the Technical Staff to be employed. He shall also examine and verify the statements made in the application in regard to their correctness, and the capability of the applicant to comply with the requirements of competent technical staff, manufacturing plants, testing equipments and the 'Requirements of Good Manufacturing Practices' and the 'Requirements of Plant and Equipment' as laid down in Schedule M read with the Requirements of Maintenance of records as laid down in Schedule U.]

[414]**[80.Report by Inspector.**—(1) The Inspector shall forward a detailed descriptive report giving his findings on each aspect of inspection along with his recommendations after completion of his inspection in accordance with the provisions of rule 79, to the licensing authority or Central Licence Approving Authority, as the case may be.]

81. Procedure of licensing authority.—(1) If the licensing authority [417][or Central Licence Approving Authority as the case may be] after such further enquiry, if any, as he may consider necessary, is satisfied that the requirements of the Rules under the Act have been complied with and that the conditions of the licence and the rules under the Act will be observed, he shall issue a licence [418][under this Part].

(2) If the licensing authority [417][or Central Licence Approving Authority as the case may be,] is not so satisfied, he shall reject the application and shall inform the applicant of the reasons for such rejection and of the conditions which must be satisfied before a licence can be granted and shall supply the applicant with a copy of the inspection report.

[419]**[82.Further application after rejection.**—If within a period of six months from the rejection of an application for a licence the applicant informs the licensing authority [417][or Central Licence Approving Authority, as the case may be,] that the conditions laid down have been satisfied and deposits an inspection [420][fee of rupees two hundred and fifty] the licensing authority [421][or Central Licence Approving Authority, as the case may be,] may, if after causing a further inspection to be made, he is satisfied that the conditions for the grant of a licence have been complied with, [421][in respect of drugs notified under rule 68A] issue a licence in Form 28 [422][or Form 28B].

[423]**[83.Duration of loan licence.**—(1) A loan licence issued in Form 28A and Form 28DA shall remain valid, if the licencee deposits a licence retention

fee referred to in sub-rule (2) before the expiry of period of every succeeding five years from the date of its issue, unless it is suspended or cancelled by the licensing authority.

(2) The licence retention fee referred to in sub-rule (1) shall be equivalent to the respective fee required for the grant of such licence excluding inspection fee paid for grant of licence.

(3) If the licencee fails to pay licence retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay licence retention fee along with a late fee calculated at the rate of two per cent, of the licence fee for every month or part thereof up to six months, and in the event of non-payment of such fee, the licence shall be deemed to have been cancelled.]

83A. [424]**[***]**

83AA. [425]**[***]**

84. The provisions of this part shall apply to the manufacture of drugs for sale notwithstanding that such drugs are manufactured for sale outside India.

[426]**[**[427]**[84A. Provisions for appeal to the State Government or Central Government by party whose licence has not been granted** [428]**[***]**—Any person who is aggrieved by the order passed by the licensing authority or the CentralLicence Approving Authority, as the case may be, refusing to grant [429][***] a licence [430][under this Part], may within thirty days from the date of receipt of such order, appeal to the State Government or Central Government, as the case may be, and the State Government or the Central Government may, after such enquiry into the matter, as is considered necessary and after giving the said person an opportunity for representing his views, may pass such order in relation thereto as it thinks fit.]]

[431]**[84AA. Additional information to be furnished by an applicant for** licence **or a licensee to the licensing authority.**—The applicant for the grant of a licence or any person granted a licence under this Part shall, on demand, furnish to the licensing authority, before the grant of the licence or during the period the licence is in force, as the case may be, documentary evidence in respect of the ownership or occupation on rental or other basis of the premises, specified in the application for licence or in the licence granted, constitution of

the firm or any other relevant matter which may be required for the purpose of verifying the correctness of the statements made by the applicant or the licensee, while applying for or after obtaining the licence, as the case may be.]

[432]**[84AB. Information to be uploaded by the licensee on online portal SUGAM.—**(1) The licensee granted license under this Part shall register with portal SUGAM (www.cdscoonline.gov.in) and upload information, as per the format provided in the said portal, pertaining to the licences granted for manufacture for sale or distribution of drugs and the information so provided shall be updated from time to time.

(2) The information uploaded by the licensee with SUGAM portal under sub-rule (1), shall be verified by the concerned Licensing Authority.]

[433]**[84B. Prohibition for the manufacture for sale of cyclamates and preparations containing cyclamates.**—No persons shall manufacture for sale cyclamates and preparations containing cyclamates.]

[434]**[84C.Inspection for verification of compliance.**—(1) Before a licence in Form 28 or Form 28A or Form 28B or Form 28D or Form 28DA, is granted the licensing authority or Central Licence Approving Authority, as the case may be, shall cause the establishment in which the manufacture of drugs is proposed to be conducted or being conducted to be inspected jointly by the Drugs Inspectors appointed by the Central Government and the State Government under this Act, who shall examine the establishment intended to be used or being used for the manufacture of drugs.

(2) The premises licensed under sub-rule (1) shall be inspected jointly by Inspector appointed by the Central Government and State Government to verify the compliance, with the conditions of licence and the provisions of the Act and these rules, not less than once in three years or as needed as per risk based approach.]

[435]**[84D. Agreement for marketing.**—No marketer shall adopt any drug manufactured by another manufacturer for marketing of such drug by labeling or affixing his name on the label of the drug with a view for its sale and distribution without an agreement as referred to in clause (ea) of rule 2.]

[436][84E. **Responsibility of marketer of the drugs.**—Any marketer who sells or distributes any drug shall be responsible for quality of that drug as well as other regulatory compliances along with the manufacturer under these rules.]

[437][85. **Cancellation and suspension of licences.**—(1) The Central Licence Approving Authority may, after giving the licensee an opportunity to showcause, why such an order should not be passed by an order in writing stating the reasons therefor, cancel a licence issued under this Part, or suspend it for such period as he thinks fit either wholly or in respect of any of the drugs to which it relates [438][or direct the licensee to stop manufacture, sale or distribution of the said drugs and [439][thereupon order the destruction of drugs and] the stock thereof in the presence of an inspector], if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act or rules made thereunder.

(2) The licensing authority may, for such licences granted [440][***] by him, after giving the licensee an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, cancel a licence issued under this part or suspend it for such period as he thinks fit either wholly or in respect of any of the drugs to which it relates [438][or direct the licensee to stop manufacture, sale or distribution of the said drugs and [439][thereupon order the destruction of drugs and] the stocks thereof in the presence of an Inspector], if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act or rules made thereunder.]

[441][(3) A licensee whose licence has been suspended or cancelled by the Central Licence Approving Authority or licensing authority under sub-rule (1) or sub-rule (2), as the case may be, may within ninety days of the receipt of a copy of the order by him prefer an appeal to the Central Government or the State Government, as the case may be, and the Central Government or the State Government may after giving the licensee an opportunity of being heard, confirm, reverse or modify such order.]

[442][PART VIIA
[443][MANUFACTURE FOR SALE OR FOR DISTRIBUTION] OF HOMOEOPATHIC MEDICINES

85A. Manufacture on more than one set of premises.—If Homoeopathic medicines are manufactured in more than one set of premises a separate application shall be made and a separate licence shall be obtained in respect of each such set of premises.

85B. Application for licence to manufacture Homoeopathic medicines.—

(1) Application for grant or renewal of [445][licences to manufacture for sale or for distribution] of Homoeopathic medicines shall be made to the licensing authority appointed by the State Government for the purpose of this Part (hereinafter in this Part referred to as the licensing authority) and shall be made in Form 24C.

[444][(2) The application in Form 24C shall be accompanied—

(a) by a fee of [445][rupees two hundred] for the manufacture of Homoeopathic mother tinctures and potentised preparations and aninspection fee of [446][rupees one hundred] for the first inspection or [447][rupees fifty] in case of inspection for renewal of licence;

(b) by a fee of [448][rupees two hundred] for the manufacture of Homoeopathic potentised preparations only, and an inspection fee of [446][rupees one hundred] for the first inspection and [449][rupees fifty] in case of inspection for renewal of licence;

(c) by a fee of [450][rupees two hundred] for the manufacture of potentised preparations from back potencies by pharmacies which are already licensed to sell Homoeopathic medicines by retail and an inspection fee of [446][rupees one hundred] for the first inspection or [449][rupees fifty] in case of inspection for renewal of licence.

(3) If a person applied for renewal of a licence after its expiry but within six months of such expiry, the fee payable for the renewal of such a licence shall be—

(a) [450][rupees two hundred] plus an additional fee at the rate of [450][rupees one hundred] per month or part thereof and an inspection fee of [449][rupees fifty] for the manufacture of Homoeopathic mother tinctures and potentised preparations;

[451][(b) [452][rupees two hundred] plus an additional fee at the rate of [452][rupees one hundred] per month or part thereof and an inspection fee of [449][rupees fifty] for the manufacture of Homoeopathic potentised preparations only;]

(c) [452][rupees two hundred] plus an additional fee at the rate of [452][rupees one hundred] per month or part thereof and an inspection fee of [449][rupees fifty] for the manufacture of potentised preparations from back potencies by pharmacies who are already licensed to sell Homoeopathic medicines by retail.]

(4) A fee of [449][rupees fifty] shall be paid for a duplicate copy of the licence for the manufacture of Homoeopathic mother tincture and potentised preparations issued under sub-rule (1) if the original is defaced, damaged or lost; while the fee to be paid for such a duplicate copy of the licence for the manufacture of Homoeopathic potentised preparations only shall be [449][rupees fifty].

[453][(5) Applications by licensee to manufacture additional items of Homoeopathic medicines shall be made to the licensing authority and such applications shall be accompanied by a fee of [449][rupees fifty] for each additional item.]

85C. Application to manufacture 'New Homoeopathic medicines'.— Subject to the other provisions of these Rules,—

(1) No 'New Homoeopathic medicine' shall be manufactured unless it is previously approved by the licensing authority mentioned in Rule 21;

(2) the manufacture of 'New Homoeopathic medicine', when applying to the licensing authority mentioned in sub-rule (1) shall produce such documents and other evidence as may be required by the licensing authority for assessing the therapeutic efficacy of the medicine including the minimum provings carried out with it;

(3) while applying for a licence to manufacture a 'New Homoeopathic medicine' an applicant shall produce alongwith his application evidence that the 'New Homoeopathic medicine' for the manufacture of which application is made has already been approved.

Explanation.—The term 'New Homoeopathic medicine' in this rule shall have the same meaning as in rule 30AA.

[454][**85D. Form of licence to manufacture Homoeopathic medicines.**—Licence for manufacturer of Homoeopathic medicines is a license to manufacture potentised preparations from back potencies by Pharmacies who are already licensed to sell Homoeopathic medicines by retail shall be granted in Form 25C.]

85E. Conditions for the grant or renewal of a licence in Form 25C.—Before a licence in Form 25C is granted or renewed the following conditions shall be complied with by the applicant:—

(1) The manufacture of Homoeopathic medicines shall be conducted under the direction and supervision of competent technical staff consisting at least of one person who is a whole time employee [455][and who is—

(a) a graduate in Science with Chemistry as one of the subjects with three years' experience in manufacture of Homoeopathic medicines; or

(b) a graduate in Pharmacy with 18 months of experience in the manufacture of Homoeopathic medicines; or

(c) holds qualification as defined under sub-clause (g) of clause (1) of section 2 of the Homoeopathy Central Council Act, 1973 (59 of 1973) with 18 months of experience in the manufacture of Homoeopathic medicines:

Provided that the persons who are already in employment with five years' experience in the manufacture < f Homoeopathic medicines and whose name was accordingly entered in any licence granted in Form 25C for manufacture of different classes of Homoeopathic medicines included in them shall be deemed to be qualified for the purpose of this rule.]

[456][(2) The factory premises shall comply with the requirements and conditions specified in Schedule M1:

Provided that where the licensing authority considers it necessary or expedient so to do, it may be having regard to the nature and extent of

manufacturing operations, relax or suitably alter the said requirements or conditions in any particular case for reasons to be recorded in writing.]

[457][(2A) Certificate of Good Manufacturing Practice.- The certificate of Good Manufacturing Practice to manufacturers, who comply with the requirements of Good Manufacturing Practices of Homeopathy drugs, as specified in Schedule M-I, shall be issued up to the date of validity of licence]

(3) The applicant for manufacture of Homoeopathic mother tinctures shall either (i) provide and maintain adequate staff, premises and laboratory equipment for identifying the raw materials and for testing the mother tinctures wherever possible, or (ii) make arrangements with some institution approved by the licensing authority [458][under Part XV (A) of these rules] for some tests, wherever possible, to be regularly carried out on his behalf by that institution.

(4) The premises where Homoeopathic medicines are manufactured shall be distinct and separate from the premises used for residential purposes.

(5) Homoeopathic medicines shall not be manufactured simultaneously with drugs pertaining to other systems of medicine.

(6)The applicant shall make arrangements for proper storage of Homoeopathic medicines manufactured by him:

[459][Provided that in case potentised preparations are made in a Pharmacy holding licence in Form 20C, the conditions (2) and (3) shall not apply. The licensee shall ensure to the satisfaction of the licensing authority that the products manufactured by it, conform to the claims made on the label.]

[460]**[85EA.Inspection before grant or renewal of licence.**—Before a licence under this Part is granted or renewed in Form 25C or Form 26C, the licensing authority shall cause the establishment, in which the manufacture is proposed, to be conducted or being conducted, to be inspected by one or more Inspectors appointed under the Act. The inspector or Inspectors shall examine all portions of the premises, plant and appliances and also inspect the process of manufacture intended to be employed or being employed alongwith the means to be employed or being employed for standardising and testing the substances

to be manufactured and inquire into the professional qualifications of the technical staff to be employed. He shall also examine and verify the statements made in the application in regard to their correctness, and the capability of the applicant to comply with the requirements of competent technical staff, manufacturing plants, testing equipments and the requirements of plant and equipment as laid down in Schedule MI read with the requirements of maintenance of records as laid down in Schedule U.]

[461][**85EB.Report by Inspector.**—The Inspector of Inspectors shall forward a detailed descriptive report giving his or their findings on each aspect of inspection alongwith his or their recommendations after completion of his or their inspection to the licensing authority.]

[462][**85EC.Grant or refusal of licence.**—(1) If the licensing authority after such further enquiry, if any, as he may consider necessary is satisfied that the requirements of the rules under the Act have been complied with and that conditions of the licence and the rules under the Act shall be observed, he shall grant or renew a licence in Form 25C or Form 26C.

(2) If the licensing authority is not so satisfied he shall reject the application and shall inform the applicant of the reasons for such rejection and of the conditions which must be satisfied before a licence can be granted or renewed and shall supply the applicant with a copy of inspection report.]

[463][**85ED. Further application after rejection.**—If within a period of six months from the rejection of an application for a licence, the applicant informs the licensing authority that the conditions laid down have been fulfilled and deposits an inspection fee of [465][rupees two hundred], the licensing authority may, if after causing further inspection to be made, he is satisfied that the conditions for the grant of licence have been complied with, issue a licence in Form 25C or Form 26C.]

[464][**85EE. Appeal to the State Government.**—Any person who is aggrieved by the order passed by the Licencing Authority refusing to grant or renew a licence under this Part may within ninety days from the date of receipt of such order, appeal to the State Government and the State Government, may, after such enquiry into the matter as is considered necessary and after giving the said person an opportunity for representing the case pass such order as it thinks fit.]

85F. Duration of licence.—An original licence or a renewed licence unless it is sooner suspended or cancelled shall be [465][valid for a period of five years on and from the date on which], it is granted or renewed:

[466][Provided that if the application for renewal of a licence in force is made before its expiry or if the application is made within six months of its expiry, after payment of additional fee, the licence shall continue to be in force until orders are passed on the application and the licence shall be deemed to have expired if application for its renewal is not made within six months of its expiry.]

85G. Certificate of renewal.—The certificate of renewal of a licence in Form 25C shall be issued in Form 26C.

85H. Conditions of licence.—A licence in Form 25C shall be subject to the conditions stated therein and to the following further conditions, namely:—

(a) the licensee shall provide and maintain staff and premises as specified in rule 85E;

(b) the licensee shall allow an [467][Inspector appointed under the Act] to enter, with or without prior notice, any premises wheie the manufacture of a Homoeopathic medicine in respect of which the licence is issued is carried on, to inspect the premises and to take samples of the manufactured Homoeopathic medicines;

(c) the licensee shall allow an Inspector to inspect all registers and records maintained under these rules and shall supply to the Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and the rules made thereunder have been observed;

[468][(d) the licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and defects notice;]

(e) the licensee shall comply with the following conditions in respect of mother tinctures manufactured by him:—

(i) the crude drug used in the manufacture of the mother tincture shall be identified and records of such identification shall be kept [469][for a period of five years];

(ii) the total solids in the mother tincture shall be determined and records of such tests shall be kept [469][for a period of five years];

(iii) the alcohol content in the mother tincture shall be determined and records of the same shall be maintained [2][for a period of five years];

(iv) the containers of mother tinctures shall preferably be of glass and shall be clean and free from any sort of impurities of adhering matter. The glass shall be neutral as far as possible;

(v) in the process of manufacture of mother tinctures hygienic conditions shall be scrupulously observed by the licensee. Storage and handling conditions shall also be properly observed by the licensee according to Homoeopathic principles;

[470][(ea) no colour shall be added to any Homoeopathic medicines:

Provided that caramel may be added to combinations of Homoeopathic preparations with syrup base;]

(f) records shall be maintained of Homoeopathic medicines containing alcohol and the quantities sold together with names and addresses of parties to whom sold. [468][Such records shall be maintained for a period of five years.]

[471]**[85HH. Additional information to be furnished by an applicant for licence or a licensee to** the **licensing authority.**—The applicant for the grant of licence or any other person granted a licence under this Part shall, on demand, furnish to the licensing authority, before the grant of the licence or during the period the licence is in force, as the case may be, documentary evidence in respect of the ownership or occupation in rental or other basis of the premises, specified in the application for licence or in the licence granted, constitution of the firm, or any other relevant matter which may be required for the purpose of verifying the correctness of the statements made by the applicant or the licensee, while applying for or after obtaining the licence as the case may be.]

85-I. Cancellation and suspension of licences.—(1) The licensing authority may, after giving the licensee an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons

therefor, cancel a licence issued under this Part or suspend it for such period as he thinks fit, either wholly or in respect of some of the substances to which it relates if, in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act or rules made thereunder.

[472][(2) A licensee whose licence has been suspended or cancelled may, within three months of the date of the order under sub-rule (1), prefer an appeal against that order to the State Government, which shall decide the same.]]

PART VIII
MANUFACTURE FOR EXAMINATION, TEST OR ANALYSIS

86.Conditions relating to manufacture for examination, test or analysis.—Theprovisions of section 18 of the Act shall not apply to the manufacture of any drug in small quantities for the purpose of examination, test or analysis if the conditions prescribed in this Part are fulfilled.

87. Labelling.—Any drug manufactured for the purpose of examination, test or analysis shall be kept in containers bearing labels, indicating the purpose for which it has been manufactured.

88.Labelling of drugs supplied to other persons.—If any drug manufactured for the purpose of examination, test or analysis is supplied by the manufacturer to any other person, the container shall bear a label on which shall be stated the name and address of the manufacturer, the accepted scientific name of the substance if known, or if not known a reference which will enable the substance to be identified and the purpose for which it has been manufactured.

89. Licence.—If the person proposing to manufacture a drug for the purpose of examination, test or analysis does not hold a licence in Form 25 or Form 28 in respect of such drugs he shall, before commencing such manufacture, obtain a licence in Form 29:

[473][Provided that in the case of a drug the composition of which is such that the drug is not generally recognised among experts qualified by scientific training and experience to evaluate the safety of drugs as safe for use, no licence in Form 29 shall be granted unless the applicant produces a certificate from the

licensing authority mentioned in rule 21, to the effect that there would be no objection to such licence being granted.]

90. Form of application.—[474][(1)] An application for a licence in Form 29 shall be made to the licensing authority appointed by the State Government for the purposes of this Part (hereafter in this Part referred to as the licensing authority) in Form 30 and shall be made by or countersigned by the head of the institution in which, or a director of the firm or company by which, the substance will be manufactured.

[475][(2) Every application in [476][Form 30] shall be accompanied by [477][a fee of rupees two hundred and fifty].]

[478][(3) The license in Form 29 may be granted by the licensing authority within a period of seven working days from the date of receipt of the application duly completed in Form 30, and in case where no communication is received by the applicant from licensing authority within the said period of seven days, the licensing authority shall be deemed to have granted the license.]

91.Duration of licence.—A licence in Form 29 shall, unless sooner cancelled, be in force for a period of [479][three years from the date of issue], and may thereafter be renewed for periods of one year at a time.

92. Conditions of Licence.—A licence in Form 29 shall be subject to the following conditions:—

(a) the licensee shall use the drugs manufactured under the licence exclusively for purpose of examination, test or analysis, and shall carry on the manufacture and examination, test or analysis at the place specified in the licence;

(b) the licensee shall allow any [480][Inspector appointed under the Act] to enter, with or without notice, the premises where the drugs are manufactured and to satisfy himself that only examination, test or analysis work is being conducted;

(c) the licensee shall keep a record of the quantity of drugs manufactured for examination, test or analysis and of any person or persons to whom the drugs have been supplied;

(d) the licensee shall comply with such further requirements, if any, applicable to the holders of licences in Form 29 as may be specified in any Rules subsequently made under the Act and of which the licensing authority has given him not less than one months' notice.

(e) the licensee shall maintain an Inspection Book to enable an Inspector to record his impressions and defects noticed.

93. Cancellation of licences.—(1)The licensing authority may, after giving the licensee an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, cancel a licence issued under this Part, either wholly or in respect of some of the substances to which it relates, if, in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provision of the Act or rules thereunder.

[481][(2) A licensee whose licence has been suspended or cancelled may appeal to the State Government within three months of the date of the order.]

PART IX

LABELLING AND PACKING OF DRUGS OTHER THAN HOMOEOPATHIC MEDICINES

94. Exemption of certain drugs from certain provisions of this Part.—(1)Labels on packages or containers of drugs for export shall be adapted to meet the specific requirements of the law of the country to which the drug is to be exported but the following particulars shall appear in a conspicuous position on the innermost container in which the drug is packed and every other covering in which that container is packed—

(a) name of the drug;

(b) the name, address of the manufacturer and the number of the licence under which the drug has been manufactured;

(c) batch or lot number;

(d) date of expiry, if any:

[482][Provided that where a drug, not classified under Schedule F, Schedule F(l) and Schedule X, [483][or blood products defined under rule 122 EA] is required by the consignee to be not labelled with the name and address of the manufacturer, the labels on packages or containers shall bear a code number as approved by the licensing authority mentioned in rule 21.]

[484][Provided further that where a drug classified as Narcotic Drug or Psychotropic Substance is to be exported under a code number, the same may be permitted by the said Licensing Authority on the following conditions, namely:—

(i) each consignment of export shall be accompanied with requisite import licence from the importing country;

(ii) the applicant shall obtain a no objection certificate from the Drugs Controller, India for manufacture of such formulations to be exported with code number against each export order alongwith certificate from the regulatory authority of the importing country controlling Narcotics drugs and Psychotropic Substances that they do not have any objection for the import of the drug with code number;

(iii) the state Licensing Authority shall issue the manufacturing licence for these formulations on each export order on the basis of a no objection certificate from Drugs Controller, India;

(iv) a no objection certificate shall be obtained from the Drugs Controller, India for export of each consignment; and

(v) a no objection certificate shall be obtained from the Narcotic Commissioner of India, Gwalior for export of each consignment of the drug.]

[485][(2) The provisions or rules 96 to 101 inclusive, shall not apply to a medicine made up ready for treatment, whether after or without dilution, which is supplied on the prescription of a registered medical practitioner provided that—

(i) the medicine is labelled with the following particulars:—

(a) the name and address of the supplier;

(b) the name of the patient and the quantity of the medicine;

(c) the number representing serial number of the entry in the prescription register;

(d) the dose, if the medicine is for internal use;

[486][(e) the words Tor External use only' shall be printed on the label if the medicine is for external application;]

(ii) Condition (3) of the conditions in rule 65 is satisfied.]

95. Prohibition of sale or distribution unless labelled.—Subject to the other provisions of these rules, no person shall sell or distribute any drug (including a patent or proprietary medicine) unless it is labelled in accordance with these rules.

[487]**[96. Manner of Labelling.**—(1) Subject to the other provisions of these rules, the following particulars shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container of any drug and on every other covering in which the container is packed, namely:—

(i) The name of the drug:

(A) [488][For this purpose, the proper name of the drug or fixed dose combination drug other than fixed dose combinations of vitamin and other fixed dose combinations containing three or more drugs, shall be printed or written in a conspicuous manner which shall be [489][***] at least two font size larger than the brand name or the trade name, if any, and in other cases the brand name or the trade name, if any, shall be written [490][***] below or after the proper name and shall be.]—

(a) for drugs included in Schedule F or Schedule F(l), the name given therein;

(b) for drugs included in the Indian Pharmacopoeia or the official Pharmacopoeias and official compendia of drug standards prescribed in rule 124, the name or synonym specified in the respective official pharmacopoeias and official compendia of drug standards followed by the letters 'L.P.' or, as the case may be, by the recognised abbreviations of the

respective official pharmacopoeia and official compendia of drug standards;

(c) for drugs included in the National Formulary of India, the name or synonym specified therein followed by the letters 'N.F.I';

(d) for other drugs, the international non-proprietary name, if any, published by the World Health Organisation or where an international non-proprietary name is not published, the name descriptive of the true nature or origin of the substance.

[491][***]

[492][(AA) Notwithstanding anything contained in these rules, the additional requirements of labeling specified *vide* notification number G.S.R. 222(E) dated the 13th March, 2018 published in the Gazette of India, Extraordinary, Part-II - Section (3) - Sub-section(i) shall be on voluntary basis for a period beginning on the 13th September, 2018 and ending on the 31st March, 2019 and thereafter shall be mandatory.]

(ii) A correct statement of the net contents in terms of weight, measure, volume, number of units of contents, number of units of activity, as the case may be, and the weight, measure and volume shall be expressed in Metric system.

(iii) The content of active ingredients—

This shall be expressed—

(a) for oral liquid preparations in terms of the content per single dose, the dose being indicated in 5 millilitres [493][***]:

Provided that where the dose is below 5 millilitres the contents of active ingredients may be expressed in terms of one millilitre [494][or fraction thereof];

[495][Provided further that where the single dose is more than 5 millilitre, the content of active ingredients shall be expressed in terms of minimum single dose as approved by the licensing authority,]

(b) for liquid parenteral preparations ready for administration, in terms of 1 millilitre or percentage by volume or per dose in the case of a single dose container:

Provided that if the preparation is contained in an ampoule it will be enough if the composition is shown on the label or wrapper affixed to any package in which such ampoule is issued for sale;

(c) for drugs in solid form intended for parenteral administration in terms of units or weight per milligramme or gramme;

(d) for tablets, capsules, pills and the like, in terms of the content in each tablet, capsule, pill or other unit, as the case may be;

(e) for other preparations, in terms of percentage by weight or volume or in terms of unitage per gram or millilitre as the case may be:

Provided that clause (ii) shall not apply to a pharmacopoeial preparation where the composition of such preparation is specified in the respective pharmacopoeia and to a preparation included in the National Formulary of India;

(iv) [496][The name of the manufacturer and the address of the premises of the manufacturer where the drug has been manufactured:]

Provided that if the drug is contained in an ampoule or a similar small container, it shall be enough if only the name of the manufacturer and his principal place of [497][manufacture] is shown.

(v)A distinctive batch number, that is to say, the number by reference to which details of manufacture of the particular batch from which the substance in the container is taken are recorded and are available for inspection, the figure representing the batch number being preceded by the words 'Batch No.' or 'B No.' or 'Batch' or 'Lot No.' or 'Lot'.

Notes.

(1) In the case of drugs manufactured by a continuous process, like manufacture of magnesium sulphate, pharmaceutical chemicals, etc., the

production resulting in one homogeneous mix of the finished products shall be considered as one "Batch":

(2) In the case of powers, liquid orals, ointments, etc., one "Batch Number" shall be assigned to all the containers filed from one homogeneous bulk.

(3) In the case of tablets, capsules, lozenges, torches, etc. one "Batch Number" shall be assigned to the products manufactured from one homogeneous mix ready for compression or filing.

(4) In case of parental preparations sterilized by steam under pressure, one "Batch Number" shall be assigned to all containers filed from one homogeneous bulk solution and sterilized load.

(5) In the case of containers of parental preparations filed from one homogeneous bulk solution and sterilized in more than one sterilizer load, the "Batch Number" as signed to the containers in the different sterilizer loads shall be same "Batch Number" as is assigned to the homogeneous bulk solution, provided the samples taken from all the sterilizer loads pass the sterility test, and kept separate from one another until the report of the sterility test is available.

Explanation.—For the purpose of chemical and other tests, representative samples from all containers filled from the homogeneous bulk solution should be taken.

(6) In the case of parental and other sterile products filled aseptically a "Batch Number shall be assigned to all containers filled from one homogeneous mix during one filling operation, the filling operation being completed in a period of not more than a day during which no schedule change in the filling assembly is made. When containers are filled from one homogeneous mix, in a number of filling operations, the "Batch Number" assigned to the containers filled in individual filling operations shall be the same "Batch Number" as is assigned to the homogeneous mix, provided the samples taken from all the direction filling operations pass the sterility tests, and are kept separate from one another until the report of the sterility test is available. *Explanation*.—

For the purpose of chemical and other tests, representative samples from all containers filled from the homogeneous mix should be taken.

(7) In the case of medicinal gases produced by a continuous process of operation a week's production from one tank load shall be considered as a Batch.

(vi) Every drug manufactured in India shall bear on its label the number of the licence under which the drug is manufactured, the figure representing the manufacturing licence number being preceded by the words 'Manufacturing Licence Number' or 'Mfg. Lie. No.' or 'M.L.'.

(vii) Drugs specified in Schedule P and their preparations including combinations with other drugs shall bear on their labels the date of manufacture and the date of expiry of potency, and the period between the date of manufacture and the date of expiry shall not exceed that laid down in the said Schedule [498][under the conditions of storages specified therein. [499][Drugs and their] preparations not included in Schedule P, shall bear on their labels the date of their manufacture and also the date of their expiry which shall not exceed sixty months from the date of manufacture]:

Provided that this period may be extended by the licensing authority specified in clause (b) of rule 21 in respect of any specified drug if satisfactory evidence is produced by the manufacturer to justify such an extension.

[500][(viii) drugs specified in schedule C(l) and their preparations including combinations in other drugs shall bear on their labels (a) the date of manufacture, and (b) date of expiry of potency fixed by the manufacturer:]

[501][Provided that drugs in bulk form included in Schedule C(l) which are not ready for use and not included in Schedule P need not bear on the label the date of expiry of potency:]

Provided further that no reference shall be made to any other licence number granted by any authority outside India on any label or container or in any covering in which the container is packed or in any other matter or advertisement enclosed therewith.

(ix) Every drug intended for distribution to the medical profession as a free sample shall, while complying with the labelling provisions under clauses (i) to (viii), further bear on the label of the container the words 'Physician's sample—Not to be sold' which shall be overprinted.

[502][(x) If any preparation contains not less than 3 per cent, by volume of alcohol the quantity of alcohol shall be stated in terms of the average percentage by volume of absolute alcohol in the finished products.]

[503][(xi) [504][In addition to the other particulars which are required to be printed or written under these rules, the label of inner most container of the following categories of drugs and every other covering in which thecontainer is packed shall bear a caution or warning, as applicable, depending on whether the drug is covered under Schedule G or Schedule H or Schedule H 1 or Schedule X, as specified in rule 97, in legible black coloured font size in a completely red rectangular box without disturbing other conditions printed on the label under these rules, namely:—-

Narcotic analgesics, hypnotics, sedatives, tranquillisers, corticosteroids, hormones, hypoglycemic, antimicrobials, antiepileptics, antidepressants, anticoagulants, anti-cancer drugs and all other drugs falling under Schedules G, H, H 1 and Schedule X whether covered or not in the above list:

Provided that if any of the drug referred above category is not covered under any of the Schedule, namely, Schedule G, ScheduleH, Schedule H 1 and Schedule X, the label of inner most container of drugs and every other covering in which the container is packed shall bear caution or warning, as the case may be, applicable for that drugs covered under Schedule H as specified in rule 97:]

[505][Provided further that] the provisions of this clause shall not apply to—

(a) preparations intended for animal treatment;

(b) preparations intended for external use;

(c) ophthalmic preparations and ear drops; and

(d) sterile preparations such as sutures, surgical dressings and preparations intended for parenteral use.]

[506][(xii) Drugs and their preparations including combinations with other drugs imported into the country shall also bear on the label, the licence number under which the drug is imported, preceded by the words "Import Licence" and the name arid address of the importer.]

[507][(xiii) The name of the marketer of the drug and its address, in case the drug is marketed by a marketer:

Provided that if the drug is contained in an ampoule or a similar small container, it shall be enough if only the name of the marketer is shown.]

(2) (i) The particulars to be printed or written on the label of a mechanical contraceptive shall be as specified in Schedule R.

(ii) The following particulars, in addition to those specified under sub-rule(1) shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container and on every other covering in which the container of a contraceptive, other than a mechanical contraceptive, is packed, namely:—

(a) the date of manufacture;

(b) the date up to which the contraceptive is expected to retain its properties;

(c) the storage conditions necessary for preserving the properties of the contraceptive up to the date indicated in sub-clause (b):

Provided that for oral contraceptives it shall be sufficient to display on the label of the container the date of manufacture only.

(3) (i) The particulars prescribed in sub-rule (1) shall be printed or written in indelible ink either on the label borne by a container or vaccine lymph or on a label or wrapper affixed to any package in which the container is issued for sale. The said particulars shall be indelibly marked on the sealed container of surgical ligature or suture or printed or written in indelible ink on a label enclosed therein.

(ii) Nothing in these rules shall be deemed to require the labelling of any transparent cover or of any wrapper, case or other covering used solely for the purpose of packing, transport or delivery.

(4) Where by any provision of these rules any particulars are required to be displayed on a label on the container such particulars may, instead of being displayed on a label, be etched, painted or otherwise indelibly marked on the container:

Provided that, except where otherwise provided in these rules, the name of the drug or any distinctive letters intended to refer to the drug shall not be etched, painted or otherwise indelibly marked on any glass container other than ampoules.

[1333][(5) Every active pharmaceutical ingredient (bulk drug) manufactured or imported in India shall bear Quick Response code on its label at each level packaging that store data or information readable with software application to facilitate tracking and tracing. The stored data or information shall include the following minimum particulars, namely:—

(i) Unique product identification code,
(ii) Name of the API,
(iii) Brand name (if any),
(iv) Name and address of the manufacturer,
(v) Batch no.,
(vi) Batch size,
(vii) Date of manufacturing,
(viii) Date of expiry or retesting,
(ix) Serial shipping container code,
(x) Manufacturing licence no. or import licence no.
(xi) Special storage conditions required (if any).]

[1339][(6) The manufacturers of drug formulation products as specified in Schedule H2 shall print or affix Bar Code or Quick Response Code on its primary packaging label or, in case of inadequate space in primary package label, on the secondary package label that store data or information legible with software application to facilitate authentication.

(7) The stored data or information referred to in sub-rule (6) shall include the following particulars, namely:—

(i) unique product identification code;
(ii) proper and generic name of the drug;
(iii) brand name;
(iv) name and address of the manufacturer;
(v) batch number;
(vi) date of manufacturing;
(vii) date of expiry; and
(viii) manufacturing licence number.]

Explanation.—For the purpose of this rule, the date of expiry shall be in terms of month and year and it shall mean that the drug is recommended till the last day of the month. The date of expiry shall be preceded by the words 'Expiry date'.]

97. Labelling of medicines.— [508][(1) The container of a medicine for internaluse shall—

[509][(a) if it contains a drug substance specified in Schedule G, be labeled with following words in legible black coloured font size in completely red rectangular box:

SCHEDULE G PRESCRIPTION DRUG - CAUTION It is dangerous to take this preparation except under medical supervision.

(b) if it contains a drug substance specified in Schedule H, be labeled with symbol Rx and conspicuously displayed on the left top comer of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box:

SCHEDULE H PRESCRIPTION DRUG - CAUTION Not to be sold by retail without the prescription of a Registered Medical Practitioner.

(c) if it contains a drug substance specified in Schedule H and comes within the purview of the Narcotic Drugs and Psychotropic Substances Act, 1985 (61 of

1985) be labeled with symbol NRx, which shall be in red and conspicuously displayed on the left top comer of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box:

SCHEDULE H PRESCRIPTION DRUG - WARNING To be sold by retail on the prescription of a Registered Medical Practitioner only.

(d) if it contains a drug substance specified in Schedule X, be labeled with symbol XRx, which shall be in red and conspicuously displayed on the left top comer of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box:

SCHEDULE X PRESCRIPTION DRUG - WARNING To be sold by retail on the prescription of a Registered Medical Practitioner only.

(e) if it contains a drug substance specified in Schedule H1, be labeled with symbol Rx, which shall be in red and conspicuously displayed on the left top comer of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box:

SCHEDULE HI PRESCRIPTION DRUG - CAUTION - It is dangerous to take this preparation except in accordance with the medical advice. - Not to be sold by retail without the prescription of a Registered Medical Practitioner.

(f) if it contains a drug substance specified in Schedule H1 and comes within the purview of the Narcotic Drugs and Psychotropic Substances Act, 1985 (61 of 1985) be labeled with symbol NRx, which shall be in red and conspicuously displayed on the left top comer of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box:

SCHEDULE H1 PRESCRIPTION DRUG - CAUTION - It is dangerous to take this preparation except in accordance with the medical advice.

- Not to be sold by retail without the prescription of a Registered Medical Practitioner.]

(2) The container of an embrocation, liniment, lotion, [510][ointment, antiseptic cream,] liquid antiseptic or other liquid medicine for external application shall be labelled with the words in capital Tor External use only'.]

[511][(3) The container of a medicine made up ready only for treatment of an animal shall be labelled conspicuously with the words 'Not for human use; for animal treatment only', and shall bear a symbol depicting the head of a domestic animal.]

[512][(3A) The container of a medicine for treatment of food producing animals shall be labelled with the withdrawal period of the drug for the species on which it is intended to be used:

Provided that if the specific withdrawal period has not been validated, the withdrawal period shall not be less than seven days for eggs or milk, twenty eight days for meat from poultry and mammals including fat and offal, five hundred degree days for fish meat.

Explanation.—For the purpose of this rule, the withdrawal period is the period of interval between the last administration of a veterinary medicine to animals under the normal conditions of use and the production of food stuff from such animals to ensure that food stuffs do not contain residues in quantities in excess of the maximum residue limits laid down.]

[513][(4) The container of a medicine prepared for treatment of human ailments shall if the medicine contains industrial methylated spirit, indicate this fact on the label and be labelled with the words—

"FOR EXTERNAL USE ONLY".]

[514][(5) Substances specified in Schedule X in bulk form shall bear a label wherein the symbol as specified in sub-rule (1) shall be given conspicuously in red letters.]

[515]**[97A. Modified application of rules 96 and 97 for certain period.—** Notwithstanding anything contained in these rules, the modified or additional

requirements of labelling as may be specified in the notification of the Government of India in the Ministry of Health and Family Welfare number G.S.R. 408(E), dated the 26th April, 2018, shall be on voluntary basis for a period commencing on the date of coming into force of this rule and ending on the 31st day of March, 2019, and thereafter shall be mandatory.]

[516][***]

[517]**[102. Non-Sterile Surgical Ligature and Suture.**—Every container of, and wrapper enclosing surgical ligature or suture other than a ligature or suture offered or intended to be offered for sale as sterile, shall bear a label on which are printed or written in a conspicuous manner in indelible red ink the words "Non-sterile surgical ligature (suture)—not to be used for operations upon the human body unless efficiently sterilized".]

103. [518]**[***]**

(2) The name and address of the manufacturer shall be printed on the label of the container of a patent or proprietary medicine.

[519][(3) The true formula or list of the ingredients shall be printed or written in indelible ink on the outer label of every package containing patent or proprietary medicine]

[520]**[104. Use of letters I.F., etc.**—The letters T.P., and recognised abbreviations of pharmacopoeias and official compendia of drug standards prescribed under these rules shall be entered on the label of the drug only for the purpose of indicating that the drug is in accordance with standards set out in the Indian Pharmacopoeia or in any such pharmacopoeia or official compendium of drug standards recognised under the rules.]

[521]**[104A. Prohibition against altering inscriptions on containers,** labels or **wrappers of drug.**—No person shall alter, obliterate or deface any inscription or mark made or recorded by the manufacturer on the container, label or wrapper of any drug: Provided that nothing in this rule shall apply to any alteration, any inscription or mark made on the container, label or wrapper of any drug at the instance or direction or with the permission of the licensing authority.]

[522][**105. Packing of drugs.**—(1) The pack sizes of drugs meant for retail sale shall be as prescribed in Schedule PI to these rules.

(2) The pack sizes of drugs not covered by the Schedule PI shall be as given below:

Unless specified otherwise in Schedule PI,—

(i) The pack sizes for Tablets/Capsules shall be—

Where the number of Tablets (coated or uncoated)/Capsules (hard or soft gelatine) is less than 10, such packing shall be made by the integral number. For numbers above 10, the pack sizes of Tablets/Capsules shall contain multiples of 5 [1342][or 7].

(ii) The pack sizes for liquid Oral preparations shall be 30 ml. (paediatric only) 60 ml./100 ml./200 ml./450 ml.

(iii) The pack sizes for Paediatric Oral Drops shall be 5 ml./lO ml./15 ml.

(iv) The pack sizes for Eye/Ear/Nasal Drops shall be 3 ml. /5 ml./ 10 ml.

(v) The pack sizes for Eye Ointment shall be 3 gm/5 gm/10 gm: Provided that the provisions of the pack sizes covered under this rule shallnot apply to—

1. Pack sizes or dosage forms not covered by the foregoing provisions of this rule.

2. The imported formulations in finished form.

3. Preparations intended for Veterinary use.

4. Preparations intended for Export.

5. Vitamins/Tonics/Cough Preparations/Antacids/Laxatives in Liquid Oral forms, Unit dose (including applicaps).

6.Pack sizes of dosage forms meant for retail sale to Hospitals, Registered Medical Practitioners, Nursing Homes.

7. Physician's Samples.

8. Pack sizes of Large Volume intravenous Fluids:

[523][Provided further that] pack sizes of any of the new drug as and when approved by the licensing authority appointed under rule 21 and if not covered under this rule, shall be examined for the purpose of approval with specific justification by the said licensing authority:

[524][[525][Provided also that] Oxytocin injection meant for sale shall be in single unit blister pack only:]

[526][Provided also that Diclofenac injection for human use shall be in single unit dose pack only.]

[527]**[105A. Packing of drugs specified in Schedule** X.—The drugs specified in Schedule X shall be marketed in packings not exceeding—

(i) 100 unit doses in the case of tablets/capsules;
(ii) 300 ml. in the case of oral liquid preparation;
(iii) and 5 ml. in the case of injections:

Provided that nothing in this rule shall apply to packings meant for use of a hospital or a dispensary subject to the conditions that—

(i) such supplies are made by the manufacturers or distributors direct to the hospital/dispensaries; and

(ii) hospital packs shall not be supplied to a retail dealer or to a Registered Medical Practitioner.]

[528]**[106. Diseases which a drug may not purport to prevent or cure.—(1)** No drug may purport or claim to prevent or cure or may convey to the intending user thereof any idea that it may prevent or cure, one or more of the diseases or ailments specified in Schedule J.

(2) No drug may purport or claim to procure or assist to procure, or may convey to the intending user thereof any idea that it may procure or assist to procure, miscarriage in women.

[529][***]]

[530][PART IXA
LABELLING AND PACKING OF HOMOEOPATHIC MEDICINES

106A. Manner of labelling of Homoeopathic medicines.—(A) Thefollowing particulars shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container of any Homoeopathic medicine and on every other covering in which the container is packed:—

(i) The words 'Homoeopathic medicine'.

(ii) The name of the medicine—

[531][(a) For drugs included in the Homoeopathic Pharmacopoeia of India or the United States of America or the United Kingdom, or the German Homoeopathic Pharmacopoeia, the name specified in that Pharmacopoeia.]

(b) For other drugs, the name descriptive of the true nature of the drugs.

(iii) The potency of the Homoeopathic medicine—For this purpose the potency shall be expressed either in decimal, centesimal or millesimal systems.

[532][(iiiA) In case of a Homoeopathic medicine containing two or more ingredients, the name of each ingredient together with its potency and proportion expressed in metric system shall be stated on the label.]

[533][(iv) Name and address of the manufacturer when sold in original containers of the manufacturer. In case a Homoeopathic medicine is sold in a container other than that of the manufacturer—the name and address of the seller:]

[534][Provided that where such medicines are imported, the name and address of the importer shall also be mentioned on the label.]

(v) In case the Homoeopathic medicine contains alcohol, the alcohol content in percentage by volume in terms of ethyl alcohol shall be stated on the label:]

[535][Provided that in case that the total quantity of the pharmacopoeial Homoeopathic medicine in the container is 30 millilitres or less, it will not be necessary to state the content of alcohol in the label.]

(B) In addition to the above particulars the label of a Homoeopathic mother tincture shall display the following particulars:—

(i) a distinctive batch number, that is to say, that number by reference to which details of manufacture of the particular batch from which the substance in the container is taken are recorded and are available for inspection, the figures representing the batch number being preceded by the words "Batch No." or "Batch" or "Lot Number" or "Lot No." or "Lot" or any distinguishing prefix;

(ii) manufacturing licence number, the number being preceded by the words "Manufacturing Licence Number" or "Mfg. Lie No." or "M.L.".

[536]*[Explanation*.—This clause shall not apply to a Homoeopathic mother tincture manufactured outside India.

(C) No Homoeopathic medicine containing a single ingredient shall bear a proprietary name on its label.]]

[537]**[106B. Prohibition of quantity and percentage.**—No Homoeopathic medicine containing more than 12% alcohol v/v (Ethyl Alcohol) shall be packed and sold in packing or bottles of more than 30 millilitres, except that it may be sold to hospitals/ dispensaries in packings or bottles of not more than 100 millilitres.]]

PART X

SPECIAL PROVISIONS RELATING TO BIOLOGICAL AND OTHER SPECIAL PRODUCTS

[538]**[107. Name of substance.**—If any substance specified in Schedule C is advertised or sold as a proprietary medicine or is contained in a medicine so

advertised or sold, the proper name of the substance shall appear on the label in the manner prescribed in this Part.

[539][*Explanation*.—For the purpose of this rule the expression "proper name" means the proper name stated in Schedule F or if no such name is stated, the name descriptive of the true nature and origin of the substance:

Provided that in the case of veterinary biological product the expression "proper name" means the proper name stated in Schedule F(l) or if no such name is stated, the name or synonym given in the current edition for the time being of the [540][British Pharmacopoeia (Veterinary)], or, if no such name is stated either in Schedule F(l) or the [540][British Pharmacopoeia (Veterinary)], the name descriptive of the true nature and origin of the substance approved by the licensing authority.]]

108. Container.—[541][(1) No substance specified in Schedule C shall be sold or offered for sale unless it has been sealed in a previously sterilised container made of glass or any other suitable material approved for the purpose by the licensing authority appointed under rule 21, in such manner as may, in the opinion of the licensing authority, suffice to preclude the access of bacteria:

Provided that it shall not be necessary to use a previously sterilised container if the filled and sealed container is to be sterilised after the sealing and such sterilising procedure would render the products sterile. However, the licensing authority may, for any special reasons, direct the licensee to pre-sterilise such containers.]

(2) When any such substance is issued in liquid form in containers which are sealed in such a manner that portions of the contents can be withdrawn for use on different occasions, the liquid shall contain a sufficient proportion of some antiseptic to prevent the growth of any organism which may be accidentally introduced in the process of removing a portion of the contents of the container:

[542][Provided that nothing in this sub-rule shall apply to a penicillin suspension in oil and wax.]

[543][(3) The container shall comply with such further requirements, if any, as are specified in Schedule F or Schedule F(l) as the case may be, in that behalf.]

[544][(4) The licensing authority may in the case of particular preparation of any such substance dispense with any of the requirements of this rule or of Schedule F or Schedule F(l), as the case may be, and may make such additional requirement, as having regard to the nature of the preparation, they may deem necessary.]

[545]**[109.Labelling.**—(1) The following particulars and such further particulars, if any, as are specified in Schedule F or Schedule F(l), as the case may be, shall be printed or written in indelible ink on the label of every phial, ampoule or other container of a substance specified in Schedule C and on every other covering in which such phial, ampoule or container is packed:—

(a) Where a drug is imported, the number of licence under which it is imported, preceded by the words "Import Licence":

Provided that no reference shall be made to any other import licence number granted by any authority outside India on any label orcontainer or in any covering in which the container is packed or in any other matter of advertisement enclosed therein.

(b) Where a test for potency in units is required by these rules, a statement of the potency in units defined in terms of relating to the standard preparation specified in Schedule F or F(l), as the case may be:

Provided that this clause shall not apply in the case of vaccine lymph.

(c) Where a test for potency of maximum toxicity is required the date up to which the substance if kept under suitable conditions may be excepted to retain a potency not less than that stated on the label of the container or not to acquire a toxicity greater than that permitted by the test, as the case may be. The date of expiry shall be in terms of month and year and it shall mean that the drug is recommended for use till the last day of the month. The date of expiry shall be preceded by the words 'Expiry date':

Provided that nothing in these rules shall be deemed to require the labelling of any transparent cover or any wrapper, case or other covering used solely for the purpose of packing, transport or delivery.

(2) The particulars prescribed in clause (a) of the preceding sub-rule shall be printed or written in indelible ink either on the label borne by a container of vaccine lymph or on a label or wrapper affixed to any package in which the container is issued for sale. The said particulars shall be indelibly marked on the sealed container of surgical ligature or suture or printed or written in indelible ink on a label enclosed therein.

(3) The following particulars, and such further particulars, if any, as are specified in Schedule F or Schedule F(l), as the case may be, shall be printed or written in indelible ink either on the label borne by the container of any substance specified in Schedule C or on a label or wrapper affixed to any package in which any such container is issued for sale, namely:—

(a) the date on which the manufacture of the particular batch from which the substance in the container is taken was completed as defined in Schedule F or Schedule F(l) or if there is no definition in Schedule F or F(l) as hereafter defined in this rule and in the case of vaccine prepared from concentrates, the date of completion of the final products and the bottling for issue;

(b) where an antiseptic substance has been added, the nature and the percentage proportion introduced;

(c) the precaution necessary for preserving the properties of the contents up to the date indicated in clause (c) of sub-rule (1)

(4) For the purpose of clause (a) of sub-rule (3), the date of which the manufacture of a batch is completed shall be—

(a) in cases where a test for potency or toxicity is required, by these rules not being so required, is accepted by the licensing authority as sufficient for the purpose of fixing the date of completion of manufacture, the date on which the substance w[r]as removed from cold storage after having been kept at a temperature not exceeding 5°C continuously for a period not exceeding two years from the time when the last test was completed;

(b) in cases where no such test is required or accepted—

(i) if the substance is a serum obtained from a living animal, the earliest date on which any material contributing to the batch was removed from the animal;

(ii) if the substance was obtained by the growth of organisms on artificial media, the earliest date on which growth was terminated in any of the material contributing to the batch:

Provided that if a batch of the substance (including all material contributing to this batch) has for a period of not more than three years been kept in cold storage at a temperature not exceeding 5°C continuously from the earliest practicable date after that on which growth was terminated in the material as the case may be, the date of removal from cold storage shall be treated as the date on which the manufacture of the batch is completed;

(c) in all other cases, the date on which the substance is filled in the container.]

[546][**109A. Labelling of medical devices.**—Subject to the other provisions of these rules, the following particulars shall be printed in indelible ink on the label or sticker on the shelf pack of the medical device or on the outer cover of such medical device and on every outer covering in which the medical device is packed, namely;—

(a) proper name of the medical device;

(b) the details necessary for the user to identify the device and its use;

(c) the name of the manufacturer and address of the manufacturing premises where the device has been manufactured;

(d) the correct statement of the net quantity in terms of weight, measure, volume, number of units, as the case may be, and the number of the devices contained in the package shall be expressed in metric system; and

(e) the date of manufacture and date of expiry; alternately the label shall bear the shelf life of the product:

Provided that in the case of sterile devices the date of sterilisation may be given as date of the manufacture of the device:

Provided further that the device is made up of stable materials such as stainless steel or titanium, and supplied non-sterile, date of expiry may not be necessary;

(f) to provide, wherever required, an indication that the device contains medicinal or biological substance;

(g) to provide, a distinctive batch number or lot number preceded by the word "Lot No." or "Lot" or "Batch No." or "B. No.";

(h) to indicate, wherever required, any special storage or handling conditions applicable to the device;

(i) to indicate, if the device is supplied as a sterile product, its sterile state and the sterilisation method;

(j) to give, if considered relevant, warnings or precautions for the attention of the user of the medical device;

(k) to label the device, if the device is intended for single use;

(1) to overprint on the label of the container, the words "FOR CLINICAL INVESTIGATION ONLY", if the device is intended for clinical investigation;

(m) to overprint on the label of the device, the words "Physician's Sample—Not to be sold", if a medical device is intended for distribution to the medical professional as a free sample,

(n) to provide, except for imported devices, the manufacturing licence number by preceding the words "Manufacturing Licence Number" or "Mfg. Lie, No." or "M. L";

(o) Devices or In-vitro diagnostics which are not sold to customer or patient directly and are sold for use by hospitals or diagnostic labs shall provide the information affixing additional label or sticker on outer shelf pack;

(p) to provide on the label, in case of imported devices, with the approval of the licensing authority mentioned in rule 21, the import licence number, name and address of the importer and address of the actual manufacturing premises, date of manufacture, (if not already printed at the time of import):

Provided that the label may bear symbols recognised by the Bureau of Indian Standards or International Organisation for Standardisation (ISO) in lieu of text and the device safety is not compromised by a lack of understanding on the part of the user in case the meaning of the symbol is not obvious to the device user.]

[547][**109B. Exemption of certain labelling requirements for medical devices for export from India.**—The labels on packages or container of devices for export shall be adopted to meet specific requirements of the law of the country to which the device is to be exported, but the following particulars shall appear in conspicuous manner on the label of the shelf pack of the medical device in which the device is packed and every other outer covering in which the container is packed—

(a) name of the Device;

(b) the distinctive batch number or lot number preceded by the word "Lot No." or "Lot" or "Batch No." or "B. No.";

(c) the date of expiry, if any;

(d) the name and address of the manufacturer and address of actual premises where the been manufactured;

(e) the manufacturing Licence No. preceded by the letters "M.L. No" or "Manufacturing Licence No";

(f) the internationally recognised symbols in lieu of text, wherever required:

Provided that where a device is required by the consignee not to be labeled with the name and address of the manufacturer, the label on the packages or container shall bear a code number as approved by the licensing authority and the code number shall bear the name of the State or Union territory, in abbreviation, followed by the word "Device" and "manufacturing licence number:

Provided further that where a device is required by the consignee not to be labeled with the code number also, the label on the packages or container shall bear a special code number, as requested by the consignee, and approved by the licensing authority under rule 21.]

[548][**109C. Shelf life of the medical devices.**—The shelf life of the medical devices shall not exceed sixty months from the date of manufacture:

Provide that the period may be extended by the licensing authority in respect of any specified medical device, if satisfactory evidence is produced by the manufacturer to satisfy such an extension.]

110. Prohibition of sale of substance after prescribed date.—No person shall sell, or exhibit for sale any substance specified in Schedule C after the date recorded on the container, label or wrapper as the date up to which the substance may be expected to retain a potency not less than, or not to acquire a toxicity greater than that required or permitted by the prescribed test as the case may be.

[549][***]

[550][**111. Standards.**—Every substance specified in Schedules C and C(l) intended for sale shall conform with the standards of strength, quality and purity specified in these rules and in Schedule F or F(l) as the case may be, and the tests for determining such conformity shall be applied to samples taken from the final product after every manufacturing process has been completed.]

[551][**112. Tests for strength and quality.**—The tests, if any, required for determining the strength and quality of each of the substances specified in Schedules C and C(l) shall be those set out in Schedule F or Schedule F(l) [552][or as specified as the case may be].]

[553][***]

115. Application of tests for sterility.—The tests shall be applied—

(a) to samples taken from each batch of the substance before the operation of filling and sealing the containers in which it is to be issued has commenced except preparations, which after being sealed in the

containers are to be sterilized by heat, in a manner satisfactory to the licensing authority; and

(b) to the contents of sample containers when ready for issue.

554[***]

119. (1) If at this examination no growth of micro-organisms is found in any tube, the sample may be treated as having passed the test.

(2) If at the examination a growth of micro-organisms is visible, furthersamples may be taken and the tests may be repeated on the further samples taken; but no container the contents of which form part of the batch shall be issued until such further samples have passed the test. The processes of taking samples from the batch for a test may be repeated twice:

Provided that if the same organism is visible in more than one test the batchshall be treated as no sterile and the material container in the batch shall not be issued or used as part of a further batch unless and until it has been resterilized and has passed the tests.

120. Notwithstanding anything contained in the last preceding rule, in any case where—

(a) a substance is required in any emergency by a registered medical practitioner, but the licensee has not filled containers in stock, or

(b) a substance which in the opinion of the licensing authority is so unstable in solution that the delay occasioned by the completing of the sterility test on filled containers would render its issue in active form impossible, the licensee may issue the substance from a batch which has already passed the test for sterility and freedom from abnormal toxicity, without completing the sterility test on the filled containers, provided that he complies with the following conditions:—

(i) the licensee shall before the issue take samples in the required proportions from the containers into which the batch is filled, and after the required inoculation and incubation shall examine the tubes every day for five days;

(ii) if at any examination any growth is visible in any of the tubes, he shall immediately notify the licensing authority;

(iii) he shall keep available for inspection a record of all issues made under this Rule containing such particulars of the circumstances in which the issue is made as the licensing authority may require.

[555][**121.Test for freedom from abnormal toxicity.**—The test for freedom from abnormal toxicity shall be carried out as per the current edition of Indian Pharmacopoeia in the cases of each batch of the serum tested by the licensee or by an institution approved by the licensing authority for the purpose of carrying out the test on its behalf.]

[556][**121A.Test for pyrogens.**—Solution of substances intended for parenteral administration in large volumes (10 ml. or more at a time) shall be pyrogen-free and tested for pyrogens. Ifwater or any other aqueous solvent is supplied along with the substances for preparing such solutions, it shall also be pyrogen-free and tested for pyrogens.]

122. Substances specified in Schedule C(l).—The following provisions shall apply in the case of a substance specified in Schedule C(l):—

(a) The container shall comply with the requirements, if any specified in Schedule F or Schedule F(l) [557][or as specified] as the case may be.

[558][***]

(c) The substance shall conform to the standards of strength, quality and purity specified in Schedule F or Schedule F(l), [559][or as specified], as the case may be, and the tests for determining the strength, quality and purity of the substance shall be those specified in Schedule F or Schedule F(l) [559][or as specified], as the case may be.

(d) The test for determining the strength, quality and purity of a substances specified in Schedule F or Schedule F(l) [559][or as specified], as the case may be, shall be applied to samples taken from the final product after each manufacturing process has been completed.

(e) The substance should be stored in a cool place and away from light.

[560][PART XA
IMPORT OR MANUFACTURE OF NEW DRUG FOR CLINICAL TRIALS OR MARKETING

122A. Application for permission to import new drug.—[561][(1) (a) No newdrug shall be imported except under, and in accordance with the permission granted by the Licensing Authority as defined in clause (b) of rule 21.

(b) An application for grant of permission to import a new drug shall be made in Form 44 to the Licensing Authority, accompanied by a fee of [562][two lakh fifty thousand rupees]:

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims is made, the fee to accompany such application shall be [563][one lakh rupees]:

Provided further that any application received after one year of the grant of approval for the import and sale of new drug, shall be accompanied by a fee of [564][one lakh rupees] and such information and data as required by [565][Appendix I or Appendix IA or Appendix IB] of Schedule Y, as the case may be.]

(2) The importer of a new drug when applying for permission under subrule (1), shall submit data as given in [565][Appendix I or Appendix IA or Appendix IB] to Schedule Y including the results of local clinical trials carried out in accordance with the guidelines specified in that Schedule and submit the report of such clinical trials in the format given in Appendix II to the said Schedule: Provided that the requirement or submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries:

Provided further that the submission of requirements relating to Animal Toxicology Reproduction studies Teratogenic studies, Perinatal studies Mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug subject to the other provisions of these rules.

[566][(3) The Licensing Authority, after being satisfied that the drug if permitted to be imported as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, may issue an import permission in Form 45 and/or Form 45A, subject to the condition stated therein:

Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing and the conditions, which shall be satisfied before permission, could be considered.]

122B. Application for approval to manufacture new drug [567]**[***].—** [568][(1)(a) No new drug shall be manufactured for sale unless it is approved by the Licensing Authority as defined in clause (b) of rule 21.

(b) An application for grant of approval to manufacture the new drug and its formulations shall be made in Form 44 to the Licensing Authority as defined in clause (b) of rule 21 and shall be accompanied by a fee of fifty thousand rupees: Provided that where the application is for permission to import a new drug (bulk drug substance) and grant of approval to manufacture its formulation/s, the fee to accompany such application shall be fifty thousand rupees only.

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany such subsequent application shall be fifteen thousand rupees:

Provided further also that any application received after one year of the grant of approval for the manufacture for sale of the new drug, shall be accompanied by a fee of fifteen thousand rupees an such information and data as required by [565][Appendix I or Appendix IA or Appendix IB] of Schedule Y, as the case may be.]

(2) The manufacturer of a new drug under sub-rule (1) when applying for approval to the licensing authority mentioned in the said sub-rule, shall submit data as given in [565][Appendix I or Appendix IA or Appendix IB] to Schedule Y including the results of clinical trails carried out in the country in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in the format given in Appendix II to the said Schedule.

[569][(2A) The Licensing Authority as defined in clause (b) of rule 21 after being satisfied that the drug if approved to be manufacture as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, shall issue approval in Form 46 and/or Form 46A., as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission could be considered.]

(3) When applying for approval to manufacture of a new drug under sub-rule (1) or its preparations to the State licensing authority an applicant shall produce along with his application, evidence that the drug for the manufacture of which application is made has already been approved [570][in the name of the applicant] by the licensing authority mentioned in rule 21:

Provided that the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the [571][Licensing Authority in rule 21] may, in public interest decide to grant such permission on the basis of data available from other countries:

Provided further that the submission of requirements relating to Animal Toxicology, Reproduction studies, Teratogenic studies, Perinatal studies, Mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

[572][***]

[573]**[122D. Permission to import or manufacture fixed dose combination.** —(1)An application for permission to import or manufacture fixed dose combination of two or more drugs as defined in clause (c) of rule 122E shall be made to the Licensing Authority as defined in clause (b) of rule 21 in Form 44, accompanied by a fee of [574][fifteen thousand in case of application for manufacture of the fixed dose combinations and one lakh rupees in case of import application of the fixed dose combinations] and shall be accompanied by such information and data as is required in Appendix VI of Schedule Y.

(2) The Licensing Authority after being satisfied that the fixed dose combination if approved to be imported or manufactured as finished formulation shall be effective and safe for use in the country, shall issue permission in Form 45 or Form 46, as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall where the data provided or generated on the fixed dose combination is inadequate, intimate the applicant in writing, and the conditions which shall be satisfied before grant of approval/ permission could be considered.

122DA. Application for permission to conduct clinical trials for New Drug/ Investigational New Drug.—**(1)** No clinical trial for a new drug, whether for clinical investigation, or any clinical experiment by any Institution, shall be conducted except under, and in accordance with the permission, in writing, of the Licensing Authority defined in clause (b) of rule 21.

(2) An application for grant of permission to conduct,—

(a) human clinical trials (Phase-I) on a new drug shall be made to theLicensing Authority in Form 44 accompanied by a fee of fifty thousand rupees and such information and data as required under Schedule Y;

(b) exploratory clinical trials (Phase-II) on a new drug shall be made on the basis of data emerging from Phase-I trial, accompanied by a fee of twenty-five thousand rupees;

(c) confirmatory clinical trials (Phase-III) on a new drug shall be made on the basis of the data emerging from Phase-II and where necessary, data emerging from Phase-I also, and shall be accompanied by a fee of twenty-five thousand rupees.

Provided that no separate fee snail be required to be paid alongwith application for import/manufacture of a new drug based on successful completion of phase clinical trials by the apphcant.

Provided further that no fee snail be required to be paid alongwith the application by Central Government or State Government Institutes involved in clinical research for conducting trials for academic or research purposes.

(3) The Licensing Authority after being satisfied with the clinical trials, shall grant permission in Form 45 or Form 45 A or Form 46 or Form 46A, as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall, where the data provided on the clinical trials is inadequate, intimate the apphcant in writing, within six months, from the date of such intimation or such extended period, not exceeding a further period of six months, as the Licensing Authority may, for reasons to be recorded, in writing, permit, intimating the conditions which shall be satisfied be fore permission could be considered:

[575][(4) Nopermission for conduct of clinical trial intended for academic purposes in respect of approved drug formulation shall be required for any new indication or new route of administration or new dose or new dosage form where,—

(a) the trial is approved by the Ethics Committee; and

(b) subject to the provisions of sub-rule 5, the data generated is not intended for submission to licensing authority.]

[576][(5) The Ethics Committee shall however inform the licensing authority about the cases approved by it and also about cases where there could be an overlap between the clinical trial for academic and regulatory purposes and where the said authority does not convey its comments to the Ethics Committee within a period of thirty days from the date of receipt of communication from the Ethics Committee, it shall be presumed that no permission from the licensing authority is required.]

[577]*[Explanation.*—For the purpose of these rules,—

(a) "Clinical Trial" means a systematic study of any new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamics and

pharmacokinetic), and/or adverse effects with the objective of determining safety and/or efficacy of the new drug;

(b) "Global Clinical Trial" means any clinical trial which is conducted as part of multi-national clinical development of a drug;

(c) "Investigational New Drug" means a new chemical entity or a product having therapeutic indication but which has never been tested earlier on human being;

(d) "New Chemical Entity" means an active substance in developmental stage which may be specified as a drug under the Act, after undergoing any clinical trial.]

[578][***]

[579]**[122DAB. Compensation in case of injury or death during clinical trial.—**[580]**[(1)** In case ot an injury occurring to the subject during the clinical trial, free medical management snail be given as long as required on till such time it is established that the injury is not related to the clinical trial, whichever is earlier.]

(2) In case the injury occurring to the trial subject is related to the clinical trial, such subject shall also be entitled for financial compensation as per order of the Licensing Authority defined under clause (b) of rule 21, and the financial compensation will be over and above any expenses incurred on the medical management of the subject.

[581][(2A) In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages of the subject.]

(3) In the case of clinical trial related death of the subject, his/her nominee(s) would be entitled for financial compensation, as per the order of the Licensing Authority defined under clause (b) of rule 21, and the financial compensation will be over and above any expenses incurred on the medical management of such subject.

(4) The expenses on medical management and financial compensation in the case of clinical trial injury or death of the trial subject shall be borne by the sponsor of the clinical trial.

(5) Any injury or death of the subject occurring in clinical trial due to following reasons shall be considered as clinical trial related injury or death and the subject or his/her nominee(s), as the case may be, are entitled for financial compensation for such injury or death:

(a) adverse effect of investigational product(s);

(b) violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the investigator;

(c) failure of investigational product to provide intended therapeutic effect [1][where, the standard care, though available, was not provided to the subject as per the clinical trial protocol];

(d) use of placebo in a placebo-controlled trial[1] [where, the standard care, though available, was not provided to the subject as per the clinical trial protocol];

(e) adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;

(f) for injury to a child in-utero because of the participation of parent in clinical trial;

(g) any clinical trial procedures involved in the study.

(6) The Sponsor, whether a pharmaceutical company or an institution shall give an undertaking along with the application for clinical trial permission to the Licensing Authority defined in clause (b) of Rule 21, to provide compensation in the case of clinical trial related injury or death for which subjects are entitled to compensation.

(7) In case the Sponsor fails to provide medical management for the injury to the subject and/or financial compensation to the trial subject for clinical trial related injury or financial compensation to the subject's nominee(s) in case of clinical trial related death of the subject, the Licensing Authority may after

giving an opportunity to show cause why such an order should not be passed, by an order in writing, stating the reasons thereof, suspend or cancel the clinical "trial and/or restrict Sponsor including his representative(s) to conduct any further clinical trials in the country or take any other action deemed fit under the rules.]

[582][**122DAC. Permission to conduct clinical trial.—(1)** The Licensing Authority as defined in clause (b) of rule 21, on being satisfied that the data submitted along with the application in support of the proposed clinical trial is adequate in all respects, issue permission for conduct of clinical trial, subject to the following conditions, namely:—

(a) Clinical trial shall be conducted in compliance with the approved protocols, requirements of Schedule Y annexed to these rules, Good Clinical Practice Guidelines for conduct of clinical trials in India and other applicable regulations;

(b) Approval of the Ethics Committee shall be obtained before initiation of the study;

(c) Clinical trial shall be registered at Clinical Trials Registry of India before enrolling the first patient for the study;

(d) Annual status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Licensing Authority, and iii case of termination of any clinical trial the detailed reasons for the same shall be communicated to the said Licensing Authority;

(e) Any report of serious adverse event occurring during clinical trial to the subject, after due analysis, shall be forwarded within ten days of its occurrence as per Appendix XI and in compliance with the procedures prescribed in Schedule Y;

(f) Incase of an injury or death during the clinical trial to the subject of the clinical trial, the apphcant shall provide complete medical management and compensation m the case of trial related injury or death in accordance with rule 122 DAB and the procedures prescribed under Schedule Y, and the details of compensation provided in such cases shall be intimated to

the Licensing Authority within thirty days of the receipt of the order of the said authority;

(g) The premises of Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites shall be open to inspection by the officers authorised by the Central Drugs Standard Control Organisation, who may be accompanied by an officer of the State Drug Control Authority concerned, to verify compliance to the requirements of Schedule Y, Good Clinical Practices guidelines for conduct of clinical trials in India and other applicable regulations;

(h) The Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites and the Investigator shall allow officers authorised by the Central Drugs Standard Control Organisation, who may be accompanied by an officer of the State Drug Control Authority concerned, to enter with or without prior notice, any premises of Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial sites to inspect, search and seize, any record, data, document, books, investigational drugs, etc. related to clinical trials and provide adequate replies to any queries raised by the inspecting authority in relation to the conduct of clinical trial.

(2) Notwithstanding the conditions specified in sub-rule (1), the Licensing Authority, on being satisfied that the data submitted along with the application in support of the proposed clinical trial is adequate in all respect, may also impose such additional conditions for issuance of permission in respect of specific clinical trials, if considered necessary, regarding the objective, design, subject population, subject eligibility, assessments, conduct and treatment of such clinical trial.

(3) If any Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors, Investigators conducting clinical trial and clinical trial sites fail to comply with any of the above conditions, the Licensing Authority, may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons thereof,

(a) issue warning letter giving details of deficiency found during the inspection, which might affect the right or well-being of the clinical trial subject or the validity of the study conducted at that site;

(b) recommend that study may be rejected or discontinued;

(c) suspend or cancel the clinical trial permission;

(d) debar the Investigator(s), Sponsor including their employees, subsidiaries and branches, their agents, contractors and subcontractors to conduct any clinical trial in future.

(4) The Sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors and clinical trial Investigators, against whom action as mentioned in sub-rule (3) has been taken by the Licensing Authority, may, within ninety days of the receipt of the copy of the order of the Licensing Authority prefer an appeal to the Central Government, and the Central Government may, after giving such appellant an opportunity of being heard, confirm, reverse or modify such order.]

122 DB. Suspension or cancellation of Permission/Approval.—If the importer or manufacturer under this Part fails to comply with any of the conditions of the permission or approval, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, suspended or cancel it.

122DC. Appeal.—Any person aggrieved by an order passed by the Licensing Authority under this Part, may within sixty days from the date of such order, appeal to the Central Government, and the Central Government may after such enquiry into the matter as is considered necessary, may pass such order in relation thereto as it thinks fit.

[583]**[122DD. Registration of ethics Committee.**—(1) No Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of rule 21:

Provided that any Ethics Committee, existing on the date of commencement of the Drugs and Cosmetics (Third Amendment) Rules. 2013, who has already reviewed and accorded approval to clinical trial protocol, shall obtain

registration within a period of forty-five days from the date of commencement of the Drugs and Cosmetics (Third Amendment) Rules, 2013.

(2) An application for registration of Ethics Committee shall be made to the Licensing Authority in accordance with the requirements as specified in the Appendix VIII of Schedule Y

(3) The Licensing Authority after being satisfied that the requirements have been complied with, may grant registration to the Ethics Committee subject to such conditions as may be stated therein.

(4) The Ethics Committee shall review and accord its approval to a clinical trial and also carry ongoing review of the trial at appropriate intervals, as specified in Schedule Y, and the Good Clinical Practice Guidelines for Clinical Trials in India and other applicable regulatory requirements for safeguarding the rights, safety and well-being of the trial subjects.

(5) In the case of any serious adverse event occurring to the clinical trial subjects during the clinical trial, the Ethics Committee shall analyse and forward its opinion as per procedures specified under APPENDIX XII of Schedule Y

(6) The Ethics Committee shall allow inspectors or officials authorised by the Central Drugs Standard Control Organisation to enter its premises to inspect anyrecord, data or any document related to clinical trial and provide adequate replies to any query raised by such inspectors or officials, as the case may be, in relation to the conduct of clinical trial.

(7) The registration unless it is suspended or cancelled, shall be valid for a period of three years from the date of issue;

Provided that if the application for re-registration is received by the Licensing Authority within three months before the expiry, the registration shall continue to be in force until orders are passed by the said authority.

Provided further that the Licensing Authority shall be Informed in writing in case of any change in the membership or the constitution of the Ethics Committee takes place.

(8) If the Licensing Authority is not satisfied, he shall reject the application and shall inform the applicant of the reasons for such rejection and the conditions which must be satisfied before the registration can be granted.

(9) If the Ethics Committee falls to comply with any of the conditions of registration, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, suspend or cancel the registration of the Ethics Committee for such period as considered necessary.

(10) The Ethics Committee whose registration has been suspended or cancelled by the Licensing Authority, may, within ninety days of the receipt of the copy of the order, prefer an appeal to the Central Government and the Central Government may after giving an opportunity of being heard, confirm, reverse or modify such order.

Explanation.—For the purpose of this rule an Ethics Committee is a committee comprising of medical, scientific, non-medical and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and wellbeing of human subjects involved in a clinical trial and it shall be responsible for reviewing and approving the protocol, the suitability of the investigators, facilities, methods and adequacy of information to be used for obtaining and documenting informed consent of the study subjects and adequacy of confidentiality safeguards.]

122E. Definition of new drug.—For the purpose of this part, new drug shall mean and include—

[584][(a) A drug, as defined in the Act including bulk drugs substance [585][or phytopharmaceutical drug] which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labelling thereof and has not been recognised as effective and safe by the licensing authority mentioned under rule 21 for the proposed claims:

Provided that the limited use, if any, has been with the permission of the licensing authority.]

(b) A drug already' approved by the licensing authority mentioned inrule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

(c) A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, *viz.*, indications dosage, dosage form (including sustained release dosage form) and route of administration. *(See* items (b) and (c) of Appendix VI to Schedule Y).

Explanation.—For the purpose of this rule—

[586][(i) all vaccines and Recombinant DNA (r-DNA) derived drugs shall be new drugs unless certified otherwise by the Licensing Authority under rule 21;]

(ii) a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval [587][***].]

[588][PART XB

REQUIREMENTS FOR THE COLLECTION, STORAGE, PROCESSING AND DISTRIBUTION OF WHOLE HUMAN BLOOD, HUMAN BLOOD COMPONENTS BY [589][BLOOD CENTRES] [590][, MANUFACTURE OF BLOOD PRODUCTS AND COLLECTION, PROCESSING, TESTING, STORAGE, BANKING AND RELEASE OF UMBILICAL CORD BLOOD STEM CELLS]

[591][**122EA. Definitions.**—**(1)** In this Part and in the Form contained in Schedule A and in Part X1IB [592][Part XIIC and Part XIID] of Schedule F, unless there is anything repugnant in the subject of context,—

(a) apheresis" means the process by which blood drawn from a donor, after separating plasma or platelets or leucocytes, is retransfused simultaneously into the said donor;

(b) "autologous blood" means the blood drawn from the patient for retransfusion into himself later on;

(c) "blood" means and includes whole human blood, drawn from a donor and mixed with an anti-coagulant;

[593][(d)'Blood Centre' is an authorized premises in an organization or institution as the case may be, for carrying out all or any of the operations including collection, apheresis, processing, storage and distribution of blood drawn from donors or received from another licensed Blood Centre and for preparation, storage and distribution of blood components;]

(e)"blood component" means a drug prepared, obtained, derived or separated from a unit of blood drawn from a donor;

(f) "blood product" means a drug manufactured or obtained from pooled plasma of blood by fractionation, drawn from donors;

[594][(fa)'cord blood bank' means a place or organization or unit for carrying out and responsible for operations of collection, processing, testing, banking, selection and release of cord blood units;]

(g) "donor' means a person who voluntarily donates blood after he has been declared fit after a medical examination, for donating blood, on fulfilling the criteria given hereinafter, without accepting [595][against donated unit] in return any consideration in cash or kind from any source, but does not include a professional or a paid donor;

Explanation.—For the purposes of this clause, benefits or incentives like pins, plaques, badges, medals, commendation certificates, time-off from work, membership of blood assurance programme, gifts of little or intrinsic monetary value shall not be construed as consideration,

(h) "ieucapheresis" means the process by which the blood drawn from a donor, after leucocyte concentrates have been separated, is retransfused simultaneously into the said donor;

(i) "plasmapheresis" means the process by which the blood drawn from a donor, after plasma has been separated, is re-transfused during the same sitting into the said donor;

(j) "plateletpheresis" means the process by which the blood drawn from a donor, after platelet concentrates have been separated, is retransfused simultaneously into the said donor;

(k) "professional donor" means a person who donates blood for a valuable consideration, in cash or kind, from any source, on behalf of the recipient-patient and includes a paid donor or a commercial donor;

(l) "replacement donor" means a donor who is a family friend or a relative of the patient recipient.]

[596][(m) 'umbilical cord blood' is the whole blood including Hematopoietic Progenitor Cells collected from placental and or Umbilical cord blood vessels after the umbilical cord have been clamped.]

[597][(n) 'Erythrocytapheresis' means selective collection of one or two units of red cells from a donor or patient using a cell separator and retransfusing the remaining blood into the donor or patient.]

122F. Form of application for licence for operation of [598][Blood Centre]/ processing of whole human blood for components/manufacture of blood products for sale or distribution [596][, collection, processing, testing, storage, banking and release of umbilical cord blood stem cells],—(1)Application for the grant and/or renewal of licence for the operation of a [598][Blood Centre],/ processing of human blood for components/manufacture of blood products [596][/ Collection, processing, testing, storage, banking and release of umbilical cord blood stem cells] shall be made to the licensing authority appointed under Part VII in [599][Form 27C [600][, Form 27E or Form 27F], as the case may be,] and shall be accompanied by [601][licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred for every inspection thereof or for the purposes of renewal of licence]:

Provided that if the applicant applies for renewal of licence after its expiry but within six months of such expiry the fee payable for the renewal of the licence [601][shall be rupees six thousand and inspection fee of rupees one thousand and five hundred plus an additional fee at the rate of rupees one thousand per month or a part thereof in addition to the inspection fee]:

[602][Provided further that a licensee holding a licence in Form 28C, Form 28E or Form 28F as the case may be, for operation of [598][Blood Centre]/processing of whole human blood for components/manufacture of blood products/collection, processing, testing, storage, banking and release of umbilical cord blood stem cells shall apply for grant of licence under sub-rule (1) before the expiry of the said licence on Form 27C, Form 27E or Form 27F as the case may be, and he shall continue to operate the same till the orders on his application are communicated to him.]

[603][***]

(2) A fee of rupees [604][one thousand] shall be paid for a duplicate copy of a licence issued under this rule, if the original is defaced, damaged or lost.

(3) Application by a licensee to manufacture additional drugs listed in the application shall be accompanied by fee of [605][rupees three hundred] for each drug listed in the application.

(4) On receipt of the application for the grant or renewal of such licence, the licensing authority shall,—

(i) verify the statements made in the application form.

(ii) cause the manufacturing and testing establishment to be inspected in accordance with the provision of rule 12.2.1; and

(iii) in case the application is for renewal of licence, call for informations of past performance of the licensee.

(5) If the licensing authority is satisfied that the applicant is in a position to fulfil the requirements laid down in the rules, he shall prepare a report to that effect and forward it [606][alongwith the application and the licence (in triplicate) to be granted or renewed, duly completed] to the Central Licence Approving Authority:

Provided that if the licensing authority is of the opinion that the applicant is not in a position to fulfil the requirements laid down in these rules, he may, by order, for reasons to be recorded in writing, refuse to grant or renew the licence, as the case may be.

(6) If, on receipt of the application and the report of the licensing authority referred to in sub-rule [607][(5)] and after taking such measures including inspection of the premises, by the Inspector, appointed by the Central Government under section 21 of the Act, and/or along with the Expert in the field concerned if deemed necessary, the Central Licence Approving Authority, is satisfied that the applicant is in a position to fulfil the requirements laid down in these rules, he may grant or renew the licence, as the case may be:

Provided that if the Central Licence Approving Authority is of the opinion that the applicant is not in a position to fulfil the requirements laid down in these rules he may, notwithstanding the report of the licensing authority, by order, for reasons to be recorded in writing, reject the application for grant or renewal of licence, as the case may be and shall supply the applicant with a copy of the inspection report.

122G. Form of licence for the operation of a [608][Blood Centre] /processing of whole human blood for components and [609][/manufacture of blood products/ collection, processing, testing, storage, banking and release of umbilical cord blood stem cells] and the conditions for the grant or renewal of such licence.—[610][(1)] A licence for the operation of a [608][Blood Centre] or for processing whole human blood for components and [609][/manufactureof blood products/ collection, processing, testing, storage, banking and release of umbilical cord blood stem cells] shall be issued in [611][Form 28C or Form 28E or [612][Form 28F or Form 26G or Form 26-I or Form 26], as the case may be, before a licence in Form 28C or Form 28E or Form 28F or Form 26G or Form 26-I or Form 26J], as the case may be] is granted or renewed the following conditions shall be complied with by the applicant:—

[613][(i) The operation of Blood Centre or processing or both of whole human blood for components shall be conducted under the active direction and personal supervision of competent technical staff consisting of at least one person who is whole time employee and who is Medical Officer, and possessing—

(a) Degree in Medicine M.B.B.S. having experience of working in Blood Centre, not less than one year during regular service and also has adequate knowledge and experience in blood group serology, blood group

methodology and medical principles involved in the procurement of blood or preparation of its components or both; or

(b) Degree in Medicine M.B.B.S. with Diploma in Clinical Pathology or Diploma in Pathology and Bacteriology with six months' experience in a licensed Blood Centre; or

(c) Degree in Medicine M.B.B.S. with Diploma in Transfusion Medicine or Diploma in Immunohematology or Blood Transfusion with three months' experience in a licensed Blood Centre; or

(d) Doctor of Medicine Pathology or Diplomate of National Board Pathology with three months' experience in a licensed Blood Centre; or

(e) Postgraduate degree in Transfusion Medicine - Doctor of Medicine Transfusion Medicine or Diplomate of National Board Transfusion Medicine, Doctor of Medicine Immunohematology and Blood Transfusion,the degree or diploma being from a University recognized by the Central Government or State Government.

Explanation. —For the purposes of this condition, the experience in Blood Centre shall not apply in the case of persons who are approved by the Licensing Authority or Central Licence Approving Authority or both prior to the commencement of the Drugs and Cosmetics (Second Amendment) Rules, 1999.]

(ii) The applicant shall provide adequate space, plant and equipment for any or all the operations of blood collection or blood processing. The space, plant and equipment required for various operations is given in Schedule F, Part XIIB and/or XIIC [614][or XIID],

(iii) The applicant shall provide and maintain adequate technical staff as specified in Schedule F, Part XIIB and/or XIIC [614][or XIID].

(iv) The applicant shall provide adequate arrangements for storage of whole human blood, human blood components and blood products.

(v) The applicant furnish to the licensing authority, if required to do so, data on the stability of Whole Human Blood, its components or blood products

which are likely to deteriorate, for fixing the date of expiry which shall be printed on the labels of such products on the basis of the data so furnished.

[615][(2) Applications for grant or renewal of license for operation of Blood Centre or processing of Human blood components shall be made by the Blood Centre run by the Government, Indian Red Cross Society, Hospital, Charitable Trust or Voluntary organization and Blood Centre run by Charitable Trust or Voluntary organization need to be approved by a State or Union territory Blood Transfusion Council as per procedure laid down in this regard by the National Blood Transfusion Council.

Explanation:—For the purpose of this sub-rule, "renewal" shall include renewal of any license issued after the commencement of the Drugs and Cosmetics (Sixth Amendment) Rules, 2005).]

122H. Duration of licence.—An original licence in [616][Form 28C or Form 28E [614][or Form 28F] or a renewed licence in Form 26G or Form 26-I] [617][or Form 26J] unless sooner suspended or cancelled shall be [620][valid for a period of five years on and from the date on which] it is granted or renewed.

122-I. Inspection before grant or renewal of licence for operation of [621][Blood Centre], processing of whole human blood for components and manufacture of blood products.—Before a licence in [616][Form 28C or Form 28E [618][or Form 28F] is granted or a renewal of licence in Form 26G or Form 26-I [619][or Form 26J] is made, as the case may be,] the licensing authority or the Central Licence Approving Authority, as the case may be, shall cause the establishment in which [621][Blood Centre] is proposed to be operated /whole human blood for component is processed [622][/] blood products are manufactured to be inspected by one or more inspectors, appointed under the Act and/or alongwith the Expert in the field concerned. The Inspector or Inspectors shall examine all portions of the premises and appliances/equipments and inspect the process of manufacture intended to be employed or being employed alongwith the means to be employed or being employed for operation of [621][Blood Centre]/processing of whole human blood for components/manufacture of blood products together with their [622][testing] facilities and also enquire into the professional qualification of the expert staff and other technical staff to be employed.

122J. Report by Inspector.—The Inspector or Inspectors shall forward a detailed descriptive report giving his findings on each aspect of inspection along with his recommendation in accordance with the provisions of rule 122-I to the licensing authority or to the Central Licence Approving Authority.

122K. Further application after rejection.—If within a period of six months from the rejection of application for a licence the applicant informs the licensing authority mat the conditions laid down have been satisfied and deposits an inspection [623][fee of rupees two hundred and fifty] the licensing authority may, if after causing further inspection to be made is satisfied that the conditions for the [624][grant or renewal of a licence have been complied with, shall grant or renew the licence in Form 28C or Form 28E [625][or Form 28F]:

Provided that in the case of a drug notified by the Central Government under rule 68A, the application, together with the inspection report and the Form of licence (in triplicate to be granted or renewed), duly completed shall be sent, to be Central Licence Approving Authority, who may approve the same and return it to the licensing authority of issue for the licence.]

122L. Delegation of powers by the Central Licence Approving Authority.— The Central Licence Approving Authority may, with the approval of the Central Government, by notification delegate his powers of signing licence and any other power under rules to persons under his control having same qualifications as prescribed for controlling authority under rule 50A, for such areas and for such periods as may be specified.

122M. Provision for appeal to the State Government by a party whose licence has not been granted or renewed.—Any person who is aggrieved by the order passed by the licensing authority or Central Licence Approving Authority as, the case may be, may within thirty days from the date of receipt of such order, appeal to the State Government or Central Government, as the case may be, after such enquiry, into the matter as it considers necessary and after giving the said person an opportunity for representing his view in the matter may pass such order in relation thereto as it thinks fit.

122N. Additional information to be furnished by an [626][applicant] for licence or by a licensee to the licensing authority.—The applicant for the grant of licence or any person granted a licence under the Part shall, on demand furnish to the licensing authority, before the grant of the licence or during the

period the licence is in force, as the case may be, documentary evidence in respect of the ownership or occupation, rental or other basis of the premises, specified in the application for licence or in the licence granted, constitution of the firm or any other relevant matter, which may be required for the purpose of verifying the correctness of the statement made by the applicant or the licensee, while applying for or after obtaining the licence, as the case may be.

122-0. Cancellation and suspension of licences.—(1) The licensing authority or Central Licence Approving Authority may for such licences granted or renewed by him after giving the licensee an opportunity to show cause by such an order should not be passed by an order in writing stating the reason thereof, cancel a licence issued under this part or suspend it for such period as he thinks fit, either wholly or in respect of some of the substances to which it relates, [627][or direct the licensee to stop collection, storage, processing, manufacture and distribution of the said substances and [628][thereupon order the destruction of substances and] stocks thereof in the presence of an Inspector] if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provision of the Act or rules thereunder.

(2) A licensee whose licence has been suspended or cancelled may, within three months of the date of the order under sub-rule (1) prefer an appeal against that order to the State Government or Central Government, which shall decide the same.

122P. Conditions of licence.—[629][A licence in Form 28C, Form 28E, [630][Form 28F, Form 26G, Form 26-I or Form 26J shall be subject to the special conditions set out in Schedule F, Part XIIB and Part XIIC, Part XIID], as the case may be, which relate to the substance in respect of which the licence is granted or renewed and to the following general conditions, namely:—]

(i) (a) The licensee shall provide and maintain adequate staff, plantand premises for the proper operation of a [631][Blood Centre] for processing whole human blood, its components and/or manufacture of blood products.

(b) The licensee shall maintain staff, premises and equipment as specified in rule 122G. The licensee shall maintain necessary records and registers as specified in Schedule F, Part XIIB and XIIC.

(c) The licensee shall test in his own laboratory whole human blood, its components and blood products and [632][maintain records and] registers in respect of such tests as specified in Schedule F, Parts XIIB and XIIC [633][or XIID], The records and register shall be maintained for a period of five years from the date of manufacture.

(d) The licensee shall maintain/preserve reference [634][sample and] supply to the Inspector the reference sample of the whole human blood collected by him in an adequate quantity to conduct all the prescribed tests. The licensee shall supply to the Inspector the reference sample for the purpose of testing.

(ii) The licensee shall allow an Inspector appointed under the Act to enter, with or [635][without] prior notice, any premises where the activities of the [631][Blood Centre] are being carried out, for the processing of whole human blood and/or blood products, to inspect the premises and plant and the process of manufacture and the mean employed for standardising and testing the substance.

(iii) The licensee shall allow an Inspector appointed under the Act to inspect all registers and records maintained under these rules and to take samples of the manufactured product and shall supply to Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and Rules thereunder have been observed.

(iv) The licensee shall from time to time report to the licensing authority any changes in the expert staff responsible for the operation of a [631][Blood Centre]/processing of whole human blood for components and/ or manufacture of blood products and any material alterations in the premises or plant used for that purpose which have been made since the date of last inspection made on behalf of the licensing authority before the grant of the licence.

(v) The licensee shall on request furnish to the licensing authority, or Central Licence Approving Authority or to such authority as the licensing authority, or the Central Licence Approving Authority may direct, from any batch unit of drugs as the licensing authority or Central Licence Approving Authority may from time to time specify, sample of such quantity as may be considered adequate by such Authority for any examination and, if so required, also furnish full protocols of the test which have been applied.

(vi) If the licensing authority or the Central Licence Approving Authority so directs, the licensee shall not sell or offer for sale any batch/unit in respect of which a sample is, or protocols are furnished under the last preceding sub-paragraph until a certificate authorising the sales of batch/unit has been issued to him by or on behalf of the licensing authority or the Central Licence Approving Authority.

(vii) The licensee shall on being informed by the licensing authority or the controlling authority that any part of any batch/unit of the substance has been found by the licensing authority or the Central Licence Approving Authority not to conform with the standards of strength, quality or purity specified in these rules and on being directed so to do, withdraw, from sales and so far as may in the particular circumstances of the case be practicable recall all issues already made from that batch/unit.

(viii) No drug manufactured under the licence shall be sold unless the precautions necessary for preserving its properties have been observed throughout the period after manufacture. Further no batch/ unit manufactured under this licence shall be supplied/distributed to any person without prescription of Registered Medical Practitioner.

(ix) The licensee shall comply with the provisions of the Act and of these rules and with such further requirements, if any, as may be specified in any rules subsequently made under Chapter IV of the Act, provided mat where such further requirements are specified in the rules, these would come in force four months after publication in the Official Gazette.[636]

(x) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impression and defects noticed.

(xi) The licensee shall destroy the stocks of batch/unit which does not comply with standard tests in such a way that it would not spread any disease/infection by way of proper disinfection method.]

[637][(xii) All bio-medical waste shall be treated, disposed off or destroyed as per the provisions of the Bio-Medical Wastes (Management and Handling) Rules, 1996.

(xiii) The licensee shall neither collect blood from any professional donor or paid donor nor shall he prepare blood components and/or manufacture blood products from the blood drawn from such a donor.]

[638][(xiv) The whole human blood and blood components may be transferred, under prescribed storage conditions, to another blood bank which have facilities to store and monitor blood distribution.

(xv) The recipient [639][blood centres] shall not further transfer units obtained from another [640][blood centre] except to another blood storage centre or a patient.]

PART XI
EXEMPTIONS

123. The drugs specified in Schedule K shall be exempted from the provisions of Chapter IV of the Act and the rules made thereunder to the extent and subject to the conditions specified in that Schedule.

PART XII
STANDARDS

[641]**[124.Standards of drugs.** (1) Drugs included in the Indian Pharmacopoeia:

(a) The standards for identity, purity and strength shall be those as may be specified in the edition of the Indian Pharmacopoeia for the time being in force.

(b) In case the standards for identity, purity and strength for drugs are not specified in the edition of the Indian Pharmacopoeia for the time being in force but are specified in the edition of the Indian Pharmacopoeia immediately preceding, the standards for identity, purity ana strength shall be those occurring in such immediately preceding edition of the Indian Pharmacopoeia.

(2) For other drugs:

(a) The standards for identity, purity and strength shall be those as may be specified in the edition of the official pharmacopoeia, or the time being in force, of any country to which the drug claims to comply with.

(b) In case the standards for identity, purity and strength for drugs are not specified in the edition of such official pharmacopoeia, for the time being in force, but are specified in the edition immediately preceding, the standards for identity, purity and strength shall be those occurring in such immediately preceding edition of such official pharmacopoeia to which the drug claims to comply with.

(c) For drugs for which standards are not included in the edition of the official pharmacopoeia, for the time being in force, of any country or in its edition immediately preceding but included in the official compendia of drugs standards, namely:—

The British Pharmaceutical Codex or the National Formulary of the United States, for the time being in force, to which the drug claims to comply with.]

[642][***]

[643]**[124B. Standards for patent or proprietary medicines.**—The standards for patent or proprietary medicines shall be those laid down in Schedule V and such medicines shall also comply with the standards laid down in the Second Schedule to the Act.]

[644]**[124C. Standards for Surgical Dressings.—**The standards for Surgical Dressings shall be such as are laid down in Schedule F(II).]

[645]**[124D. Standards for Sterilised Umbilical tapes.—**The standards for Sterilised Umbilical tapes shall be as laid down in Schedule F(III).]

[646]**[125. Standards for substances (other than food) intended to affect the structure or any function of human body—Contraceptives.**—(1) The standards for mechanical contraceptives shall be such as are laid down in Schedule R.

(2) The standards which other contraceptives will have to comply with shall be in conformity with the formulae approved as safe and efficacious by the

Central Government. Such formula shall be displayed on the label of every container of such contraceptive.]

[647][**125A. Standards for Medical Devices.**—The standards for the Medical Devices shall be such as are laid down in Schedule Rl.]

[648][**126. Standards for substances intended to be used for the destruction of vermin or insects which cause** [649][***] **disease in human beings or animals—Disinfectants.**—The standards for disinfectants shall be such as are laid down in Schedule O.]

[650][**126A.Standards for ophthalmic preparations** [651][**including Homoeopathic ophthalmic preparations].—**The standards for ophthalmic preparations including Homoeopathic ophthalmic preparations] shall be those laid down in Schedule FF, and such preparations shall also comply with the standards set out in the Second Schedule to the Act.]

[652][**127. List of colours permitted to be used in drugs.**—**(1)** No drug shall contain a colour other than that specified below:

(1) *Natural Colours*

Annatto
Carotene
Chlorophyll
Cochineal
Curcumin
Red Oxide of iron
Yellow Oxide of iron
[653][Titanium Oxide]
[654][Black Oxide of Iron]
[655][Titanium dioxide coated mica pearlescent pigments]

(2) *Artificial Colours*

Caramel
[656][Riboflavin]

(3) *Coal Tar Colours*

Common name of the Colour	Colour Index Number	Chemical Name
1	2	3
GREEN		
Quinazarine Green SS	61565	1, 4-bis (p-Toluino)-anthraquinone.
Alizarin Cyanine Green F	61570	Disodium salt of 1, 4-bis(O-sulfo-p-toluino) anthraquinone.
[657][Fast Green FCF	42053	Disodium salt of 4-{[4-(N-ethyl- p-sulfobenzyl-amino)-phenyl-]-(4-hydroxy-2-sulfonium-phenyl) methylene) [1-N-ethyl-N-p-sulfobenzyl] 1*2, 5, cyclohexa-dienimine]
[658][***]		
YELLOW		
Tartrazine	19140	Trisodium salt of 3-carboxy-5-hydroxy-1- p-sulfophenyl-4-p sulfophenyl azopyrazole.
Sunset Yellow FCF	15985	Disodium salt of 1-p sulfophenyl-azo-2-naphthol-6-sulfonic acid.
[659][Quinoline Yellow WS RED	47005	Disodium salt of disulfonic acid of 12-(2-quinolyl)-l/ 3-indandione.]
[660][***]		
Erythrosine	45430	Disodium salt of 9-0-carboxyphenyl -6-hydroxy 2,4,5,7-tetraiodo-3-isoxanthone.
Eosin YS or Eosine G	45380	Disodium salt of 2, 4, 5, 7-Tetrabrome-9-p-carboxyphenyl-6-hydroxy-3-isoxanthone.
Toney Red or Sudan III	26100	l-p-phenylazophenylazo-2-napnthol.
Ponceau 4 R	16255	Trisodium salt of l-(4-sulpho-l-l-napth y lazo)-2-naphthol-6:3-disulphonic acid.
Carmoisine	14720	Disodium salt of 2-(4-sulph-l-napthylazo)-l-naphthol-4-sulphonic acid.
[660][***]		
[1335][Allura Red	16035	Disodium 6-hydroxy-5-[(2-methoxy-5-methyl-4-sulfophenyl)azo]-2-Naphthalenesulfonic acid]
BLUE		

Indigo Carmine	73015	Disodium salt of indigotin-5:-5 Disulphonic Acid.]
[661][Brillium Blue FCF	42090	Disodium salt of 4{ [4-(N-ethyl-p- sulpho-benzylamino-phenyl-(2-sulphoniumphenyl)-inethylene]-l-(N-ethyl-N-p-sulfobenzyl)- *2*, 5-cyclohexa-dienomine]
[662][***]		
ORANGE		
Orange G	16230	Disodium salt on l-phenylazo-2-naphthol 6, 8-disulfonic acid.
BROWN		
Resorcin Brown	20170	Monosodium salt of 4-p-sulfophenylazo 2-(2, 4-xylozo)-l, 3-resorcinol.
BLACK		
Naphthol Blue Black.	20470	Disodium salt of 8-amino-7-p-nitrophenylazo-2-phenylazo-naphthol-3,6-disulfonic acid

(4) *Lakes*

The aluminium or calcium salts (lakes) of any of the water-soluble colours listed above:

[663][Provided that in case of disinfectants, in addition to the above said colours, the colours referred in IS 4707 (Part I) as amended by Bureau of Indian Standards from time to time or any of the colours listed in the table below, which is non-staining shall be permissible to use.

Serial Number	**Common name of colour**	**Colour Index Number**	**Chemical name of colour**
(1)	(2)	(3)	(4)
1.	Guinea Green B	42085	Monosodium salt of 4-(N-ethyl-p-sulfobenzylamino)–diphenylmethylone-(1-(N-ethyl-N-p-sulfoniumbenzyl)Δ 2,5-cyclohexadienimine).
2.	Light Green SF Yellowish	42095	Disodium salt of 4-[4-(N-ethyl-p-sulfobenzylamine)-phenyl)-4-sulphoniumphenyl) methylene]-2(-(N-ethyl-N-sulfobenzyl) Δ 2,5-Cyclohexadienimine.
3.	Tartrazine	19140	Trisodium salt of 3-carboxy-5-

Serial Number	Common name of colour	Colour Index Number	Chemical name of colour
(1)	(2)	(3)	(4)
			hydroxy-1-p-sulfophenyl-4-p-sulfophenylazo-pyrazole.
4.	Sunset yellow FCF	15985	Disodium salt of 1-p-sulfophenylazo-2- naphthol-6-sulfonicacid.
5.	Ponceau 3R	16155	Disodium salts of a mixture of 1-alkyl- phenylazo-2-napthol 3, 6-disulfonic acids.
6.	Amarnath.	16185	Trisodium salt of 1-(4-sulfo-1-napthylazo) 2-naphthol 3, 6-disulfonic acid.
7.	Erythrosine.	45430	Disodium salt of 9-0-carboxyphenyl-6- hydroxy 2,4,5, 7-tetraiodo-3- isoxanthone.
8.	Ponceau SX.	14700	Disodium salt of 2-(5 sulfo-2, 4-xylyl- azo)-1-naphthol-4-sulfonic acid.
9.	Brilliant Blue FCF	42090	Disodium salt of 4-(9-4-(N-ethyl-p-sulfobenzylamino)-phenyl)-2-sulfonium phenyl)- methylene)-(1-(N-ethyl-N-p-sulfobenzyl)-Δ 2, 5-cyclohexadienimine).
10.	Indigocarmine.	73015	Disodium salt of 5,5'-indigotindisulfonic acid.
11.	Wool Violet 5 BN (Acid- violet 6B)	42640	Monosodium salt of 4-(N-ethyl-p-sulfobenzylamino)-phenyl)-(4- (N-ethyl-p-(sulfonium-benzylamine)-phenyl) methylene)-(N, N- dimethyl-Δ 2,5-cyclohexadienimine)
12.	Light Green SF Yellowish	42095	Calcium salt of 4-(4-(N-ethyl-p-sulfobenzyl) (minophenyl) (4- sulfonium-phenyl)methylene), (1-(N-ethyl-N-p-sulfobenzyl)-Δ2,5-cyclohexadienimine).
13.	Alizarin Cyanine Green F	61570	Disodium salt of 1,4-bis (O-sulfo-p-toluino) anthraquinone
14.	Quinazarine Green SS	61565	1,4-bis-(p-Toluino)-anthraquinone
15.	Fast Green FCF	42053	Disodium salt of 4-(4-(ethyl-p-sulfobenzylamino)-phenyl) (4-hydroxy-2 sulphoniumphenyl) methylene)-(1-N-ethyl-N-p-sulfobenzyl) Δ 2, 5, cyclohexadienimine).
16.	Acid Fast Green	42100	Monosodium salt of 4-(4-N-ethyl-p-sulfobenzylomino) phenyl)- (o-chlorophenyl)-methylene)- 1-(N-ethyl-N- p-sulfonium benzyl- Δ 2,5, cyclohexadienimine).
17.	Pyranine	59040	Trisodium salt of 10-hydroxy-3,5,8-

Serial Number	Common name of colour	Colour Index Number	Chemical name of colour
(1)	(2)	(3)	(4)
	Concentrated		pyrene-trisulfonic Acid
18.	Quinoline Yellow WS	47005	Disodium indandione.
19.	Quinoline Yellow SS	47000	2-(2-quinolyl)-1, 3 indandiene.
20.	Poneceau 2 R	16150	Disodium salt of 1-xylylazo-2-naphthol-3, 6-disulfonic acid.
21.	Lithol Rubin B.	15850	Monosodium salt of 4-(o-sulfo-p-tolylazo)3 hydroxy-2-naphthoic acid.
22.	Lithol Rubin BCA	15850	Calcium salt of 4-(o-sulfo-p-tolylazo)-3-hydroxy-2-naphthoic acid
23.	Lake Red D.	15500	Monosodium salt of 1-0-carboxyphenylazo-2-naphthol.
24.	Lake Red DBA	15500	Barium salt of 1-o-carboxyphenylazo-2-naphthol.
25.	Lake Red DCA.	15500	Calcium salt of 1-o-carboxyphenylazo-2-naphthol.
26.	Toney Red.	26100	I-p-phenylazophenylazo-2-naphthol.
27.	Oil Red OS.	26125	I-Xylylazoxylylazo-2-napththol
28.	Tetrabromofluorescein	45380	2,4,5,7-Tetrabromo-3, 6-flurandiol.
29.	Eosin TS	45380	Disodium salt of 2,4,5,7-tetrabromo-9-0 carboxyphenyl-6- hyroxy-3-isoxanthone.
30.	Eosin YSK.	45380	Dipotassium salt of 2,4,5,7-tetrabromo-9-0 carboxyphenyl-6-hyroxy-3-isoxanthone
31.	Tetrachlorofluorescein NA	45366	2,4,5,7- tetrachloro-S, 6-Fluorandiol
32.	Tetrachlorofluorescein K.	45366	Disodium salt of 9-0-carboxyphenyl-2,4,5,7-tetrachloro-6- hydroxy-3-isoxanthone.
33.	Tetrachloro Tetrabromo fluorescein	45410	2,4,5,7-Tetrabromo-12,13,14,15-tetrachloro-3, 6-fluorandiol.
34.	Phloxine B	45410	Disodium salt of 2,4,5,7-tetrabromo-9 (3,4,5,6-tetra chloro- o-carboxyphenyl)-6-hydroxy-3-isoxanthone
35.	Bluish Orange T.R.	45457	1,4,5,8, 15-Pentabromo-2, 7-dicarboxy-3, 6-fluoran diol.
36.	Helindone Pink CN.	73360	5, 5-Dichloro-3, 3‘ dimethyl-thioindigo
37.	Deep Maroon (Fanchon Maroon)	15880	Calcium salt of 4-(I-sulfo-2-naphthylazo 3- hydroxy-2- naphthoic

Serial Number	Common name of colour	Colour Index Number	Chemical name of colour
(1)	(2)	(3)	(4)
			acid.
38.	Toluidine Red. .	12120	1-(o-Nitro-p-tolylazo)-2-naphthol.
39.	Flaming Red.	12085	I- (o-Chloro-p-nitrophenylazo)-2-naphthol
40.	Deep Red (Maroon).	12350	3-Hydroxy-N- (m-nitrophenyl)-4-(o-nitro-p-tolylazo)-2- naphthamide.
41.	Alba Red.	13058	o-(p,β,β-Dihydroxy-diethylamino)-phenylazo)-benzoic acid.
42.	Orange G.	16230	Disodium salt of 1-phenylazo-2-naphthol-6-8-disulfonic acid
43.	Orange II	15510	Monosodium salt of 1-p-sulfophenylazo-2-naphthol.
44.	Dichlorofluorescein	45365	4,5-Dichloro-3, 6-fluorandiol.
45.	Dichlorofluorescein. NA	45365	Disodium salt of 9-o-carboxyphenyl-1-4,5- dichloro-6- hydroxy-3-isoxanthone
46.	Diiodofluorescein.	45425	4,5 –Diiodo-3, 6-fluorandiol
47.	Erythrosine Yellowish NA.	45425	Disodium salt of 9-o-carboxyphenyl-6-hydroxy-4, 5- diiodo-3-isoxanthone.
48.	Erythrosine Yellowish K.	45425	Dipotassium salt of 9-o-carboxyphenyl-6-hydroxy-4, 5- diiodo-3-isoxanthone.
49.	Erythrosine Yellowish NH	45425	Dipotassium salt of 9-o-carboxyphenyl-6-hydroxy-4, 5- diiodo-3-isoxanthone
50.	Orange TR	45456	4,5, 15-Tribromo 2, 7-dicarboxy-3, 6-fluorandiol.
51.	Alizarin.	58000	1,2- Anthraquinonediol.
52.	Dibromodiiodofluorescein.	45371	4 ,5- Dibromo-2, 7-diiodo-3, 6-fluorandiol.
53.	Alphazurine FG.	42090	Diammonium salt of 4-(N-ethyl-p-sulfobenzyl amino)- phenyl)-(2-sulfoniumphenyl)-Methytlene)-(-(1 (N-ethyl-N- p-sulfobenzyl) Δ 2 ,5-cyclohexadienimine).
54.	Allarin Astrol B.	61530	Monosodium salt of 1-methylamino-4-(o-sulfo-p-toluino)- anthroquinone.
55.	Indigo.	73000	Indigotin.
56.	Patent Blue NA.	42052	Monosodium salt of 4-(4- (N-ethyl-benzyl-amino)-phenyl – (5-hydroxy-4-sulfo-2-sulfoniumphenyl-methylene)(N-ethyl- Benzyl- Δ 2, 5-cyclohexadienimine).
57.	Patent Blue CA.	42052	Calcium salt of 4-(4- (N-ethyl- benzyl-amino)-phenyl)-(5 hydroxy-4-sulfo-2-

Serial Number	Common name of colour	Colour Index Number	Chemical name of colour
(1)	(2)	(3)	(4)
			sulfoniumphenyl, methylene)- (N-ethyl- N-benzyl- Δ 2- 5-cyclohexadienimine).
58.	Carbrantherene Blue	69825	3, 3- Dichloroindanthrene.
59.	Napthol Blue Black	20470	Disodium salt of 8-amino-7-p-nitrophenylazo 3- phenylazo-1-naphthol-3, 6-disulfonic acid
60.	Alizurol purple SS	60725	I-hydroxy-4-p-toluino-anthraquinone.
61.	Acid Red 89	23910	----
62.	Acid Red 97	22890	----
63.	Acid Blue 1	42045	----
64.	Food Blue 3	42045	----
65.	Natural Orange	75480	----
66.	Solvent Blues 4	44045	----
67.	Solvent Yellow 18	12740	----
68.	Food Yellow 12.	12740	----
69.	Solvent Yellow 32.	48045	----
70.	Fanchon Yellow (Hansa Yellow G).	11680	(α) -(O-Nitro-p-tolylazo) accetoacetanilide]

(2) The label on the container of a drug containing a permitted colour shall indicate the common name of the colour [664][except gelatine capsules wherein approved or permitted colour shall be used].]

128. The following rules are hereby repealed except as respects things done or omitted to be done under those rules, namely:—

Andhra Pradesh Drugs Rules, 1945.
Assam Drugs Rules, 1945.
Bihar Drugs Rules, 1945.
Bombay Drugs Rules, 1946.
East Punjab Drugs Rules, 1945.
C.P. & Berar Drugs Rules, 1945.
Madras Drugs Rules, 1945.
Orissa Drugs Rules, 1945.
Rajasthan Drugs Rules, 1953.
Saurashtra Drugs Rules, 1953.
Travancore-Cochin Drugs Rules, 1953.
United Provinces Drugs Rules, 1945.

West Bengal Drugs Rules, 1946.
[665][Mysore Drugs Rules, 1954.]

PART XIII

[666] [***]

PART XIV

[667][***]

PART XV

[668][***]

[669][PART XV(A)

APPROVAL OF INSTITUTIONS FOR CARRYING OUT TESTS ON DRUGS, [670][***] AND RAW MATERIALS USED IN THEIR MANUFACTURE ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF DRUGS/ [674][***] [671][OR AN INDIVIDUAL OR ORGANISATION OR PROCUREMENT AGENCY]]

150B. Application for grant of approval for testing drugs/[672][***].—(1) Application for grant [673][***] of approval for carrying out tests for identity, purity, quality and strength of drags [674][***] or the raw materials used in the manufacture thereof on behalf of licensees for manufacture [675][for sale of drugs [676][***] or an individual or organisation or procurement agency shall be made in Form 36] to the licensing authority appointed by the State Government for the purposes of Part VII, VII(A) or XIV of these rules, as the case may be and referred to as the "approving authority" under this Part and shall be accompanied by an inspection fee of [678][rupees six thousand] in the case of testing of drugs specified in Schedules C and C (1) and [678][rupees one thousand and five hundred] in the case of testing of drugs other than those specified in Schedules C and C (1), homoeopathic drugs [676][***]:

Provided that the applicant shall furnish to the approving authority such additional information as may be required by him in connection with the application in Form 36:

[677][***]:

[679][(2) A separate application shall be made for grant of approval for carrying out tests on additional categories of drugs or items of [680][***] and shall be accompanied by an inspection fee of rupees one thousand and five hundred in the case of drugs specified in Schedule C and Schedule C(l) and rupees one thousand each in case of drugs other than those specified in Schedule C and Schedule C(l). Homoeopathic medicines [681][***].

Explanation.—For the purpose of this Part, the words 'drugs' [3][***] shall also mean and include raw materials used in the manufacture of drugs including homoeopathic drugs [682][***], as the case may be.]

150C. Form in which approval to be granted for carrying out tests on drugs/ [680][***] on behalf of licensees for manufacture of drugs/ [680][***] [683][or for an individual or organisation or procurement agency] and conditions for grant [684][***]of such approval.—(1) Approval for carrying out such tests of identity, purity, quality and strength of drugs [685][***] required under the provisions of these rules, on behalf of licensee for manufacture of drugs [682][***][683][or an individual or organisation or procurement agency] shall be granted in Form 37.

(2) Before approval in Form 37 is granted [686][***], the following conditions shall be complied with by the applicant:—

(1) The premises where the tests are being carried on shall be well lighted and properly ventilated except where the nature of tests of any drug [682][***] warrants otherwise. Whenever necessary, the premises shall be air-conditioned so as to maintain the accuracy and functioning of laboratory instruments or to enable the performance of special tests such as sterility tests, microbiological tests, etc.

(2) The applicant shall provide adequate space having regard to the nature and number of samples of drugs [682][***] proposed to be tested:

Provided that the approving authority shall determine from time to time whether the space provided continues to be adequate.

(3) If it is intended to carry out test requiring the use of animals, the applicant shall provide for an animal house and comply with the following requirements: —

(a) The animal house shall be adequate in area, well lighted and properly ventilated and the animals undergoing tests shall be kept in air-conditioned area.

(b) The animals shall be suitably housed in hygienic surroundings and necessary provision made for removal of excreta and foul smell.

(c) The applicant shall provide for suitable arrangements for preparation of animal feed.

(d) The applicant shall provide for suitable arrangements for quarantining of all animals immediately on their receipt in the institution.

(e) The animals shall be periodically examined for their physical fitness.

(f) The applicant shall provide for isolation of sick animals as well as animals under test.

(g) The applicant shall ensure compliance with the requirements ofthe Prevention of Cruelty to Animals Act, 1960 (59 of 1960).

(h) The applicant shall make proper arrangements for the disposalof the carcasses of animals in a manner as not to cause hazardto public health.

(4) The applicant shall provide and maintain suitable equipment having regard to the nature and number of samples of drugs [687][***] intended to be tested which shall be adequate in the opinion of the approving authority.

(5) The testing of drugs [688][***], shall be under the active direction of a person whose qualifications and experience are considered adequate in the opinion of the approving authority and who shall be held responsible for the reports of test or analysis issued by the applicant.

(6) The testing of drugs [688][***], for identity, purity, quality and strengthshall be carried out by persons whose qualifications and

experience of testing are adequate in the opinion of the approving authority.

(7) The applicant shall provide books of standard recognised under the provisions of the Act and the rules made thereunder and such books of reference as may be required in connection with the testing or analysis of the products for the testing of which approval is applied for.

[689][**150D. Duration of approval.**—(1) A licence issued under Form 37 shall remain valid if the licencee deposits a licence retention fee referred to in sub-rule (2) before the expiry of period of every succeeding five years from the date ofits issue, unless, it is suspended or cancelled by the licensing authority.

(2) The licence retention fee referred to in sub-rule (1) shall be equivalent to the respective fee required for the grant of such licence.

(3) If the licence holder fails to pay licence retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay licence retention fee along with a late fee calculated at the rate of two per cent, of the licence fee for every month or part thereof up to six months, and in the event of non-payment of such fee, the licence shall be deemed to have been cancelled.]

150E.Conditions of approval.—An approval in Form 37 shall be subject to the following general conditions:—

(a) The institution granted approval under this Part (hereinafter referred to as the approved institution) shall provide and maintain an adequate staff and adequate premises and equipment as specified in rule 150C [690][and Schedule L-l].

(b) The approved institution shall provide proper facilities for storage so as to preserve the properties of the samples to be tested by it.

(c) The approved institution shall maintain records of tests for identity, purity, quality and strength carried out on all samples of drugs, [691][***] and the results thereof together with the protocols of tests showing the readings and calculation in such form as to be available for inspection and such records shall be retained in the case of substances for which an expiry

date is assigned for a period of two years from the expiry of such date and in the case of other substances for a period of six years.

(d) The approved institution shall allow the Inspector appointed under this Act to enter with or without prior notice the premises where the testing is carried on and to inspect the premises and the equipment used for test and the testing procedures employed. The institution shall allow the Inspectors to inspect the registers and records maintained under these rules and shall supply to such Inspectors such information as they may require for the purpose of ascertaining whether the provisions of the Act and rules made thereunder have been observed.

(e) The approved institution shall from time to time report to the approving authority any changes in the person-in-charge of testing of drugs [691][***] or in the expert staff responsible for testing as the case may be and any material alterations in the premises or changes in the equipment used for the purposes of testing which have been made since the date of last inspection made on behalf of the approving authority before the grant [692][***] of approval.

[693][(f) The approved institution shall furnish reports of the results of test or analysis on the samples received from manufacturer in Form 39 and from an individual or organisation or procurement agency in Form 39A.]

(g) In case any sample of a drug [694][***] is found on test to be not of standard quality, the approved institution shall furnish the approving authority [695][and the licensing authority of the State where the manufacturer and/or sender of the drug [691][***] is located] with a copy of the test report on the sample with the protocols of tests applied.

(h) The approved institution shall comply with the provisions of the Act and rules made thereunder and with such further requirements, if any, as may be specified in the rules subsequently made under Chapter IV of the Act of which the approving authority has given the approved institution not less than four months' notice.

(i) The approved institution shall maintain an Inspection Book to enable the Inspector to record his impressions or defects noticed.

150F. Inspection before grant of approval.—Before an approval in Form 37 is granted, the approving authority shall cause the institution at which the testing of drugs [696][***] is proposed to be earned out to be inspected jointly by the Drugs Inspectors of the Central Drugs Standard Control Organisation and the State Drugs Control Organisation who shall examine the premises and the equipment intended to be used for testing of drugs [697][***] and inquire into the professional qualifications of the expert staff to be employed.

150G. Report of Inspection.—The Drugs Inspector mentioned in rule 150F shall forward to the approving authority a detailed report of the results of the inspection.

150H. Procedure of approving authority.—(1) If the approving authority after such further **enquiry,** if any, as he may consider necessary, is satisfied that the requirements of the rules made under the Act have been complied with and that the conditions of the approval and the rules made under the Act will be observed, he shall grant an approval in Form 37.

(2) If the approving authority is not so satisfied, he shall reject the application and shall inform the applicant of the reasons for such rejection and of the conditions which must be satisfied before an approval could be granted.

150-I. Further application after rejection.—If within a period of six months from the rejection of an application for approval, the applicant informs the approving authority that the conditions laid down have been satisfied and deposits inspection fee of [698][rupees two hundred and fifty], the approving authority may, if, after causing a further inspection to be made, he is satisfied that the conditions for grant of approval have been complied with, grant the approval in Form 37.

150-J. [699]**[***]**

150K. Withdrawal and suspension of approvals.—(1) The approving authority may, after giving the approved institution an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, withdraw an approval granted under this Part or suspend it for such period as he thinks fit either wholly or in respect of some of the categories of drugs [700][***] to which it relates, if in his opinion the approved institution

had failed to comply with any of the conditions of the approval or with any provision of the Act or the rules made thereunder.

(2) Any approved institution whose approval has been suspended or withdrawn may within three months of the date of the order, appeal to the State Government which shall dispose of the appeal in consultation with a panel of competent persons appointed by it in this behalf and notified in the Official Gazette.]

[701][PART XVI
MANUFACTURE FOR SALE OF AYURVEDIC [702][SIDDHA] OR UNANI DRUGS

151. Manufacture on more than one set of premises.—If Ayurvedic [703][Siddha] or Unani drugs are manufactured on more than one set of premises, a separate application shall be made and a separate licence shall be obtained in respect of each such set of premises.

152. Licensing authorities.—For the purpose of this Part the State Government shall appoint such licensing authorities and for such areas as may be specified in this behalf by notification in the Official Gazette.

[704]**[153. Application for licence to manufacture Ayurvedic, Siddha or Unani drugs.—(**1) An application for the grant of licence to manufacture for sale of Ayurvedic, Siddha or Unani drug, shall be made—

(a) as defined under clause (a) of section 3 of the Act, in Form 24D to the licensing authority alongwith a fee of rupees two thousand; and

(b) as defined in sub-clause (i) of clause (h) of section 3 of the Act, in Form 24D to the licensing authority alongwith a fee of mpees three thousand for the first ten products and after the said ten products, an additional fee of rupees two thousand per product, through the portal e-AUSHADHI (www.e-aushadhi.gov.in) as per the format provided in the said portal, pertaining to the licence for manufacture for sale of Ayurvedic, Siddha or Unani drugs.

Provided that this rule shall not be applicable to licence obtained under Form 25D prior to the date of commencement of the Drugs (4th Amendment) Rules, 2021 and such licence holder having a Good Manufacturing Practices

Certificate on the date of its renewal has to deposit a onetime licence retention fee of rupees one thousand for existing licenced drugs falling under clause (a) of section 3 of the Act; and rupees one thousand for first ten products and a fee at the rate of rupees one thousand per product over and above the said first ten products for existing licenced drugs falling under sub-clause (i) of clause (h) of section 3 of the Act.

Provided further that till the portal e-AUSHADHI (www.e-aushadhi.gov.in) shall come to effect [1343].[within twenty four months] of the commencement of the Drugs (4th Amendment) Rules, 2021 and during this period either of online and offline process of licence application shall be accepted.]

[705][**153A.Application for loan licence to manufacture Ayurvedic, Siddha or Unani drugs.**—(1) An application for grant of a loan licence to manufacture for sale of Ayurvedic, Siddha or Unani drug, shall be made—

(a) as defined under clause (a) of section 3 of the Act, in Form 24E to the licensing authority alongwith a fee of rupees two thousand; and

(b) as defined in sub-clause (i) of clause (h) of section 3 of the Act, in Form 24E to the licensing authority alongwith a fee of rupees three thousand for the first ten products and after the said ten products, an additional fee of rupees two thousand per product, through the portal e-AUSHADHI (www.e-aushadhi.gov.in) as per the format provided in the said portal, pertaining to the loan licence for manufacture for sale of Ayurvedic, Siddha or Unani drugs:

Provided that this rule shall not be applicable to licence obtained under Form 25E prior to the date of commencement of the Drags (4th Amendment) Rules, 2021 and such licence holder having a Good Manufacturing Practices Certificate of the manufacturing facilitieshe intends to avail on the date of renewal of its licence has to deposit a onetime licenceretention fee of rupees one thousand for existing licenced drags falling under clause (a) of section 3 of the Act; and rupees one thousand for first ten products and a fee at the rate of rupees one thousand per product over and above the said first ten products for existing licenced drags falling under sub clause (i) of clause (h) of section 3 of the Act.

Provided further that till the portal e-AUSHADHI (www.e-aushadhi.gov.in) shall come to effect [1343].[within twenty four months] of the commencement of the Drugs (4th Amendment) Rules, 2021 and during this period either of online and offline process of licence application shall be accepted.

Explanation—For the purposes of this rule, a "loan licence" means a licence issued by the Licensing Authority to an applicant who does not have his own arrangements for manufacture but intends to avail himself of the manufacturing facilities owned by a licencee in Form 25D.

153B. Application for Certificate of Good Manufacturing Practices for Ayurvedic, Siddha or Unani drugs manufacturing unit.—(1) An application for the grant of a Certificate of Good Manufacturing Practices for Ayurvedic, Siddha or Unani drugs manufacturing unit shall be made in Form 24E-1 to the licensing authority along with a fee of rupees five thousand.

(2) Every application in Form 24E-1 shall be made for a unit having premises and other requirements as prescribed under Schedule T.

(3) The application shall be made through portal e-AUSHADHI (www.e-aushadhi.gov.in) as per the format provided in the said portal, pertaining to the Good Manufacturing Practices for Ayurvedic, Siddha or Unani drugs manufacturing units.]

[706]**[154.Form of licence to manufacture Ayurvedic, Siddha or Unani drugs.—**(1) Subject to the conditions of rule 157 being fulfilled, a licence to manufacture for sale of any Ayurvedic, Siddha or Unani drags shall be issued in Form 25D within a period of two months from the date of receipt of the application or from the date of compliance by the applicant of shortcomings, if any, highlighted by the licensing authority, as the case may be.

(2) A licence under this rule shall be granted by the licensing authority after consulting such expert in Ayurvedic, Siddha or Unani Systems of medicine, as the case may be, which the State Government may approve in this behalf.

(3) The application shall be processed through portal e-AUSHADHI (www.e-ajshadhi.gov.in) and the licence in Form 25D shall be issued online as per the format provided in the said portal.]

[707]**[154A. Form of loan licence to manufacture for sale of Ayurvedic, Siddha or Unani drugs.**—(1) A loan licence to manufacture for sale of any Ayurvedic, Siddha or Unani drugs shall be issued in Form 25E within a period of two months from the date of receipt of the application or from the date of compliance of shortcomings, if any, highlighted by the licensing authority, as the case may be.

(2) A licence under this rule shall be granted by the Licensing Authority after consulting such expert in Ayurvedic, Siddha or Unani systems of medicine, as the case may be, which the State Government may approve in this behalf.

(3) The Licensing Authority after being satisfied that the manufacturing unit licenced under Form 25D has adequate equipment, staff and capacity for manufacture and facilities for testing, to undertake the manufacture on behalf of the applicant for a loan licence shall grant a loan licence.

(4) The application shall be processed through portal e-AUSHADHI (www.e-aushadhi.gov.in) and licence in Form 25E shall be issued online as per the format provided in the said portal.]

155. [708]**[***]**

155A. [709]**[***]**

[710]**[155B. Certificate of award of Good Manufacturing Practices Ayurveda, Siddha and Uriani Drugs.**—[711]**[(1)]** The certificate of Good Manufacturing Practices (GMP) to manufacturers of Ayurved-Siddha or Unani drugs shall be issued [712][in Form 26E-1] to licensee who comply with the requirements of Good Manufacturing Practice (GMP) of Ayurveda, Siddha and Unani drugs as laid down Schedule T.]

(2) [713][***]

[714]**[156. Duration of licence.—(1) A licence issued in Form** 25D **shall remain valid perpetually:**

Provided that the licencee shall submit a self-declaration of adherence to the conditions of licence and the provisions of the Drugs and Cosmetics Act and the

rules made thereunder, every year from the date of issue of licence in Form 25 D or from the date of submission of last self-declaration, as the case may be:

Provided further that such self-declaration shall be made within three months, of completion of one year from the date of issue of licence in form 25 D or from the date of submission of last self-declaration, as the case may be, and in the event of non-submission of such self-declaration, within the time mentioned in the licence of the said product shall be suspended temporarily and if the licensee fails to submit the self-declaration within a further period of three months, the licence of the said product shall be deemed to have been cancelled.]

[715][**156A. Duration of loan licence.**—A loan licence issued in Form 25E shall remain valid perpetually:

Provided that the licencee shall submit a self-declaration of adherence to the conditions of licence and the provisions of the Drugs and Cosmetics Act and the rules made thereunder, every year from the date of issue of licence in form 25 E or from the date of submission of last self-declaration, as the case may be.

Provided further that such self-declaration shall be made within three months, of completion of one year from the date of issue of licence in form 25 E or from the date of submission of last self-declaration, as the case may be, and in the event of non-submission of such self-declaration, within the time mentioned in the Licence of the said product shall be suspended temporarily and if the licensee fails to submit the self-declaration within a further period of three months, the licence of the said product shall be deemed to have been cancelled.

156B. Duration of Certificate of Good Manufacturing Practices for Ayurvedic, Siddha or Unani drugs manufacturing units—(1) A certificate issued in form 26E-1 shall remain valid unless it is cancelled by the Licensing Authority subject to deposit of a certificate retention fee of rupees one thousand before the expiry of a period of every succeeding five years from the date of its issue.

(2) If the licencee fails to pay certificate retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay certificate retention fee alongwith a late fee calculated at the rate of two per cent of the certificate retention fee for every month or part thereof up to six months, and in the event

of non-payment of such fee, the certificate shall be deemed to have been cancelled.

156C.Inspection for grant of licence and verification of compliance.— (1) Before a certificate in Form 26E-1 is granted, the licensing authority shall cause the establishment in which the manufacture of drugs is proposed to be conducted or being conducted to be inspected by one or more inspectors appointed by the State Government under this Act, with or without an expert in the field concerned and the inspector or inspectors shall examine the establishment intended to be used or being used for the manufacture of drugs.

(2) The inspectors shall verify the self-declaration of adherence to the conditions of licence and the provisions of the Drugs and Cosmetics Act and the Drugs Rules once in five years or as needed as per risk based approach.

Provided that the inspectors are allotted the inspection duty in a randomized manner ensuring that the same inspector is not assigned inspection of a particular establishment consecutively for two terms of not less than five years' duration.

Provided further that if the premises is not inspected within the period of the validity of the GMP certificate or even after submission of retention fee, the GMP certificate shall be deemed to be continued for further term of five years.

156D. Report by Inspector.—(1) The Inspector or Inspectors shall examine all areas of the premises, plant and appliances and also inspect the process of manufacture intended to be employed or being employed along with the means to be employed or being employed for standardizing and testing the drugs to be manufactured or being manufactured and enquire into the professional qualifications of the technical staff to be employed and he shall also examine and verify the statements made in the application in regard to their correctness, and the capability of the applicant to comply with the requirements of competent technical staff, manufacturing plants, testing equipments and the Requirements of Good Manufacturing Practices and Plant and Equipments as laid down in Schedule T.

(2) The Inspector after completion of his inspection shall forward a detailed report giving his findings on each aspect of inspection alongwith his recommendations, to the Licensing Authority.

156E. Procedure of Licensing Authority.—**(1)** If the Licensing Authority after such further enquiry, if any, as he may consider necessary, and after being satisfied that the requirements of the provisions referred to in the rules under the Act have been complied with and that the conditions of the licence shall be observed, shall issue a licence under this Part.

(2) If the Licensing Authority is not satisfied of the requirements under sub-rule (l), shall issue a memorandum of shortcoming, and the conditions which shall be satisfied before a licence is granted and shall supply the applicant a copy of the inspection report.

(3) The applicant within two months of issue of such memorandum under sub-rule (2) shall reply the same.

(4) On non-submission of requirements under sub-rule (2), the Licensing Authority shall reject the application and shall inform the applicant, the reasons for such rejection.

(5) For this purpose, the licensing authority shall intimate the applicant and process the application through portal e-AUSHADHI (www.e-aushadhi.gov.in).

156F. Further application after rejection.—If the applicant, within a period of six months from the rejection of an application for a licence or Certificate of Good Manufacturing Practices, as the case may be, informs the Licensing Authority that the conditions laid down have been complied with and deposit an inspection fee of rupees one thousand, the Licensing Authority may, after a further inspection, if any, is satisfied that the conditions for the grant of a licence or certificate have been complied with, issue a licence or certificate under thus Part.]

157. Conditions for the grant [716][***] of a licence in Form 25D.—Before a licence in Form 25D is granted [717][***], the following conditions shall be complied with by the applicant, namely:—

(1) The manufacture of Ayurvedic [718][Siddha] or Unani drugs shall be carried out in such premises and under such hygienic conditions as are specified in Schedule T.

[719][(1A) For issuing of the certificate of Good Manufacturing Practices, the Licensing Authority shall verify the requirements as per Schedule T and issue the Good Manufacturing Practices certificate in Form 26E-I, simultaneously along with grant [720][***] of Licence in Form 25D.]

[721][(1B) No manufacturer shall use any prefix or suffix with the name of any Ayurvedic, Siddha or Unani Tibb drug falling under clause (a) of section 3 of the Act, except as described in the authoritative books specified in the First Schedule to the Act:

Provided that a formulation without any specific name, described in the authoritative books may be named on the basis of the ingredients of that formulation.]

(1C) The name of any Ayurvedic, Siddha or Unani Tibb drug falling under clause (a) of section 3 of the Act shall not be used for naming any patent or proprietary medicine relating to Ayurvedic, Siddha or Unani Tibb systems of medicine referred to in sub-clause(i) of clause (h) of the said section:

Provided that this rule shall not be applicable for single plant-ingredient based Ayurvedic, Siddha or Unani Tibb formulation Licensed or to be Licensed as patent or proprietary medicine under sub-clause (i) of clause (h) of section 3 of the Act.

[722][(1D) Whoever contravenes the provisions of sub-rules (IB) and (1C) shall be punishable in accordance with the provisions of the Act.]

(1E) [723][***]

(2) The manufacture of Ayurvedic (including Siddha) or Unani drugs shall be conducted under the direction and supervision of competent technical staff consisting at least of one person, who is a whole-time employee and who possesses the following qualification, namely:—

(a) a degree in Ayurveda or Ayurvedic Pharmacy, Siddha or Unani system of medicine, as the case may be, conferred by a University, a State Government or Statutory Faculties, Councils and Boards of Indian Systems of Medicine recognised by the Central Government or a State Government for this purpose, or

(b) a diploma in Ayurveda, Siddha or Unani system of medicine granted by a State Government or an Institution recognised by the Central Government for this purpose, or

(c) a graduate in Pharmacy or Pharmaceutical Chemistry or Chemistry or Botany or a University recognised by the Central Government with experience of at least two years in the manufacture of drugs pertaining to the Ayurvedic or Siddha or Unani system of medicine, or

(d) a Vaid or Hakim registered in a State Register of Practitioners of indigenous system of medicines having experience of at least four years in the manufacture of Siddha or Unani drugs, or

(e) a qualification as Pharmacist in Ayurvedic (including Siddha) or Unani systems of medicine, possessing experience of not less than eight years in the manufacture of Ayurvedic or Siddha or Unani drugs as may be recognised by the Central Government.

(3) The competent technical staff to direct and supervise the manufacture of Ayurvedic drugs shall have qualifications in Ayurveda and the competent technical staff to direct and supervise the manufacture of Siddha drugs and Unani drugs shall have qualifications in Siddha or Unani, as the case may be.

[724]**[157A. Maintaining of records of raw material used by licensed manufacturing unit of Ayurveda, Siddha and Unani drugs in the preceding financial year.—**Each licensed manufacturing unit of Ayurveda or Siddha or Unani drugs shall keep a record of raw material used by each licensed manufacturing unit of Ayurveda, Siddha or Unani drugs, as the case may be, in the performa given in Schedule TA in respect of all raw materials utilized by that unit in the manufacture of Ayurveda or Siddha or Unani drugs in the preceding financial year, and shall submit the same by the 30th day of June of the succeeding financial year to the State Drug Licensing Authority of Ayurveda, Siddha and Unani drugs and to the National Medicinal Plants Board or any agency nominated by the National Medicinal Plant Board for this purpose:]

[725][Provided that the applicant shall submit the record online through portal e-AUSHADHI (www.e-aushadhi.gov.in) as per the format provided in the said

portal and such records shall be retained by the manufacturer for a period of one year after the submission.]

158. Conditions of licence.—A licence in Form 25D shall be subject to the conditions stated therein and to the following further conditions, namely:—

(a) The licensee shall maintain proper records of the details of manufacture and of the tests, if any, carried out by him, or by any other person on his behalf, of the raw materials and finished products.

(b) The licensee shall allow an Inspector appointed under the Act to enter any premises where the manufacture of a substance in respect of which the licence is issued is carried on, to inspect the premises, to take samples of the raw materials as well as the finished products, and to inspect the records maintained under these rales.

[726][(c) The applicant and inspector shall submit the record online through e-AUSHADHI (www.e-aushadhi.gov.in) portal as per the format provided in the said portal.]

[727]**[158A. Conditions of loan licence.**—A licence in Form 25E shall be subject to the following further conditions, namely:—

(a) The licence in Form 25E shall be deemed to be cancelled or suspended, if the licence owned by the licensee in Form 25D whose manufacturing facilities have been availed of by the licensee is cancelled or suspended, as the case may be, under these rules.

(b) The licensee shall comply with the provisions of the Act and of the rules and with such further requirements if any, as may be specified in any rules subsequently made under Chapter IVA of the Act, provided that where such further requirements are specified in the rules, these would come into force four months after publication in the Official Gazette.

(c) The licensee shall maintain proper records of the details of manufacture and of the tests, if any, carried out by him, or any other person on his behalf, the raw materials and finished products.

(d) The licensee shall allow an Inspector appointed under the Act to inspect all registers and records maintained under these rules and shall supply to the Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and the rules have been observed.]

[728][(e) The applicant and inspector shall submit the record online through e-AUSHADHI (www.e-aushadhi.gov.in) portal as per the format provided in the said portal.]

[729]**[158B. Guidelines for issue of license with respect to Ayurveda, Siddha or Unani drags.**—I. (A) Ayurveda, Siddha Unani Medicines under section 3(a):— Ayurveda, Siddha or Unani drugs includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in the authoritative books of Ayurvedic, Siddha and Unani Tibb system of medicine, as specified in the First Schedule;

(B) Patent or proprietary medicine under section 3(h)—

(i) In relation to Ayurvedic, Siddha and Unani Tibb system of medicine of all formulations containing only such ingredients mentioned in the formulae described in the authoritative books of Ayurveda, Siddha or Unani Tibb system of medicines specified in the First Schedule, but does not include a medicine which is administered by parenteral route and also a formulation included in the authoritative books as specified in clause (a);

(ii) Balya/Poshak/Muqawi/Unavuporutkal/posilive health Promoter formulations having ingredients mentioned in books of First Schedule of the Drugs and Cosmetics Act and recommended for promotional and preventive health;

(iii) Saundarya Prasadak (Husane afza)/Azhagh-sadhan formulation having ingredients mentioned in Books of First Schedule of the Drugs and Cosmetics Act and recommended for oral, skin, hair and body care;

(iv) Aushadh Ghana (Medicinal plant extracts - dry/wet) extract obtained from plant mentioned in books of First Schedule of the Act including Aqueous or hydro-alcohol.

II. (A) For issue of licence to the medicine with respect to Ayurvedic, Siddha and Unani, the conditions relating to safety study and the experience or evidence of effectiveness shall be such as specified in columns (5) and (6) ot The Table given below:—

Serial number	Category	Ingredient (S)	Indication (s)	Safety study	Experience / Evidence of Effectiveness	
(1)	(2)	(3)	(4)	(5)	(6)	
					Published Literature	Proof of Effectiveness
1.	(A) Ayurveda, Siddha and Unani drugs, given in 158B as referred in 3(a)	As per text	As per text	Not Required	Required	Not Required
2.	(B) Any change in dosage form of Ayurveda, Siddha and Unani drugs as described in section 3(a) of the Drugs and Cosmetics Act, 1940	As per text	As per text	Not Required	Required	Not Required
3.	(C) Ayurveda, Siddha and Unani drugs referred in 3(a) to be used for new indication	As per text	New	Not Required	If Required	Required

II. (B) For issue of license with respect to Patent or Proprietary medicine. The condition relating to Safety studies and experience or evidence of effectiveness shall be specified as follows:—

Serial number	Category	Ingredient (S)	Indication (s)	Safety study	Experience / Evidence of Effectiveness

Serial number	Category	Ingredient (S)	Indication (s)	Safety study	Experience / Evidence of Effectiveness	
(1)	(2)	(3)	(4)	(5)	(6)	
					Published Literature	Proof of Effectiveness
1.	Patent or Proprietary medicine	As per text	Textual rationale	Not Required	Of Ingredients	*Pilot study as per relevant protocol for Ayurveda, Sidha and Unani drugs.
2.	Ayurveda, Siddha, Unani drug with any of the ingredients of Schedule E(l) of The Drugs and Cosmetics Act, 1940.	As per text	Existing	Required	Required	Required

III. For issue of license with respect to Balya and Poshak medicines the person who applied for license is required to submit the following:

(i) Photo-copy of the textual reference of ingredients used in the formulation as mentioned in the book of 1st Schedule;

(ii) Conduct safety studies in case the product contains of any of the ingredients as specified in the Schedule E(l), as per the guidelines for evaluation of Ayurveda Siddha and Unani Drugs formulations;

(iii) For textual indications the safety and effectiveness study is not required.

IV. For issue of license with respect to Saundarya Prasadak (Husane afza/ Azhagu Sodhan) the person who applied for license is required to:—

(i) Submit photo-copy of the textual reference of ingredients used in the formulation as mentioned in the book of 1st Schedule;

(ii) Conduct safety studies, in case the formulation contains of any of the ingredients as specified in the Schedule E(l), as per the guidelines for evaluation of Ayurveda, Siddha and Unani formulation;

(iii) For textual indications the safety and effectiveness study is not required.

V. For issue of license with respect to medicine Aushadh Ghana [extract of medicinal plant (dry or wet).

Serial number	Category	Ingredient (S)	Indication (s)	Safety study	Experience / Evidence of Effectiveness	
(1)	(2)	(3)	(4)	(5)	(6)	
					Published Literature	Proof of Effectiveness
1.	(A)Aqueous	As per text	As per text	Not Required	Not Required	Not Required
2.	(Al) Aqueous	As per text	New indication	Not Required	Not Required	Required
3.	(B) Hydro-Alcohol	As per text	As per text	Not Required	If Required	Not Required
4.	(Bl) Hydro-Alcohol	As specified	New Indication**	Required	If Required	Required
5.	Other than Hydro/Hydro-Alcohol	As specified	As specified	Required Acute, Chronic, Mutagenicity and Teratogenicity	If Required	Required

* The standard protocol will also include concept of Anupan, Prakriti & Tridosh, etc., published by Central Research Councils Ayurveda, Siddha, Unani and other Government/Research Bodies.

** New indication means which is other than mentioned in 1st Schedule books of Drugs and Cosmetics Act, 1940.]

[730]**[158C. Form of Free Sale Certificate and Non-Conviction Certificate.**—The State Drug Controller or Licensing Authority shall, on request by the Ayurveda, Siddha and Unani Drugs manufacturer, issue, within fifteen days ;from the date of application. Free Sale Certificate in Form 26 E2-I for original License holder or in Form 26 E2-II for loan licensee and Non-Conviction Certificate for both original and loan license holder in Form 26 E3 or in the format as specified by the importing country or tenderer respectively,

after fulfillment of all requisite formalities as required in the respective formats.]

[731][*Explanation*.—For the purposes of this rule, the applicant shall apply online and licensing authority shall issue such certificate online through portal e-AUSHADHI (www.e-aushadhi.gov.in) as per the format provided in the said portal.]

159. Cancellation and suspension of licences.—(1) The licensing authority may, after giving the licensee an opportunity to show cause, within a period which shall not be less than fifteen days form the date of receipt of such notice, why such an order should not be passed, by an order in writing stating the reasons therefor, cancel a licence issued under this Part or suspend it for such period as he thinks fit, either wholly or in respect of some of the drugs to which it relates, if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act or the rules made thereunder.

(2) A licensee whose licence has been suspended or cancelled may appeal to the State Government within a period of three months from the date of receipt of the order which shall, after considering the appeal, decide the same.

160. Identification of raw materials.—Raw materials used in the preparation of Ayurvedic (including Siddha) or Unani drugs shall be identified and tested, wherever tests are available for their genuineness, and records of such tests as are carried out for the purpose and the methods thereof shall be maintained.]

[206][PART XVI (A)

APPROVAL OF INSTITUTIONS FOR CARRYING OUT TESTS ON AYURVEDIC, SIDDHA AND UNANI DRUGS AND RAW MATERIALS USED IN THEIR MANUFACTURE ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA AND UNANI DRUGS

160A. Application for grant of approval for testing Ayurvedic, Siddha and Unani drugs.—Application for grant or renewal of approval for carrying out tests for identity, purity, quality and strength of Ayurvedic, Siddha and

Unani drugs or the raw materials used in the manufacture thereof on behalf of licensees for manufacture for sale of the said Ayurvedic, Siddha and Unani drugs, shall be made in Form 47 to the Licensing Authority appointed by the State Government for the purposes of Part XVI, XVII or XVIII of these rules, as the case may be, and referred to as the "approving authority" under this Part and shall be accompanied by an inspection fee of six thousand rupees in respect of the drugs specified in First Schedule to the Act:

Provided that the applicant shall furnish to the approving authority such additional information as may be required by it in connection with the application in Form 47:

Provided further that if the applicant applies for renewal of approval after its expiry but within six months of such expiry, the inspection fee payable shall be six thousand rupees plus an additional inspection fee at the rate of one thousand rupees per month in the case of testing of Ayurvedic, Siddha and Unani drugs specified in First Schedule to the Act.

Explanation.—For the purpose of this Part, the words "Ayurvedic, Siddha and Unani drags" shall also mean and include the raw materials used in the manufacture of Ayurvedic, Siddha and Unani drugs, as the case may be.

160B. Form in which approval to be granted for carrying out tests **on Ayurvedic, Siddha and Unani drugs on behalf of licensees for manufacture of Ayurvedic, Siddha and Unani drugs and conditions** for **grant** or renewal **of such approval.**—(1) Approval for carrying out such tests of identity, purity, quality and strength of Ayurvedic, Siddha and Unani drugs as may be required under the provisions of these rules, on behalf of licensee for manufacture of Ayurvedic, Siddha and Unani drugs shall be granted in Form 48.

[207][(1A) The licence shall be issued within a period of two months, from the date of receipt of the application or from the date of fulfillment of shortcomings, if any, as the case may be, communicated by the licensing authority.]

(2) Before approval in Form 48 is granted or renewed, the following conditions shall be complied with by the applicants, namely:—

(i) The premises where the tests are carried out shall be well lighted and properly ventilated except where the nature of tests of any Ayurvedic,

Siddha and Unani drug warrants otherwise. Wherever necessary, the premises shall be air-conditioned so as to maintain the accuracy and functioning of laboratory instruments or to enable the performance of special tests such as sterility tests and microbiological tests.

(ii) (a) The applicant shall provide adequate space having regard to the nature and number of samples of drugs proposed to be tested: Provided that the approving authority shall determine from time to time whether the space provided continues to be adequate. Provided further that separate section shall be provided for (i) Chemistry, (ii) Pharmacognosy, (iii) Ayurveda, Siddha and Unani, (iv) Microbiology, (v) Sample Room, (vi) Office-cum-Record Room, with proper partitions and minimum required area is 800 sq. ft.

[208]*(b) The applicant shall provide a list of persons who may be employed with him as experts, such as Chemist, Botanist and expert in Avurveda/Siddha/Unani or Pharmacist who shall possess a degree in Chemistry, Botany, Ayurveda/Siddha/ Unani/Bachelor in Pharmacy from a recognized University or equivalent, with experience for 2 years for carrying out tests or analysis as per the Ayurvedic, Siddha and Unani pharmacopoeias.

(c) The applicant shall provide adequate equipments essential for carrying out tests for identity, purity, quality and strength of Ayurvedic, Siddha and Unani drugs as per pharmacopoeial standards or other available standards.

List of equipment recommended is given below:

CHEMISTRY SECTION

1. Alcohol determination apparatus complete set.
2. Volatile oil determination apparatus.
3. Boiling point determination apparatus.
4. Melting point determination apparatus.
5. Refractometer
6. Polarimeter.
7. Viscometer (ostwalds, Redwood viscometer).
8. Tablet disintegration apparatus.

9. Moisture determination apparatus (IC filtrator).
10. U.V. Spectro-Photometer.
11. Muffle furnace.
12. Electronic Balance.
13. Hot air oven(s) different range of temperature/vacuum oven.
14. Refrigerator.
15. Glass distillation apparatus/plant.
16. Water supply demineralised exchange equipment/Distillation equipment.
17. Air conditioner.
18. LPG Gas Cylinder with burners.
19. Water bath (temperature controlled).
20. Heating mantle (4) or as required.
21. TLC apparatus with all accessories.
22. Sieves 10 to 120 with sieve shaker.
23. Centrifuge machine.
24. Dehumidifier (where necessary).
25. PH meter.
26. G.L.C. with F.I. detector.
27. Silica crucible.
28. Tablet friability tester.
29. Tablet dissolution tester.
30. Other related equipment, regents, chemicals and glasswares.

PHARMACOGNOSY SECTION

1. Microscope binocular.
2. Dissecting Microscope
3. Microtome
4. Chemical balance
5. Microslide cabinet.
6. Aluminium slide trays.
7. Hot air oven
8. Occular Micrometer
9. Stage Micrometer
10. Camera Lucida Prism type and mirror type.
11. Hot plates.
12. Refrigerator.
13. LPG Cylinder with burners.

14. Other related equipments, reagents, glasswares, etc.

Note.—Instruments like HPLC, HPTLC, Atomic Absorption spectrophotometer could be arranged by tie up with other laboratories.

MICROBIOLOGY SECTION

1. Laminar air flow bench (L.A.F.).
2. B.O.D. Incubator.
3. Plain incubator.
4. Serological water bath.
5. Oven.
6. Autoclave/Sterilizer.
7. Microscope (high power).
8. Colony counter.
9. Other related equipment and reagents.

(3) The applicant shall provide and maintain suitable equipment having regard to the nature and number of samples of Ayurvedic, Siddha and Unani drugs intended to be tested which shall be adequate in the opinion of the approving authority.

(4) The testing of Ayurvedic, Siddha and Unani drugs, as the case may be, for identity, purity, quality and strength shall be carried out under the active direction of one of the experts stated in clause (b) of sub-rule (2) who shall be the person-in-charge of testing and shall be held responsible for the reports of test issued by the applicant.

(5) The testing of Ayurvedic, Siddha and Unani drugs, as the case may be, for identity, purity, quality and strength shall be carried out by persons whose qualifications and experience of testing are adequate as stated in clause (b) of sub-rule (2).

(6) The applicant shall provide books of standard recognized under the provisions of the Act and the rules made thereunder and such books of reference as may be required in connection with the testing or analysis of the products for the testing of which approval is applied for.

(7) The applicant shall provide list of standard Ayurvedic, Siddha and Unani drugs (with Reference samples) recognized under the provisions of the Act and rules made thereunder and such reference samples kept in the laboratory may be required in connection with the testing or analysis of the products of which approval is applied for.

160C. Duration of approval.—An approval granted in Form 41 or renewed in Form 42 unless sooner suspended or withdrawn, shall be valid for a period of three years from the date on which it is granted or renewed:

Provided that if an application for the renewal of an approval in Form 40 is made before its expiry or if the application is made within six months of its expiry after the payment of the additional inspection fee, the approval shall continue to be in force until orders to the contrary are passed on the application and the approval shall be deemed to have expired if the application for renewal is not made within six months of expiry.

160D. Conditions of approval.—An approval in Form 41 shall be subject to the following conditions, namely:

I. The Institution granted approval under this Part (hereinafter referred to as the approved laboratory) shall provide and maintain adequate staff and adequate premises and equipment as specified in rule 160 B.

II. The approved laboratory shall provide proper facilities for storage so as to preserve the properties of the samples to be tested by it.

III. The approved laboratory shall maintain records of tests for identity, purity, quality and strength carried out on all samples of Ayurvedic, Siddha and Unani drugs and the results thereof together with the protocols of tests showing the readings and calculation in such form as to be available for inspection and such records shall be retained in the case of substances for which date of expiry is assigned; for a period of two years from such date of expiry and in the case of other substances, for a period of three years.

IV. The approved laboratory shall allow the Inspector appointed under this Act to enter with or without prior notice the premises where the testing is carried out and to inspect the premises and the equipment used for test

and the testing procedures employed. The laboratory shall allow the Inspectors to inspect the registers and records maintained under these rules and shall supply to such Inspectors such information as they may require for the purpose of ascertaining whether the provisions of the Act and rules made thereunder have been observed.

V. The approved laboratory shall from time to time report to the approving authority any changes in the person-in-charge of testing of Ayurvedic, Siddha and Unani drugs or the expert staff responsible for testing, as the case may be, and any material alterations in the premises or changes in the equipment used for the purposes of testing which have been made since the date of last inspection made on behalf of the approving authority before the grant or renewal of approval.

VI. The approved laboratory shall furnish reports of the results of tests or analysis in Form 50.

VII. In case any sample of Ayurvedic, Siddha and Unani drug is found on test to be not of standard quality, the approved laboratory shall furnish to the approving authority and the licensing authority of the State where the manufacturer and/or sender of the Ayurvedic, Siddha and Unani drugs is located, a copy of the test report on the sample with the protocols of tests applied.

VIII. The approved laboratory shall comply with the provisions of the Act and rules made thereunder and with such further requirements, if any, as may be specified in the rules made from time to time under Chapter IVA of the Act of which the approving authority has given the approved laboratory not less than four months' notice.

IX. The approved laboratory shall maintain an inspection book to enable the Inspector to record his impression or defects notices.

160E. Inspection before grant of approval.—Before an approval in Form 48 is granted, the approving authority shall cause the laboratory at which the testing of Ayurvedic, Siddha and Unani drugs, as the case may be, is proposed to be carried out to be inspected jointly by the Inspectors appointed or designated by the Central Government and State Government for this purpose, who shall examine the premises and the equipment intended to be used for

testing of drugs and varify into the professional qualifications of the expert staff who are or may be employed by the laboratory.

160F. Report of inspection.—The Inspectors appointed by the Central Government as stated in rule 160E shall forward to the approving authority a detailed report of the results of the inspection.

160G. Procedure of approving authority.—**(1)** If the approving authority after such further enquiry, if any, as it may consider necessary, is satisfied that the requirements of the rules made under the Act have been complied with and that the conditions of the approval and the rules made under the Act have been observed, it shall grant approval in Form 48.

(2) If the approving authority is not so satisfied, it shall reject the application and shall inform the applicant of the reasons for such rejection and of the conditions which shall be satisfied before approval could be granted.

160H. Application after rejection.—If within a period of six months from the rejection of an application for approval, the applicant informs the approving authority that the conditions laid down have been satisfied and deposits inspection fee of two thousand rupees, the approving authority may, if, after causing a further inspection to be made and after being satisfied that the conditions for grant of approval have been complied with, grant the approval in Form 48.

160-I. Renewal—On an application being made for renewal, the approving authority shall, after causing an inspection to be made and if satisfied that the conditions of the approval and the rules made under the Act have been complied with, shall issue a certificate of renewal in Form 49.

160J. Withdrawal and suspension of approvals.—**(1)** The approving authority may, after giving the approved laboratory an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, withdraw an approval granted under this Part or suspend it for such period as it thinks fit either wholly or in respect of testing of some of the categories of Avurvedic, Siddha and Unani drugs to which it relates, if in his opinion the approved laboratory had failed to comply with any of the conditions of the approval or with any provision of the Act of the rules made thereunder.

(2) any approved laboratory, whose approval has been suspended or withdrawn, may, within three months of the date of the order of suspension or withdrawal, appeal to the State Government which shall dispose of the appeal in consultation with a panel of competent persons appointed by the Department of Indian Systems of Medicine and Homoeopathy, Government of India in this behalf and notified in the Official Gazette.]

[732]**[160K. Information to be uploaded by the licencee on online portal.**—(1) The applicant or licencee under this part shall register with portal, e-AUSHADHI (www.e-aushadhi.gov.in) and upload information, as per the format provided in the said portal, pertaining to licence application, renewal, tests carried out and other such information as required and shall be updated from time to time.

(2) The information uploaded by the licencee in the portal under sub-rule (1) shall be verified by the concerned licensing authority.]

[733]**[PART XVII**

[734][LABELLING, PACKING AND LIMIT OF ALCOHOL IN] AYURVEDIC (INCLUDING SIDDHA) OR UNANI DRUGS

161. [734][Labelling, packing and limit of alcohol].—(1) There shall be conspicuously displayed on the label of the container or package of an Ayurvedic (including Siddha) or Unani drug, the true list of all the ingredients [735][with the botanical names of plant based ingredients along with plant part(s) and form of ingredients, in which, these are] used in the manufacture of the preparation together with the quantity of each of the ingredients incorporated therein and a reference to the method of preparation thereof as detailed in the standard text and Adikarana, as are prescribed in the authoritative books specified in the First Schedule of the Act [735][and in respect of Patent or Proprietary Ayurveda, Siddha or Unani drugs, the true list of all the ingredients with the botanical names of plant based ingredients along with plant part(s) and form of ingredients, in which, these are used in the formulation, with their quantity:

Provided that if needed, standardized abbreviations prescribed for part(s) and form of Ingredient(s) in the official Ayurveda, Siddha and Unani Pharmacopoeias and Formularies, may be used on the label:]

Provided that if the list of ingredients contained in the medicine is large and cannot be accommodated on the label, the same may be printed separately and enclosed with the packing and reference be made to this effect on the label.

(2) The container of a medicine for internal use made up ready for the treatment of human ailments shall, if it is made up from a substance specified in Schedule E(l), be labelled conspicuously with the words 'Caution: to be taken under medical supervision' both English and Hindi languages.

(3) Subject to the other provisions of these rules, the following particulars shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container of any Ayurvedic (including Siddha) or Unani drug [735][and Patent or Proprietary Ayurveda, Siddha or Unani drugs] and on any other covering in which the container is packed, namely:—

(i) The name of the drug; [736][For Ayurveda, Siddha or Unani Drug] purpose the name shall be the same as mentioned in the authoritative books included in the First Schedule of the Act.

(ii) A correct statement of the net content in terms of weight, measure or number as the case may be. The weight and volume shall be expressed in metric system.

(iii) The name and address of the manufacturer.

(iv) The number of the licence under which the drug is manufactured, the figure representing the manufacturing licence number being preceded by the words 'Manufacturing Licence Number' or "Mfg. Lie. No." or "M.L.".

(v) A distinctive batch number, that is to say, the number by reference to which details of manufacture of the particular batch from which the substance in the container is taken are recorded and are available for inspection, the figure representing the batch number being preceded by the words "Batch No." or "Batch" or "Lot Number" or "Lot No." or "Lot" or any distinguishing prefix.

(vi) The date of manufacture. For this purpose the date of manufacture shall be the date of completion of the final products, or the date of bottling or packing for issue.

(vii) The words "Ayurvedic medicine" or "Siddha medicine" or "Unani medicine" as the case may be.

(viii) The words "FOR EXTERNAL USE ONLY" if the medicine is for external application.

(ix) Every drug intended for distribution to the medical profession as a free sample shall, while complying with the labelling provisions under clause (i) or (viii), further bear on the label of the container the words "Physician's sample. Not to be sold" which shall be overprinted.

[737] [(x) (a) Preparation (Asavas) with high content of alcohol as base.

Name of the drug	*Maximum size of packing*	
(i) Kapur Asava	15 ml.	
(ii) Ahiphenasava	15 ml.	
(iii) Margamadasava	15 ml.	
(b) Preparation containing self-generated alcohol.		
Name of the drug	*Maximum content of alcohol (Ethylalcohol v/v)*	*Maximum size of packing*
(i) Mritsanjivani Sura	16 per cent	30 ml.
(ii) Mahadrakshava	16 per cent	120 ml.]

(4) Nothing in these rules shall be deemed to require the labelling of airy transparent cover or of any wrapper-case or other covering used solely for the purpose of packing, transport in delivery.]

[738] **[161A. Exemption in labelling and packing provisions for export of Ayurvedic (including Siddha) and Unani Drugs.**—(1) Label and packages or containers of Ayurvedic, Siddha and Unani Drugs for export may be adapted to meet the specific requirements of the law of the country to which the said drugs is to be exported, but the following particulars shall appear in conspicuous

position on the container in which drug is packed and on every other covering in which that container is packed, namely:—

(a) name of the Ayurvedic, Siddha and Unani drug (single or compound formulation);

(b) the name, address of the manufacturer and the number of licence under which the drug has been manufactured;

(c) batch or lot number;

(d) date of manufacture, along with date for "Best for use before".

(e) main ingredients, if required by the importing country;

(f) for EXPORT:

Provided that where Ayurvedic, Siddha and Unani single or compound drug not classified under the First Schedule or Schedule E(l), is required by the consignee to be not labelled with the name and address of the manufacturer, the labels on packages or containers shall bear a code number as approved by the licensing authority mentioned in rule 152.

(2) The provisions of rule 161 shall not apply to a medicine made up “ready for treatment” whether after, or without, alteration, which is supplied on the prescription of a registered medical practitioner, if the medicine is labelled with the following particulars, namely:—

(a) the name and address of the suppliers;

(b) the words "For External Use Only", if the medicine is for external application.]

[739]**[161B. Shelf life or date of expiry of medicines.—(1)** The date of expiry of Ayurvedic, Siddha or Unani medicines shall be conspicuously displayed on the label of container or package of Ayurvedic, Siddha or Unani medicine, as the case may be, and after the said date of expiry, no medicine shall be marketed, sold, distributed or consumable;

Provided that this rule shall apply to Ayurvedic, Siddha and Unani medicines seeking licence or renewal of licence for manufacturing after the date of notification of the rules.

Provided also that this rule shall not be applicable to the Ayurvedic, Siddha or Unani medicines manufactured and marketed prior to the date of this notification.

(2) Every person applying for licence or renewal of licence for the manufacturing of Ayurveda, Siddha or Unani medicines defined under clause (h) of section 3 of the Act shall submit to the State Licensing Authority scientific data based shelf life or date of expiry of the medicine based on the Real time stability studies of medicines in accordance with the guidelines prescribed in the Ayurvedic Pharmacopoeia of India.

Provided that this sub-rule shall be applicable after three years from the date of notification of the rules.

(3) The guidelines regarding stability studies as prescribed in the Ayurvedic Pharmacopoeia of India, Part-I, Volume-VIII shall be applicable to all the medicines of Ayurvedic, Siddha and Unani.

(4) The State Licensing Authority shall, before granting license or renewal of license for an Ayurvedic, Siddha or Unani medicine, ensure validity of the data submitted by the manufacturer in support of the claimed shelf-life of that medicine.

(5) The State Licensing Authority may at any time direct the manufacturer to provide the samples of the medicine and any other related information; and may share it with the Pharmacopoeial Laboratory for Indian Medicine, Ghaziabad for analysis or independent validation.

(6) Where the manufacturer fails to comply with direction of the State licensing Authority under sub-rule (5), the license for the manufacturing of the medicine shall be liable for suspension after giving a reasonable opportunity of being heard.

(7) Any person aggrieved by an order passed by the State Licensing Authority under sub-rule (6), may within sixty days of such order, appeal to the

Central Government, and the Central Government may, after such enquiry into the matter as is considered necessary, pass such order in relation thereto as it deems fit. The decision of the Central Government shall be final and binding.

(8) The shelf life or date of expiry of an Ayurveda, Siddha or Unani medicine defined under clause (a) of section 3 of the Act shall, unless otherwise determined on the basis of scientific data, be as follows:—

(Ayurvedic medicines)

SI. No.	Dosage form	Shelf life or date of expiry with effect from the date of manufacture
(1)	(2)	(3)
(i)	Anjana	
	(a) Anjana made from Kasthaushadhi	1 year
	(b) Anjana made from Kasthaushadhi along with Rasa/ Uprasa / Bhasma	2 years
	(c) Anjana made only from Rasa/Uprasa/Bhasma	3 years
(ii)	Arka	1 year
(iii)	Asava Arista	10 years
(iv)	Avaleha, Khanda, Paka, Guda	3 years
(v)	Chuma, Kwatha Chuma, Lepa Chuma, Danta Manjan (Churna)	2 years
(vi)	Dhoopan	2 years
(vii)	Dravaka, Lavana, Kshara	5 years
(viii)	Ghrita	2 years
(ix)	Guggulu	5 years
(x)	Gutika/Vati	
	(I) Gutika or Vati containing Kasthaushadhi along with Rasa/Uprasa/Bhasma/Guggulu (including Lepa Gutika and GhanVati)	5 years
	(II) Gutika or Vati containing only Kasthaushadhi (including Lepa Gutika and Ghan Vati)	3 years
	(III) Gutika/Vati containing only	10 years

	Ras/Uprasa/Bhasma except Naga, Vanga and Tamra Bhasma	
(xi)	Kama /Nasabindu	2 years
(xii)	Kupipakva Rasayana	10 years
(xiii)	Malahar	3 years
(xiv)	Mandura-Lauha	10 years
(xv)	Naga Bhasma, Vanga Bhasma and Tamra Bhasma	5 years
(xvi)	Netrabindu	1 year
(xvii)	Parpati	10 years
(xviii)	Pishti and Bhasma except Naga, Vanga and Tamra Bhasma	10 years
(xix)	Pravahi Kwatha	3 years

(1)	(2)	(3)
(xx)	Rasayoga	
	(I) Rasayoga Containing only Rasa/Uprasa/Bhasma except Naga, Vanga and Tamra Bhasma	10 years
	(II) Rasayoga Containing Rasa/Uprasa/Bhasma along with Kasthaushadhi/Guggulu	5 years
(xxi)	Sattva (derived from medicinal plant)	2 years
(xxii)	Sharkar/Panak / Sharbat	3 years
(xxiii)	Shveta parpati	2 years
(xxiv)	Taila	3 years
(xxv)	Varti	2 years

(Siddha medicines)

SI. No.	Dosage form	Shelf life or date of expiry with effect from the date of manufacture
(1)	(2)	(3)
(i)	**Curanam**	
	Kutinir Curanam/Adai Curanam/Kanchi Curanam/Utkali Curanam/Pittu Curanam/Podithimirthal Curanam/Podi/	2 years

	Pattru Curanam/Pottanam or Kizhi Curanam/Ottratam Curanam/Vethu Curanam/Pugai Curanam/Kah Curanam/Thuvalai Curanam	
(ii)	**Mattirai/V atakam**	
	(I) Containing only Moohgai ingredients (including Kudineer Curanam Mattirai) *(e.g.* Nilavembu kutinir Mattirai)	2 years
	(II) Containing Mooligai ingredients along with Thathu Porutkal/Jeeva Porutkal/Parpam/Centuram/Cunnam. (including kutinir Curanam Mattirai)	5 years
	(m) Containing only Thathu Porutkal/Parpam/Centuram/ Cimnam/Kattu/Kalanku.	10 years
(iii)	**Rasa-Paadana Marunthugal (All Mercurial Preparation)**	
	(I) Containing Mooligai ingredients along with Thathu Porutkal/Parpan/Centuram/Cunnam/ Kattu/Kalanku	2 years
	(II) Containing only Thathu Porutkal/Parpam/ Centuram/Cunnam Kattu/Kalanku	10 years
(iv)	**Parpam/Centuram**	
	(I) Containing only Mooligai ingredients *(e.g.* Kungiliya Parpam)	2 years

(1)	(2)	(3)
	(II) Containing Mooligai ingredients with Thathu Porutkal/Parpam/Centuram/Cunnam/Kattu / Kalanku *(e.g.*, Aya Centuram)	10 years
	(HI) Containing Mooligai ingredients with Jeeva Porutkal *(e.g.*, Sangu Parpam)	10 years
(v)	**Karuppu**	
	(I) Containing only Mooligai ingredients *(e.g.*, Vasambu Sutta Kari)	2 years
	(II) Containing Mooligai ingredients with Thathu Porutkal *(e.g.*, Sivanar Amirtham, Thalaga Karuppu)	5 years
	(III) Containing Mooligai ingredients with Jeeva Porutkal *(e.g.*, Kasthuri Karuppu, Pattu Karuppu)	5 years
(vi)	**Patankam**	
	(I) Mooligai based Patankam *(e.g.*, Sambirani Patankam)	5 years

	(II) Rasa based Patankam *(eg.,* Rasa Centuram)	10 years
(vii)	**Kulampu**	
	Based on process—	
	(I) Araippu Kulampu *(e.g.,* Agathiyar Kulampu)	5 years
	(II) Erippu Kulampu *(e.g.,* Kumatti Kulampu)	3 years
(viii)	**Meluku**	
	Based on process—	
	(I) Araippu Meluku *(e.g.,* Linga Meluku)	5 years
	Based on Process—	
	(II) Idippu Meluku *(e.g.,* Rasa Gandhi Meluku/Idi Vallthi Meluku)	3 years
	Based on raw materials-	
	(III) Mooligai Meluku *(e.g.,* Malaikudara Meluku)	3 years
(ix)	**Karpam**	
	Based on raw materials—	
	(I) Mooligai Karpam *(e.g.,* Karisalai Karpam, Thiripala Karpam)	2 years
	Based on raw materials—	
	(II) Mooligai Thathu Karpam *(e.g.,* Aya Bringaraja Karpam)	5 years
	Based on process-	
	(III) Araippu Karpam *(e.g.,* Irunelli Karpam)	3 years
(x)	**Satthu**	
	(I) Satthu derived from Mooligai *(e.g.,* Seenthil Satthu)	2 years
	(II) Satthu derived from Thathu Porutkal *(e.g.,* Aya Satthu, Eya Satthu,Thurusu Satthu)	10 years

(1)	(2)	(3)
	(III) Satthu derived from Jeeva Porutkal *(e.g.,* Sembu Satthu derived from Poonagam, Mayiliragu)	5 years
(xi)	Ilakam/Legiyam/Iracayanaam	3 years
(xii)	Kallikkam/Mai/Kalimbu/Neer/Venney	1 year
(xiii)	Karam (Karanool)	2 years
(xiv)	Kattu (Medicated bandage cloth)/See!ai/Varthy/Thiri	1 year

(xv)	Kattu/Kalanku/Cunnam	10 years
(xvi)	Kutinir/Kiyazham (with preservatives)	3 years
(xvii)	Manappaku/Panagam	3 years
(viii)	Nasiyathuli/Kanthuli/Sevithuli	1 year
(xix)	Ney/Ghirutham/Kadugu	2 years
(XX)	Oothal./Nasigaparanam/Thoopasarakku	1 year
(xxi)	Pakkuvam, Thennoral	1 year
(xxii)	Panda Vaippu	10 years
(xxiii)	Peechu	2 years
(xxiv)	Sutigai	2 years
(xxv)	Tailam/Ennai/Poochu	3 years
(xxvi)	Tinir	1 year
(xxvii)	Tiravakam (derived from Thathu Porutkal)	2 years

(Unani medicines)

SI. No.	Dosage form	Shelf life or date of expiry with effect from the date of manufacture
(1)	(2)	(3)
(i)	Arq (except Arq-e-Ajeeb)	1 year
(ii)	Arq-e-Ajeeb	5 years
(iii)	Ayarij / Sunoon/Zuroor/Ghazah	2 years
(iv)	Burood	1 year
(v)	Shiyaf	2 years
(vi)	Surma/Kohal	3 years
(vii)	Habb	3 years
(viii)	Halwa	3 years
(ix)	Itrifai	3 years
(x)	lauhar/Jawahir	5 years
(xi)	Jawarish	4 years
(xii)	Khamira	3 years

(1)	(2)	(3)
(xiii)	Kushta	10 years

(xiv)	Laboob	3 years
(xv)	Laooq	3 years
(xvi)	Majoon/Dawa	3 years
(xvii)	Marham/Zimad/Qairooti	2 years
(xviii)	Mufarreh	3 years
(xix)	Murabba	1 year
(xx)	Nabeez	10 years
(xxi)	Qurs	3 years
(xxii)	Qutoor	1 year
(xxiii)	Raughaniyat/Tila	3 years
(xxiv)	Sharbat,/ Sikajabeen	3 years
(xxv)	(I) Sufoof (Without Salt)	2 years
	(II) Sufoof (Containing salt)	1 year
(xxvi)	Tiryaq	3 years.]

GOVERNMENT ANALYSTS AND INSPECTORS FOR AYURVEDIC (INCLUDING SIDDHA) OR UNANI DRUGS

162. Duties of inspectors specially authorised to inspect the manufacture of Ayurvedic (including Siddha) or Unani drugs.—Subject to the instructions of the controlling authority, it shall be the duty of an Inspector authorised to inspect the manufacture of Ayurvedic (including Siddha) or Unani drugs—

(i) to inspect not less than twice a year, all premises licensed for manufacture of Ayurvedic (including Siddha) or Unani drugs within the area allotted to him and to satisfy himself that the conditions of the licence and the provisions of the Act and the rules made thereunder are being observed;

(ii) to send forthwith to the controlling authority after each inspection a detailed report indicating whether or not the conditions of the licence and the provisions of the Act and the rules made thereunder are being observed;

(iii) to take samples of the drugs manufactured on the premises and send them for test or analysis in accordance with these rules;

(iv) to institute prosecution in respect of violation of the Act and the rules made thereunder.

[741][**162A. Qualifications for State Drug Licensing Authority for licensing of Ayurveda, Siddha and Unani drugs.**—(a) The Ayurvedic/Siddha/Unani qualifications as per Schedule II of CCIM Act 1970/B. Pharma (Ayurveda) of a recognized University.

(b) At least 5 years' experience in the Ayurveda/Siddha/Unani drug manufacturing or testing of Ayurvedic, Siddha and Unani drugs or enforcement of provisions of Chapter IVA of the Drugs and Cosmetics Act, 1940 and rules made thereunder or teaching/ research on clinical practice of Ayurveda/Siddha/Unani System.]

163. Procedure for despatch of sample to Government Analyst and its receipt by the Government Analyst.—(1) Sample for test or analysis shall be sent to the Government Analyst by registered post or by hand in a sealed package enclosed together with a memorandum in Form 18A in an outer cover addressed to the Government Analyst.

(2) The package as well as the outer cover shall be marked with distinguishing number.

(3) A copy of the memorandum and a specimen impression of the seal used to seal the package shall be sent by registered post or by hand to the Government Analyst.

(4) On receipt of the package from an Inspector, the Government Analyst or an Officer authorised by him writing in this behalf shall open the package and shall also record the conditions of the seals on the package.

(5) After the test or analysis has been completed, one copy of the results of the test or analysis shall be supplied forthwith to the sender in Form 13A. A copy of the result in Form 13A shall be sent simultaneously to the controlling authority and to the Drugs Controller, India.

[742][PHARMACOPOEIA COMMISSION FOR INDIAN MEDICINE AND HOMOEOPATHY AND CENTRAL DRUGS LABORATORY OF INDIAN MEDICINE AND HOMOEOPATHY TO FUNCTION AS CENTRAL DRUGS LABORATORY FOR THE PURPOSE OF TESTING OR ANALYSIS OF AYURVEDA, SIDDHA, UNANI AND HOMOEOPATHY DRUGS

163A. Functions.—Pharmacopoeia Commission of Indian Medicine and Homoeopathy at Ghaziabad (Uttar Pradesh) under the Central Government shall function to develop and amend standards of Ayurvedic, Siddha, Unani and Homoeopathy drugs and publish pharmacopoeial monographs, formularies and standardize procedures with the approval of the Central Government laboratory of the Pharmacopoeia Commission shall be the Central Drugs Laboratory for Indian Medicine and Homoeopathy for the purpose of testing or analysis of Ayurveda, Siddha, Unani and Homoeopathy Drugs.

163AA.—(1) The Central Government shall, by notification in the Official Gazette and with effect from such date as may be specified therein, constitute Scientific Advisory Board for the Pharmacopoeia Commission for Indian Medicine and Homoeopathy for a term of three years, to advise the Central Government, the State Governments and the stakeholders on the matters of standards, standard operating procedures and testing protocols of Ayurveda, Siddha, Unani and Homoeopathy Drugs.

(2) The Scientific Advisory Board shall consist of the following members, namely:—

(i) Retired Scientific Expert of drugs to be nominated as Chairman by the Central Government;

(ii) Director, Pharmacopoiea Commission for Indian Medicine and Homoeopathy; *ex officio* Member Secretary;

(iii) Advisor dealing with drugs, Ministry of AYUSH, *ex officio*-,

(iv) Drugs Controler General, India, *ex officio;*

(v) Scientific Director, Indian Pharmacopoeia Commission, *ex officio;*

(vi) Director General, Central Council for Research in Ayurvedic Sciences, *ex officio;*

(vii) Director General, Central Council for Research in Unani Medicine, *ex officio;*

(viii) Director General, Central Council for Research in Siddha, *ex officio;*

(ix) Director General, Central Council for Research in Homoeopathy, *ex officio;*

(x) Central Government Analyst for Ayurveda, Siddha, Unani and Homoeopathy, Drugs, *ex officio;*

(xi) One professionally experienced expert each of standardization or quality control of Ayurveda, Siddha, Unani, Homoeopathy drugs, pharmacognosy or botany, chemistry, Phyto-chemistry and pharmacy to be nominated by the Central Government from amongst the scientific institutions.

(xii) Chairman shall have the discretion to co-opt two experts for advice and guidance in specific matters of standards of Ayurvedic, Siddha, Unani and Homoeopathy drugs.

(3) The functions of Scientific Advisory Board may be exercised notwithstanding any vacancy therein.

(4) The Commission shall constitute a pharmacopoeia committee and sub-committees there under for a period of three years on the recommendation of Scientific Advisory Board.

(5) The meetings of Scientific Advisory Board, Pharmacopoeia Committee and Subcommittees shall be supported by the Commission.]

[743]**[163B.** The functions of the Central Drug Laboratory in respect of Ayurvedic, Siddha, Unani and Homoeopathy drugs shall be carried out at the Pharmacopoeia Commission for Indian Medicine and Homoeopathy, Ghaziabad, (Uttar Pradesh) and the functions of the Director in respect of the said drugs shall be exercised by the Director of the said laboratory.

163BB. (1) The laboratory of Pharmacopoeia Commission for Indian Medicine and Homoeopathy shall act as the Central Appellate Drugs Laboratory under section 6 of the Act for testing or analysis of samples of Ayurveda, Siddha, Unani and Homoeopathy Drugs as may be sent to it under sub-section(2) of section 11 or sub-section(4) of section 25 and 33H of the said Act.

(2) The Central Drugs Laboratory shall maintain reference museum and herbarium of Ayurveda, Siddha, Unani and Homoeopathy drugs, conduct training programmes for analytical and drugs quality control methods and carry out such activities and duties as may be entrusted to it by the Central Government.

(3) All functions of the Central Drugs Laboratory for Ayurvedic, Siddha, Unani and Homoeopathy drugs shall be exercised by the Director or the officer appointed on his behalf of the Pharmacopoeia Commission for Indian Medicine and Homoeopathy.]

163C. **Despatch** of **samples** for **test** or **analysis.**—(1) Samples for testing or analysis of Ayurveda, Siddha and Unani drugs under sub-section (2) of section 11 or sub-section (1) of section 25 and section 33H of the Act shall be sent by registered post in a sealed packet, enclosed with a memorandum in Form 1A, [744][Form 18 or Form 18-A] specified in Schedule A, in an outer cover addressed to the Director, [745][Pharmacopoeia Commission for Indian Medicine and Homoeopathy, Ghaziabad (Uttar Pradesh)].

(2) The packet as well as the outer cover, shall be marked with a distinguishing number.

(3) A copy of the memorandum in Form 1A and a specimen impression of the seal used to seal the packet shall be sent separately by registered post to the Director, [746][Pharmacopoeia Commission for Indian Medicine and Homoeopathy, Ghaziabad (Uttar Pradesh)].

163D. Recording of condition of seals.—On receipt of the packet, it shall be opened by an officer authorised in writing on that behalf by the Director, [746][Pharmacopoeia Commission for Indian Medicine and Homoeopathy, Ghaziabad (Uttar Pradesh)], who shall record the condition of the seal on the packet.

163E. Report of result of test or analysis.—After test or analysis, the result of the test or analysis, together with full protocols of the tests applied, shall be supplied forthwith to the sender in Form 2A [747][or Form 13] of as specified in the said Schedule.

163F. Fees.—The fees for test and analysis shall be as specified in Schedule B-l.

163G. Signature on certificates.—Certificates issued under these rules by the [746][Pharmacopoeia Commission for Indian Medicine and Homoeopathy, Ghaziabad (Uttar Pradesh)] shall be signed by the Director or by an officer authorised by the Central Government to sign such certificates.]

[748]**[164. Method of test or analysis to be employed in relation to Ayurvedic, Siddha, Unani or Homoeopathy drugs.**—The method of test or analysis to be employed in relation to an Ayurvedic, Siddha, Unani or Homoeopathy drugs shall be such as may be specified in the Ayurvedic, Siddha, Unani or Homoeopathy Pharmacopoeia, or if no such pharmacopoeias are available or if no test is specified in such pharmacopoeias, such test as the Government Analyst may employ, such tests being scientifically established to determine whether the drug contains the ingredients as stated on the label.]

165. Qualifications of Government Analyst.—A person who is appointed a Government Analyst under section 33F of the Act shall be a person possessing the qualifications prescribed in rule 44 or a degree in [749][Ayurveda, Siddha, Unani or Homoeopathy] system, as the case may be, conferred by a University, a State Government or Statutory Faculties, Councils [750][Boards of Indian Systems of Medicine and Homoeopathy Boards] recognised by the Central or State Government, as the case may be, for this purpose and has had not less than three years' post-graduate experience in the analysis of drugs in a laboratory under the control of (i) a Government Analyst appointed under the Act, or (ii) a Chemical Examiner to Government, or (iii) the head of an institution specially approved for the purpose by the appointing authority.

166. Duties of Government Analyst.—(1) The Government Analyst shall analyse or test or cause to be analysed or tested such samples of [751][Ayurveda, Siddha, Unani or Homoeopathy] drugs as may be sent to him by Inspectors or any other person or authority authorised by the Central Government or a State

Government under the provisions [752][***] of the Act and shall furnish reports of the results of test or analysis in accordance with these rules.

(2) A Government Analyst appointed under section 34F shall from time to time forward to the Government reports giving the results of analytical work and research with a view to their publication at the discretion of the Government.]

[753][**167. Qualifications of Inspector.**—A person who is appointed an Inspector under section 33 G shall be a person who—

(a) has the qualifications laid down under rule 49 and shall have undergone practical training in the manufacture of Ayurvedic, Siddha, Unani or Homoeopathy drug, as the case may be; or

(b) has a degree in Ayurvedic, Siddha, Unani or Homoeopathy system or degree in Ayurvedic, Siddha, Unani or Homoeopathy Pharmacy, as the case may be, conferred by a University or a State Government or a Statutory Faculty, Council or Board of Indian Systems of Medicine or Board of Homoeopathy recognized by the Central Government or the State Government for this purpose.]

[754][PART XIX

STANDARDS OF AYURVEDIC SIDDHA AND UNANI DRUGS

168. Standards to be complied with in manufacture for sale or for distribution of Ayurvedic, Siddha and Unani Drugs.—

S.No	*Class of Drugs*	*Standards to be complied with*
1.	[755][Drugs] included in Ayurvedic Pharmacopoeia	The standards for identity, purity and strength as given in the editions of Ayurvedic Pharmacopoeia of India for the time being in force.
2.	Asavas and Aristas	The upper limit of alcohol as self-generated alcohol should not exceed 12% v/v excepting those that are otherwise notified by the Central Government from time to time.]

[756][**169. Permitted Excipients.**—Permitted Excipients along with their standards *i.e.*, additives, preservatives, antioxidants, flavouring agents, chelating agents, etc., permitted in the Indian Pharmacopoeia (IP), Prevention of Food Adulteration Act, 1954 and Bureau of Indian Standard Act, 1986 are permitted for use in Ayurveda, Siddha and Unani drugs with the following conditions, namely:—

1. The above excipients shall be used in the permissible limits as prescribed in the Indian Pharmacopoeia/Prevention of Food Adulteration Act, 1954/Food Product Order/Bureau of Indian Standard Act, 1986 and they shall comply with the respective quality specifications, not exceeding any specified limits of usage therein, and except Hydrogenated vegetable oil.

2. Only natural colouring agents as permitted under rule 26 of Prevention of Food Adulteration Rules, 1955 will be used for Ayurveda, Siddha and Unani drugs and additionally, colours permitted under rule 127 of Drugs and Cosmetic Rules, 1945 shall be used for Proprietary Ayurveda, Siddha and Unani drugs as defined in sub-clause (i) of clause (h) of section 3 of the Drugs and Cosmetics Act, 1940, not exceeding any specified limits of usage therein.

3. Preservatives and Colouring agents shall be mentioned on the label for the information of the consumer as required under rule 161 of the Drugs and Cosmetics Rule, 1945.

4. Additives used in various processes and in formulating dosage forms shall be mentioned clearly with quantities used, in the application for licenses and the record for the same shall be maintained by the manufacturers.

5. Manufacturers shall be responsible to ensure rationality, safety and quantity used of various excipients in the formulation.

6. If any excipients or additive or preservative etc., referred in Indian Pharmacopoeia/Prevention of Food Adulteration Act, 1954/Food Product Order/Bureau of Indian Standard Act, 1986 is deleted at a

particular point of time, this will also be deleted simultaneously for the use in Ayurveda, Siddha and Unani drugs.

7. Following artificial sweeteners as per maximum limit indicated below may be used in various dosage forms of Ayurveda, Siddha, Unani Proprietary Medicines:—

Artificial sweeteners may be used only in proprietary ASU products and the label of such products should carry a statutory warning stating the name and quantity of the artificial sweetener used.

The recommended Acceptable Daily Intake (ADI) of these sweeteners as laid down by US FDA is as follows:

S. No.	Sucralose	Aspartame	Saccharin	Acesulfame K
1.	5mg/kg body weight	40 mg/kg body weight	3 mg/kg body weight	15 mg/kg body weight

One-third of the above ADI would be permissible for use in Ayurveda, Siddha, Unani Patent and Proprietary drugs.

8. Any previous notification issued by the Department of AYUSH regarding use of excipients/additives or preservatives in Ayurveda, Siddha and Unani medicines stands superseded.]

757.**[170.]** **Error! Reference source not found.**[*****]

SCHEDULE A

FORM 1

(See rule 4)

MEMORANDUM TO THE CENTRAL DRUGS LABORATORY

Serial Number.....

To the Director,

Central Drugs Laboratory.....

From.....

I send herewith, under the provisions of section 25(4) of the Drugs and Cosmetics Act, 1940, sample(s) of a drug purporting to be..... for test or analysis and request that a report of the result of the test or analysis may be supplied to this Court.

2. The distinguishing number on the packet is.....

3.Particulars of offence alleged.....

4. Matter on which opinion is required.....

5. A fee of Rs.....has been deposited in Court.

Date..... Magistrate……..

[758]**[Form 1A**

(See rule 163C)

[759]**[Pharmacopoeia Commission for Indian Medicine and Homoeopathy, Ghaziabad (Uttar Pradesh)]**

From.....

(Full name, Designation and Postal address of the sender)

Serial No.....

To the Director,

Pharmacopoeial Laboratory for Indian Medicine,

I send herewith under the provisions of section 11 (2)/section 25(4) and section 33H of the Drugs and Cosmetics Act, 1940, sample(s) of a drug purporting to be.....for test or analysis and request that a report of the result of the test or analysis may be supplied to this Court.

2. The distinguishing number on the packet is.....

3. Particulars of offence alleged.....

4. Matter on which opinion is required.....

5. A fee of Rs.....has been deposited in Court.

Date..... .....

Magistrate/Authorized Signatory.]

FORM 2

(See rule 6)

CERTIFICATE OF TEST OR ANALYSIS BY THE CENTRAL DRUGS LABORATORY

Certified that the samples, bearing number.....purporting to be a sample of .....received on .....with memorandum No. ..... dated .....from .....has been tested/analysed and that the result of such test/analysis is as stated below.

2. The condition of the seals on the packet on receipt was as follows:—

*3. In the opinion of the undersigned the sample is of standard quality is not of standard quality as defined in the Drugs and Cosmetics Act, 1940, and rules thereunder for the reasons given below:

Director

Date..... Central Drugs Laboratory or other Authorised Officer

Details of results of test or analysis with protocols of test applied

Director

Date..... Central Drugs Laboratory or other Authorised Officer

* If opinion is required on any other matter, the paragraph should be suitably amended.

[760][FORM 2A

(See rule 163E)

CERTIFICATE OF TEST OR ANALYSIS FROM THE [761][PHARMACOPOEIA COMMISSION FOR INDIAN MEDICINE AND HOMOEOPATHY] OR GOVERNMENT ANALYST

Certified that the samples, bearing number.....purporting to be a sample of.....received on.....with memorandum No..... dated.....from.....has been tested/ analysed and that the result of such test/analysis is as stated below.

2. The condition of the seals on the packet on receipt was as follows:—

*3. In the opinion of the undersigned the sample is of standard quality as defined in the Drugs and Cosmetics Act, 1940, or rules thereunder for the reasons given below.

Or

In the opinion of the undersigned the sample is not of standard quality as defined in the Drugs and Cosmetics Act, 1940, or rules thereunder for the reasons given below.

"Note.—* delete whichever is not applicable."

(Signature of the Analyst Person-in-Charge of testing)

Date.....

Place..... Name & Designation & Seal.....

Name & Address of the Laboratory.....]

[762][***]

[763][FORM 8

(See rule 24)

APPLICATION FOR LICENCE TO IMPORT DRUGS (EXCLUDING THOSE SPECIFIED IN SCHEDULE X) TO THE DRUGS AND COSMETICS RULES, 1945

I/we* .....(full address with telephone number, fax number and e-mail address) hereby apply for a licence to import drugs specified below manufactured by M/s.....(full address, with telephone number, fax, and e-mail no.)

2. Names of the drugs to be imported:

(1)

(2)

(3)

3. I/we*, ..., enclose herewith an undertaking in Form 9 dated.....signed by the manufacturer as required by rule 24 of the Drugs Rules, 1945.

4. I/we, ..., enclose herewith a copy of Registration Certificate concerning the drugs to be imported in India, issued under Form 41 of the rules, *vide* Registration Certificate No ..... Dated .....issued.....through M/s..... (name and full address)..... valid upto.....

5. I/we*,....., hold a valid wholesale licence for sale or distribution of drugs or valid licence to manufacture drugs, under the provisions of the Act and rules made thereunder. A copy of the said licence is enclosed.

6. A fee of.....has been credited to Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines." under the Drugs Rules, 1945—Central *vide* Challan No..... dated..... (attached in original)

Signature.....

Name.....

Designation.....

Seal/Stamp of Manufacturer's agent in India

Place: .....

Date: .....

* Delete whichever is not applicable]

[764][FORM 8A

(See rule 24)

APPLICATION FOR LICENCE TO IMPORT DRUGS SPECIFIED IN SCHEDULE X TO THE DRUGS AND COSMETICS RULES, 1945

I/we*,....., (full address with telephone number, fax number and e-mail address) hereby apply for a licence to import drugs specified below manufactured by M/s.....(full address with telephone no, fax and e- mail no.)

2. Names of the drugs to be imported

(1)

(2)

(3)

3. I/we*, ..., enclose herewith an undertaking in Form 9 dated .....signed by the manufacturer as required by rule 24 of Drugs Rules, 1945.

4. I/we*, ..., enclose herewith a copy of Registration Certificate concerning the drugs to be imported in India issued under Form 41 of the rules, *vide* Registration Certificate No..... Dated..... issued through M/s..... name and full address..... valid upto .....

5. I/we*,..... hold a valid wholesale licence for sale or distribution of drugs or licence to manufacture drugs, under the provisions of the Act and rules made thereunder. A copy of the said licence is enclosed.

6. A fee of.....has been credited to Government under the Head of Account "0210—Medical and Public Health, 04—Public Health, 104—Fees and Fines" under the Drugs Rules, 1945—Central *vide* Challan No..... dated ..... (attached in original).

Signatures.....

Name.....

Designation.....

Seal/Stamp of Manufacturer's agent in India

Place.....

Date.....

* Delete whichever is not applicable.]

FORM 9

(See rule 24)

FORM OF UNDERTAKING TO ACCOMPANY AN APPLICATION FOR AN IMPORT LICENCE

Whereas.....of.....intends to apply for a licence under the Drugs Rules, 1945, for the import into India, of the drugs specified below manufactured by us, we .....of .....hereby give this undertaking that for the duration of the said licence—

(1) the said application shall be our agent for the import of drugs into India;

(2) we shall comply with the conditions imposed on a licence by [765][Rules 74 and 78] of the Drugs Rules, 1945;

(3) we declare that we are carrying on the manufacture of the drugs mentioned in this undertaking at the premises specified below, and we shall from time to time report any change of premises on which manufacture will be carried on and in cases where manufacture is carried on in more than one factory any change in the distribution of functions between the factories;

(4) we shall comply with the provisions of Part IX of the Drugs Rules, 1945;

(5) every drug manufactured by us for import under licence into India shall as regards strength, quality and purity conform with the provisions of Chapter ID of the Drugs and Cosmetics Act, 1940, and the Drugs Rules, 1945;

(6) we shall comply with such further requirements, if any, as may be specified by Rules, by the Central Government under the Act and of which the licensing authority has given to the licensee not less than four months' notice.

Names of drugs and classes of drugs

Particulars of premises where manufacture is carried on.

Dated..... [766][Signature .....
Name.....
Designation.....
Seal/Stamp of manufacturer or on behalf of the manufacturer]

[767][FORM 10

(See rules 23 and 27)

LICENCE TO IMPORT DRUGS (EXCLUDING THOSE SPECIFIED IN SCHEDULE X) TO THE DRUGS AND COSMETICS RULES, 1945

Licence Number..... Date.....

1.....(name and Full address of the importer)..... is hereby licensed to import into India during the period for which this licence is in force, the drugs specified below, manufactured by M/s.....(name and full address) and any other drugs manufactured by the said manufacturer as may from time to time be endorsed on this licence.

2. This licence shall be in force from.....to.....unless it is sooner suspended or cancelled under the said rules.

3. Names of drugs to be imported:

Place.....
Date.....

LICENSING AUTHORITY
Seal /Stamp

Conditions of Licence

1. A photocopy of licence shall be displayed in a prominent place in a part of the premises, and the original licence shall be produced, whenever required.

2. Each batch of drug imported into India shall be accompanied with a detailed batch test report and a batch release certificate, duly signed and authenticated by the manufacturer with date of testing date of release and date of forwarding such reports. The imported batch of each drug shall be subjected to examination and testing as the licensing authority deems fit prior to its marketing.

3. The licencee shall be responsible for the business activities of the manufacturer in India alongwith the registration holder and his authorised agent.

4. The licensee shall inform the licensing authority forthwith in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the

current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

[768][FORM 10A

(See rules 23 and 27)

LICENCE TO IMPORT DRUGS SPECIFIED IN SCHEDULE X TO THE DRUGS AND COSMETICS RULES, 1945

Licence Number..... Date .....

..... (Name and full address of the importer) is hereby licensed to import into India during the period for which this licence is in force, the drugs specified below, manufactured by M/s..... (Name and full address) and any other drugs manufactured by the said manufacturer as may from time to time be endorsed on this licence.

2. This licence shall be in force from.....to ..... unless it is sooner suspended or cancelled under the said rules.

3. Name of drugs to be imported.

Place.....

Date..... LICENSING AUTHORITY

Seal/Stamp

Conditions of Licence

1. A photocopy of licence shall be displayed in a prominent place in a part of the premises, and the original licence produced, whenever required.

2. Each batch of drug imported into India shall be accompanied with a detailed batch test report and a batch release certificate, duly signed and authenticated by the manufacturer with date of testing, date of release and date of forwarding such reports. The imported batch of each drug shall be subjected

to examination and testing as the licensing authority deems fit prior to its marketing.

3. The licencee shall be responsible for the business activities of the manufacturer in India alongwith the registration holder and his authorised agent.

4. The licencee shall inform the licensing authority forthwith in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

FORM 11

(See rule 33)

LICENCE TO IMPORT DRUGS FOR THE PURPOSES OF EXAMINATION, TEST OR ANALYSIS

1 ....., of .....is hereby licensed to import from .....the drugs specified below for the purposes of examination, test or analysis at.....or in such other places as the licensing authority may from time to time authorise.

2. This licence is subject to the conditions prescribed in the Rules under the Drugs and Cosmetics Act, 1940.

3. This licence shall, unless previously suspended or revoked, be in force for a period of [769][three years] from the date specified below:

Names of drugs	*Quantity which may be imported*

Date..... LICENSING AUTHORITY

Seal/Stamp

Names of drugs	*Quantity which may be imported*

Place..... LICENSING AUTHORITY

Date..... Seal/Stamp

Conditions of Licence

1. The licence shall be displayed in the office of the Medical Superintendent of Government Hospital/Head of Institution of Autonomous Medical Institution.

2. The licencee shall store the drugs imported under this licence under proper storage conditions.

3. The drugs under this licence shall be exclusively used for the treatment of patients, and a record shall be maintained in this regard, by a registered pharmacist giving the full name(s) and address(es) of the patients, diagnosis, dosage schedule, total quantity of drugs imported and issued, and shall be countersigned by the Medical Superintendent of the Government Hospital of Head of the Autonomous Medical Institution which shall be produced, on demand by an Inspector appointed under the Act.]

[770] **[FORM 11A**

(See rule 33A)

LICENCE TO IMPORT DRUGS BY A GOVERNMENT HOSPITAL OR AUTONOMOUS MEDICAL INSTITUTION FOR THE TREATMENT OF PATIENTS

Licence No ……. Date…….
Dr. …… Designation…….
……
of……
(Name of College/Hospital/Autonomous Institution)
is hereby licenced to import from M/s .....(name and full address) the drugs specified below for the purpose of treatment of patients for

the disease (name of the disease)..... at ..... or in such other places as the licensing authority may from time to time authorise.

2. This licence shall, unless previously suspended or revoked, be in force for a period of one year from the date of issue specified above.

3. Names of drugs to be imported:

Names of drugs	*Quantity which may be imported*

Place..... LICENSING AUTHORITY

Date..... Seal/Stamp

Conditions of Licence

1. The licence shall be displayed in the Office of the Medical Superintendent of Government Hospital / Head of Institution of Autonomous Medical Institution.

2. The licensee shall store the drugs imported under this licence under proper storage conditions.

3. The drugs imported under this licence shall be exclusively used for the treatment of patients, and a record shall be maintained in this regard, by a registered pharmacist giving the full name(s) and address(es) of the patients, diagnosis, dosage schedule, total quantity of drugs imported and issued, and shall be countersigned by the Medical Superintendent of the Government Hospital or Head of the Autonomous Medical Institution which shall be produced, on demand by an Inspector appointed under the Act.]

FORM 12

(See rule 34)

APPLICATION FOR LICENCE TO IMPORT DRUGS FOR PURPOSE OF EXAMINATION, TEST OR ANALYSIS

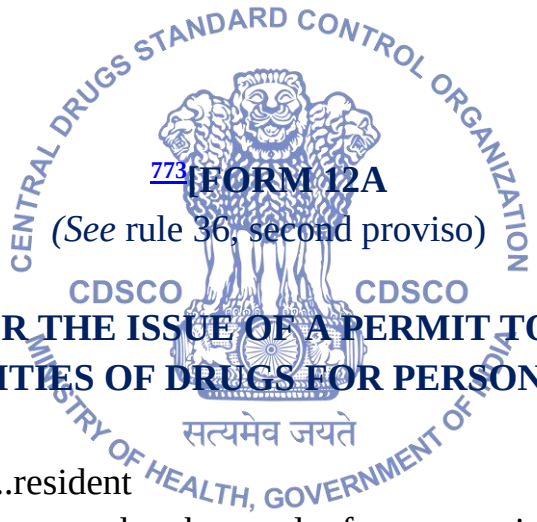
1....., resident of .....by occupation..... hereby apply for a licence to import the drugs specified below for the purpose of examination, test or analysis at .....from

.....and I undertake to comply with the conditions applicable to the licence.

[771][[772][A fee of rupees ..... has been credited to Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines under the Drugs and Cosmetics Rules, 1945—Central *vide* Challan No..... dated..... (attached in original).]]

Names of drugs	***Quantity which may be imported***

Place.....
Date.....LICENSING AUTHORITY



[773]**[FORM 12A**

(See rule 36, second proviso)

APPLICATION FOR THE ISSUE OF A PERMIT TO IMPORT SMALL QUANTITIES OF DRUGS FOR PERSONAL USE

1.....resident of.....by occupation..... hereby apply for a permit to import the drugs specified below for personal use from I attach a prescription from a registered medical practitioner in regard to the need for the said drugs.

Names of drugs	*Quantity which may be imported*

Date..... Signature.....]

[774]**[FORM 12AA**

(See rule 34A)

APPLICATION FOR LICENCE TO IMPORT SMALL QUANTITIES OF NEW DRUGS BY A GOVERNMENT HOSPITAL OR AUTONOMOUS MEDICAL INSTITUTION FOR THE TREATMENT OF PATIENTS

I,..... (name) (and designation) ..... of ..... (name of the Hospital/Autonomous Medical Institution) ..... hereby apply for a licence to import small quantities of new drugs specified below for the purpose of treatment of patients for the disease.....(name of the disease) at.....(name and place of the hospital) and I undertake to comply with the conditions applicable to the licence and other provisions of the Drugs and Cosmetics Act, 1940 and the rules made thereunder, from time to time.

1. A fee of rupees.....has been credited to Government under the Head of Account "0210-Medical and Public Health, 04-Medical and Public Health, 104-Fees and Fines" under the Drugs and Cosmetics Rules, 1945—Central *vide* Challan No....., dated ....., (attached in original).

2. Name of new drug to be imported—

Names of drugs	*Quantity which may be imported*

Place.....

Date..... Signature……..

Name…….....

Seal/Stamp.

CERTIFICATE

Certified that the drugs specified above for import are urgently required for the treatment of patients suffering from.....and that the said drug(s) is/ are not available in India.

Signature.....

Medical Superintendent of the Government Hospital/ Head of Autonomous Medical Institution

Seal/Stamp

Place.....
Date.....]

[775][FORM 12B

(See rule 36, second proviso)

PERMIT FOR THE IMPORT OF SMALL QUANTITIES OF DRUGS FOR PERSONAL USE

.....is hereby permitted to import from ..... the drugs specified below for personal use.

2. This permit is subject to the conditions prescribed in the Rules under the Drugs and Cosmetics Act, 1940.

3. This permit shall, unless previously suspended or revoked, be in force [776][till such time as the patient requires the drug as per the prescription of a registered medical practitioner and the permit holder shall submit details of drugs imported and utilised to the licensing authority on yearly basis] from the date specified below.

Names of drugs	*Quantity which may be imported*

Date..... Licensing Authority.]

FORM 13

(See rule 46)

CERTIFICATE OF TEST OR ANALYSIS BY GOVERNMENT ANALYST UNDER SECTION 25(1) OF THE DRUGS AND COSMETICS ACT, 1940

1. Name of Inspector from whom received .....

2. Serial No. and date of Inspector's memorandum .....

3. Number of sample .....

4. Date of receipt.....

5. Names of drugs purporting to be contained in the sample.....

6. Condition of seals on the [777][packet or on portion of sample or container].....

7. Result of test or analysis with protocols or test or analysis applied.....

In the opinion of the undersigned the sample referred to above (is of standard/is not of standard) quality as defined in the Drugs and Cosmetics Act, 1940, and Rules thereunder for the reasons given below:—

Dated..... Government Analyst.....

[778]**[FORM 13A**

[See rule 163(5)]

CERTIFICATE OF TESTS OR ANALYSIS BY GOVERNMENT ANALYST UNDER SECTION 33H OF THE DRUGS AND COSMETICS ACT, 1940

1. Name of Inspector from whom received .....

2. Serial No. and date of Inspector's memorandum.....

3. Number of sample.....

4. Date of receipt .....

5. Names of ingredients purporting to have been used in the preparation of the sample.....

6. Condition of seal on the package.....

7.Results of test or analysis.....

[779][In the opinion of the undersigned the sample referred to above is of standard/is not of standard quality as defined in the Drugs and Cosmetics Act, 1940 and the rules made thereunder for the reasons given below:]

Date..... Government Analyst.....]

FORM 14A

(See rule 47)

APPLICATION FROM A PURCHASER FOR TEST OR ANALYSIS OF A DRUG UNDER SECTION 26 OF THE DRUGS AND COSMETICS ACT, 1940

1. Full name and address of the applicant.....

2. Occupation.....

3. Name of drug purporting to be contained in the sample.....

4. Name and full address of the pharmacy or concern where the drug was purchased……

5. Date on which purchased.....

6. Reasons why the drug is being submitted for test or analysis.....

[780][7. A fee of rupees.....*vide* Schedule B to the Drugs Rules, 1945, has been credited to Government under the head of account "080-Medical-Miscellaneous-Fees under the Drugs Rules, 1945—Central/State"—*vide* treasury receipt attached.]

I hereby declare that the drug being submitted for test was purchased by or for me. I further declare that the sample of the drug being sent for test or analysis is exactly as it was purchased and has not been tampered with in any way to reduce its potency.

Date..... Signed.....

FORM 14B

(See rule 47)

CERTIFICATE OF TEST OR ANALYSIS BY GOVERNMENT ANALYST UNDER SECTION 26 OF THE DRUGS AND COSMETICS ACT, 1940

1. Name of person from whom sample received.....

2. Date of receipt.....

3. Name of drug purporting to be contained in the sample.....

4. *Opinion of the Government Analyst*—The sample referred to above is/is not of standard quality as defined in the Drugs and Cosmetics Act, 1940, and rules thereunder.

Date.....Government Analyst.....

[781][FORM 15

(See rules 54 and 145C)

ORDER UNDER SECTION 22(1) (C) OF THE DRUGS AND COSMETICS ACT, 1940 REQUIRING A PERSON NOT TO DISPOSE OF STOCK IN HIS POSSESSION

Whereas, I have reason to believe that the stocks of drugs/[782][***] in your possession detailed below contravene the provisions of section 18 of the Drugs and Cosmetics Act, 1940;

Now, therefore, I hereby require you under clause (c) of sub-section (1) of section 22 of the said Act, not to dispose of the said stock for a period of.....days from the date of this order.

Date..... Inspector.....

Details of stock of drugs/[782][***].

Date..... Inspector]

[783][FORM 16

(See rules 55 and 145B)

RECEIPT FOR STOCK OF DRUGS [784][***] FOR RECORD, REGISTER DOCUMENT OR MATERIAL OBJECT SEIZED UNDER SECTION 22(1)(C) OR (CC) OF THE DRUGS AND COSMETICS ACT, 1940

The stock of drugs or [782][***] or records, registers, documents or material objects, detailed below has/have this day been seized by me under the provisions of clause (c) or clause (cc) of sub-section (1) of section 22 of the Drugs and [782][***] Act, 1940 (23 of 1940), from the premises of ..... situated at.....

Date..... Inspector.....

Details of drugs, [782][***], records, registers, documents or material objects seized.

Date..... Inspector.....]

[785][FORM 17

(See rules 56 and 145A)

INTIMATION TO PERSON FROM WHOM SAMPLE IS TAKEN

To

…….

I have this day taken from the premises of ..... situated at……..samples of the drugs / [786][***] specified below for the purpose of test or analysis.

Date..... Inspector.....

Details of sample taken

Date..... Inspector.....

[787][FORM 17A

(See rules 56A and 145AA**)**

RECEIPT FOR SAMPLES OF DRUGS [788][***] TAKEN WHERE FAIR PRICE TENDERED THEREOF UNDER SUB-SECTION (1) OF SECTION 23 OF THE DRUGS AND COSMETICS ACT, 1940 IS REFUSED

To

……

Whereas I, this.....day of.....[789][20]....., have taken from the premises of situated at..... samples of drugs/cosmetics as specified below:—

Details of samples.....

And whereas I had offered to pay you rupees.....as the fair price of the samples of drugs/cosmetics taken:

And whereas, you have refused to accept the fair price tendered thereof;

Now, therefore, I give you this receipt as the fair price tendered for the samples of the drugs/cosmetics taken by me.

Date.....Inspector.....]

FORM 18

(*See* rule 57)

MEMORANDUM TO GOVERNMENT ANALYST

Serial No. of Memorandum.....

From

To

The Government Analyst

The portion of sample/container described below is sent herewith for test or analysis under the provisions of clause (i) of sub-section (4) of section 23 of the Drugs and Cosmetics Act, 1940.

The portion of sample/container has been marked by me with the following mark. Details of portion of sample or container with name of [790][drug/[786][***]] which it purports to contain—

Date..... Inspector.....

[791][FORM 18A

[See rule 163(1)]

MEMORANDUM TO GOVERNMENT ANALYST

Serial No.....

From

To

The Government Analyst

The portion of sample/container described below is sent herewith for test or analysis under the provision of section 33H of the Drugs and Cosmetics Act, 1940.

The portion of sample/container has been marked by me with the following mark.

Details of portion of sample or container with name of ingredients from which it is claimed to be made.

Date..... Inspector.....

[792][FORM 19

[See rule 59(2)]

APPLICATION FOR GRANT [793]*[***]* OF A [792][LICENCE TO SELL, STOCK, EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] DRUGS OTHER THAN THOSE SPECIFIED IN SCHEDULE X

1. I/We, ..., hereby apply for licence to sell by wholesale/retail drugs specified in Schedules C and C(l) excluding those specified in Schedule X* and /or drugs other than those specified in Schedules C, C(l) and X to the Drugs Rules, 1945* and also to operate a pharmacy on the premises situated at.....

2. ! The sale and dispensing of drugs will be made under the person supervision of the qualified persons namely:—

..... (Name).....(Qualification).

3. Categories of drugs to be sold.

4. # Particulars for special storage accommodation.

5. A fee of rupees.....has been credited to the Government account under the head of account.....

Date.....Signature.....

* Delete whichever is not applicable
! To be deleted if drugs will be sold only by wholesale
Required only if products requiring special storage are to be sold.

FORM 19A

[See rule 59(2)]

APPLICATION FOR THE GRANT [794][***] OF A RESTRICTED [795][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] DRUGS BY RETAIL BY [796][***] DEALERS WHO DO NOT ENGAGE THE SERVICE OF QUALIFIED PERSON

1. I/We, ... of.....hereby apply for a licence to sell by retail (i) [797][Drugs other than those specified in Schedules C, C(l) and X] on the premises situated at...../ [796][***]

or (ii) Drugs specified in [798][Schedule C(l)] on the premises situated at...../ Drugs specified in [798][Schedule C(l)] as vendor in the area.....

2. Sales shall be restricted to such drugs as can be sold without the supervision of a qualified person under the Drugs and Cosmetics Rules.

3. Names or classes of drugs proposed to be sold.....

*4. Particulars of the storage accommodation for the storage of Schedule C(l) drugs on the premises referred to above.

!5. The drugs for sale will be purchased from the following dealers and such other dealers as may be endorsed on the licence by the licensing authority from time to time.

Name of the dealers .....Licence No.....

6. A fee of rupees [796][***]/#twenty has been credited to Government under the head of account.....

Date.....Signature.....

* Delete if not required.
! Applies only to an itinerant vendor.
Rupees five for itinerant vendors and applicants from a village or town having a population of 5,000 or less, and rupees twenty for other restricted licence.

[799][FORM 19AA

(See rule 62C)

APPLICATION FOR GRANT [794][***] OF A [795][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE BY WHOLESALE, OR DISTRIBUTE] DRUGS FROM A MOTOR VEHICLE

1. I/We,....., of.....hereby apply for [796][licence to sell, stock or exhibit or offer for sale by wholesale, or distribute] drugs specified in Schedules C and C(l) and/or drugs other than those specified in Schedule C and Schedule C(l) from the vehicle bearing registration No..... assigned under the Motor Vehicles Act, 1939.

2. Categories of drugs to be sold/distributed.....

3. A fee of rupees.....has been credited to Government under the head of account.....

*4. Particulars of the storage accommodation for the storage of drugs specified in Schedules C and C(l) on the vehicle referred to above.

Date..... Signature.....]

* Delete if not required.

FORM 19B

(See rule 67A)

APPLICATION FOR [795][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] HOMOEOPATHIC MEDICINES

1. I/We, ..., of .....hereby apply for a licence to sell by #wholesale/retail ..... Homoeopathic medicine on the premises situated at.....

*2. The sale and dispensing of Homoeopathic medicines shall be made under the person supervision of the following competent person-in-charge.

Name.....

3. A fee of rupees .....has been credited to Government under the head of account .....

Date.....Signature.....

To be deleted if Homoeopathic medicines will be sold by wholesale.

* Delete whichever is not applicable.

[800][FORM 19C

[See rule 59(2)]

APPLICATION FOR GRANT [801][***] OF A [800][LICENCE TO SELL, STOCK, EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] DRUGS SPECIFIED IN SCHEDULE X

1. I/We,..... of.....hereby apply for a licence to sell by *wholesale/retail drugs specified in Schedule **X** to the Drugs Rules, 1945. We operate a pharmacy on the premises, situated at.....

!2. The sale and dispensing of drugs will be made under the personal supervision of the qualified persons mentioned below:

(Name) ..... (Qualification)

(Name) ..... (Qualification)

3. Name of drugs to be sold.

4. #Particulars of storage accommodation.

5. A fee of rupees.....has been credited to Government account under the head of account.....

Date..... .Signature .....]

* Delete whichever is not applicable.
! To be deleted if drugs will be sold only by wholesale.
Required only if products requiring special storage are to be sold.]

FORM 20

[See rule 61(1)]

[802][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] DRUGS BY RETAIL OTHER THAN THOSE SPECIFIED IN [802][SCHEDULES C, C(l) AND X]

1. ....., is hereby [803][licensed to sell, stock or exhibit or offer for sale or distribute] by retail drugs other than those specified in [803][Schedules C, C(l) and X] of the Drugs Rules. 1945, * and to operate a pharmacy on the premises situated at.....subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940 and the rules thereunder.

[804][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

3. Name(s) of qualified person(s)-in-charge.....

4. Categories of drugs.....

Name of the dealer.....*Licence No*.....

Date..... Licence No.....

Licensing Authority.....

* Delete if not applicable.

Conditions of Licence

1. This licence shall be displayed in a prominent place in a part of the premises open to the public.

2. The licensee shall comply with the provisions of the Drugs and Cosmetics Act, 1940 and the Rules thereunder for the time being in force.

3. The licensee shall report to the licensing authority any change in the qualified staff incharge within one month or such change.

4. No drug shall be sold unless such drug is purchased under case or credit memo from a duly licensed dealer or a duly licensed manufacturer.

5. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

FORM 20A

[See rule 61(1)]

RESTRICTED [805][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] DRUGS BY RETAIL OTHER THAN THOSE SPECIFIED IN [806][SCHEDULE C, C(l) AND X] FOR

[807][***] DEALERS WHO DO NOT ENGAGE THE SERVICES OF A QUALIFIED PERSON

1.,..... is hereby [805][licensed to sell, stock or exhibit or offer for sale, or distribute] on the premises situated at [807][***] .....the following drugs being drugs other than those specified in [806][Schedules C, C(l) and X] of the Drugs Rules, 1945 subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940 and the rules made thereunder.

[808][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

3. The licensee can deal only in such drugs as can be sold without the supervision of a "qualified person" under the Drugs and Cosmetics Rules, 1945.

[809][***]

Date..... Licensing Authority.....

Conditions of Licence

1. The licence shall be displayed in a prominent place in a part of the premises open to the public [807][***]

2. The licensee shall comply with the provisions of the Drugs and Cosmetics Act, 1940 and the Rules thereunder for the time being in force.

3. No drugs shall be sold unless such drug is purchased under a case or credit memo from duly licensed dealer or a duly licensed manufacturer.

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

FORM 20B

[*See* rule 61(1)]

[805][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] BY WHOLESALE, DRUGS OTHER THAN THOSE SPECIFIED IN [806][SCHEDULES C, C(l) AND X]

1,..... is hereby [805][licensed to sell, stock or exhibit or offer for sale, or distribute] by wholesale drugs other than those specified in [806][Schedules C, C(l) and X] on the premises situated at.....subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940, and the rules thereunder.

[808][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

Conditions of Licence

1. This licence shall be displayed in a prominent place in a part of the premises open to the public.

2. The licensee shall comply with the provisions of the Drugs and Cosmetics Act, 1940 and the Rules thereunder for the time being in force.

[810][3. (i) No drug shall be sold unless such drug is purchased under a cash or credit memo from a duly licensed dealer or a duly licensed manufacturer.

(ii) No sale of any drug shall be made to a person not holding the requisite licence to sell, stock or exhibit for sale or distribute the drug. Provided that the condition shall not apply to the sale of any drug to—

(a) an officer or authority purchasing on behalf of Government, or

(b) a hospital, medical, educational or research institution or a registered medical practitioner for the purpose of supply to his patients, or]

[811][(c) a manufacturer of beverages, confectionary biscuits and other non-medicinal products, where such drugs are required for processing these products;]

[812][* * *]

5. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

[813][FORM 20BB

(See rule 62D)

[814][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE BY WHOLESALE, OR DISTRIBUTE] DRUGS OTHER THAN THOSE SPECIFIED IN SCHEDULE C AND SCHEDULE C(l) TO DRUGS AND COSMETICS RULES, 1945, FROM A MOTOR VEHICLE

1.,....., is hereby [814][licensed to sell, stock or exhibit or offer for sale by wholesale, or distribute] drugs other than those specified in Schedule C and Schedule C(l) from the vehicle bearing registration No.....assigned under Motor Vehicles Act, 1939, subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940 and the Rules made thereunder.

[815][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

3. Categories of drugs .....

Date..... Licence No.....

Licensing Authority.....

Conditions of Licence

1. This licence shall be displayed in a prominent place on the vehicle.

2. The licensee shall comply with the provisions of the Drugs and Cosmetics Act, 1940 and the rules made thereunder for the time being in force.

3. (i) No drug shall be sold by wholesale or distributed unless such drug is purchased under a cash or credit memo from a duly licensed dealer or a duly licensed manufacturer.

(ii) No sale wholesale or distribution of any drug shall be made to a person not holding the requisite licence to sell, stock, or exhibit for sale or distribute the drug:

Provided that the condition shall not apply to the sale of any drug to—

(a) an officer or authority purchasing on behalf of Government, or

(b) a hospital, medical, educational or research institution or a registered medical practitioner for the purpose of supply to his patients, or

(c) a manufacturer of beverages, confectionary biscuits and other non-medicinal products, where such drugs are required for processing these products;

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

5. The licensee shall inform the licensing authority in writing in the event of any change in ownership of the vehicle specified in this licence within seven days of such change.]

[816][FORM 20C

(See rule 67C)

[817][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] HOMOEOPATHIC MEDICINES BY RETAIL

1., ..., is hereby [817][licensed to sell medicines by retail, stock or exhibit or offer for sale, or distribute] by retail Homoeopathic medicines on the premises situated at ..... subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940 and the Rules made thereunder.

2. The licence shall be in force from .....to.....

3. Name of the competent person-in-charge.

Date..... Licensing Authority.....

Conditions of Licence

1. This licence shall be displayed in a prominent place in a part of the premises open to the public.

2. The licensee shall comply with the provisions applicable to Homoeopathic medicine under the Drugs and Cosmetics Act, 1940 and the Rules made thereunder for the time being in force.

3. The licence shall report to the Licencing Authority any change in the competent staff within one month of such change.]

[818][4. This licence authorises the sale of Homoeopathic medicines made from one earlier potency up to a quantity of 30 ml. at a time.]

[819][5. Where any change in the constitution of the firm takes place, a licensee shall inform the licensing authority in writing about the same and the current licence shall be valid only for a period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

[820][FORM 20D

(See rule 67C)

[821][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] HOMOEOPATHIC MEDICINES BY WHOLESALE

I ,....., is hereby [821][licensed to sell, stock or exhibit or offer for sale, or distribute] by wholesale Homoeopathic medicines on the premises situated at.....subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940, and the rules made thereunder.

2.The licence shall be in force from.....to .....

Date.....

Licensing Authority.....

Conditions of Licence

1. This licence shall be displayed in a prominent place on the premises.

2. The licensee shall comply with the provisions as applicable to Homoeopathic medicines under the Drugs and Cosmetics Act, 1940 and the rules made thereunder for the time being in force.

3. No sale of any drug shall be made to a person not holding the requisite licence to sell, stock or exhibit for sale or distribute the drug. Provided that this condition shall not apply to the sale of any drug to (a) an authority purchasing on behalf of Government, or

(b) a hospital, medical, educational or research institution or a Homoeopathic medical practitioner for the purpose of supply to his patients.]

[822][4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence and the current licence shall be valid only for a period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

[823]**[FORM 20E**

(See rule 67EE)

CERTIFICATE OF RENEWAL OF [824][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] HOMOEOPATHIC MEDICINES

1. Number of licence and date of issue.....

Certified that licence No.....in Form 20C/ 20D granted on the..... to.....for sale of Homoeopathic medicines at the premises situated at..... has been renewed for a period from..... to.....

2. Name of competent person-in-charge.

Date..... Licensing Authority.....]

[825][FORM 20F

[See rule 61(3)]

LICENCE TO SELL, STOCK OR EXHIBIT FOR SALE OR DISTRIBUTE BY RETAIL DRUGS SPECIFIED IN SCHEDULE X

1.....is hereby licensed to sell, stock or exhibit for sale or distribute by retail drugs specified in Schedule X to the Drugs and Cosmetics Rules, 1945 on the premises situated at.....

2. Names of drugs.

[826][3. The licence unless sooner suspended or cancelled shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

4. Name(s) of qualified person-in-charge.

5. The licence is subject to the conditions stated below and the provisions of the Drugs and Cosmetics Act, 1940 and the Rules, made thereunder.

Date..... Licence No.....

Licensing authority.....

Conditions of Licence

1. This licence shall be displayed in a prominent place in a part of the premises open to the public.

2. The licensee shall report to the licensing authority any change in the qualified staff-in-charge within one month of such change.

3. No drug shall be stocked or sold unless such drug has been purchased under cash/credit memo from a duly licensed dealer or a duly licensed manufacturer.

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

[827][FORM 20G

[See rule 61(3)]

[828][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] BY WHOLESALE DRUGS SPECIFIED IN SCHEDULE X

1....., is hereby [828][licensed to sell, stock or exhibit or offer for sale, or distribute] by wholesale drugs specified in Schedule X to the Drugs and Cosmetics Rules, 1945, on the premises situated at.....

2. Names of drugs .....

[829][3. The licence unless sooner suspended or cancelled shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

4. This licence is subject to the conditions stated below and the provisions of the Drugs and Cosmetics Act, 1940 and the Rules made thereunder.

Date..... Licence No.....

Licensing Authority.....

Conditions of Licence

1. This licence shall be displayed in a prominent place in a part of the premises open to the public.

2. The licensee shall comply with the provisions of the Drugs and Cosmetics Act, 1940 and the Rules made thereunder.

3. No drug shall be stocked or sold unless such drug has been purchased under a cash or credit memo from a duly licensed dealer or a duly licensed manufacturer.

4. The licensee shall forward to the licensing authority copies of the invoices of sales made to the retail dealers.

5. No sale of any drug by wholesale shall be made to a person not possessing the requisite licence to sell, stock or exhibit for sale or distribute the drugs specified in Schedule X:

Provided that the condition shall not apply to the sale of any drug to—

(a) an officer or authority purchasing on behalf of Government;

(b) a hospital, medical, educational or research institution, nursing home, Registered Medical Practitioner for the purpose of supply to its/his patients, or manufacturer holding a licence in Form 25E or 28B to manufacture the drugs containing drugs included in Schedule X.]

[830][The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence, where any change in the constitution of the firm takes place. The current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless in the meantime a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

FORM 21

[See rule 61(2)]

[831][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] BY RETAIL DRUGS SPECIFIED IN SCHEDULES C AND C(l) [832][EXCLUDING THOSE SPECIFIED IN SCHEDULE X]

[833][1. .....is hereby [832][licensed to sell, stock or exhibit or offer for sale or distribute] by retail the following categories of drugs specified in Schedules C and C(l) [832][excluding those specified in Schedule X] to the Drugs and Cosmetics Rules, 1945* and to operate a pharmacy on the premises situated at.....subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940 and the Rules thereunder.]

[834][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.";

3. Name(s) of qualified persons in charge.....

[833][4. Categories of drugs.....]

Date ..... Licence No.....

Licensing Authority.....

* Delete if not applicable

Conditions of Licence

1. This licence shall be displayed in a prominent place in a part of the premises open to the public.

2. The licensee shall report to the licensing authority any change in the qualified staff in charge within one month of the such change.

[835][***]

4. If the licensee wants [1][to sell, stock or exhibit or offer for sale, or distribute] during the currency of the licence, additional categories of drugs listed in Schedules C and C(l) [2][excluding those specified in Schedule X] but not included in this licence, he should apply to the licensing authority for the necessary permission. This licence will be deemed to extend to the categories of drugs in respect of which such permission is given. This permission shall be endorsed on the licence by the licensing authority.

[836][5. No drug shall be sold unless such drug is purchased under a cash or credit memo from a duly licensed dealer or a duly licensed manufacturer.]

6. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

FORM 21A

[See rule 61(2)]

RESTRICTED [837][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] BY RETAIL DRUGS SPECIFIED IN [838][SCHEDULE C(l)] [839][EXCLUDING THOSE SPECIFIED IN SCHEDULE X] FOR [840][***] DEALERS WHO DO NOT ENGAGE THE SERVICES OF A QUALIFIED PERSON

1.....is hereby [837][licensed to sell, stock or exhibit or offer for sale, or distribute] by retail on the premises situated at [840][***]..... the following drugs being drugs specified in [838][Schedule C(l)] [839][excluding those specified in Schedule X] to the Drugs and Cosmetics Rules, 1945, subject to the conditions specified below and to the provisions of the Drugs and Cosmetics Act, 1940, and Rules thereunder.

[841][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

3. Particulars of [838][Schedule C(l)] [839][excluding those specified in Schedule X] drugs to be sold.....

[842][***]

Date..... Licensing Authority .....

Conditions of Licence

1. This licence shall be displayed in a prominent and conspicuous place in a part of the premises open to the public [843][***].

[844][***]

3. The licensee shall deal only in such drugs as can be sold without the supervision of a "qualified person" as defined in the Explanation to sub-rule (15) of Rule 65 of the Drugs and Cosmetics Rules, 1945.

4. No drug shall be sold unless such drug is purchased under cash or credit memo from a duly licensed dealer or a duly licensed manufacturer.

[845][5. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

FORM 21B

[See rule 61(2)]

[846][LICENCE TO SELL, STOCK OR EXHIBIT OR OFFER FOR SALE, OR DISTRIBUTE] BY WHOLESALE DRUGS SPECIFIED IN SCHEDULES C AND C(l) [847][EXCLUDING THOSE SPECIFIED IN SCHEDULE X]

1,....., is hereby [846][licensed to sell, stock or exhibit or offer for sale, or distribute] by wholesale on the premises situated at.....the following categories of drugs specified in Schedules C and C(l) [847][excluding those specified in Schedule X] to the Drugs and Cosmetics Rules, 1945.

Categories of drugs

[848][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the

provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

[849][2A. The sale shall be made under the personal supervision of a competent person. (Name of the competent persons.)]

3. This licence is subject to the conditions stated below and to the provisions of Drugs and Cosmetics Act, 1940, and the Rules thereunder.

Date..... Licence No.....

Licensing Authority.....

Conditions of Licence

1. This licence shall be displayed in a prominent place in a part of the premises open to the public.

[850][***]

3. If the licensee wants to sell, stock and exhibit for sale or distribute during the currency of the licence additional categories of drugs listed in Schedule C(l) [849][excluding those specified in Schedule X] but not included in this licence, he should apply to the licensing authority for the necessary permission. This licence will be deemed to extend to the categories of drugs in respect of which such permission is given. This permission shall be endorsed on the licence by the licensing authority.

[851][4. (i) No drug shall be sold unless such drug is purchased under a cash or credit memo from a duly licensed dealer or a duly licensed manufacturer.

(ii) No sale of any drug shall be made for purposes of resale to a person not holding the requisite licence to sell, stock or exhibit for sale or distribute the drug:]

Provided that this condition shall not apply to the sale of any drug to—

(a) an officer or authority purchasing on behalf of Government,

(b) a hospital, medical, educational or research institution or a registered medical practitioner for the purpose of supply to his patients, or

[852][(c) a manufacturer of hydrogenated vegetable oils, beverages, confectionery and other non-medicinal products, where such drugs are required for processing these products.]

[853][5. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the Lisensing Authority in the name of the firm with the changed constitution.]

[854]**[FORM 21BB**

(See rule 62D)

LICENCE TO SELL BY WHOLESALE OR TO DISTRIBUTE DRUGS SPECIFIED IN SCHEDULE C AND SCHEDULE C(l) TO THE DRUGS AND COSMETICS RULES, 1945 FROM A MOTOR VEHICLE

1,....., is hereby licensed to sell by wholesale, or to distribute drugs specified in Schedule C and Schedule C(l) from the vehicle bearing registration No. ..... assigned under Motor Vehicles Act, 1939 subject to the conditions specified below to the provisions of the Drugs and Cosmetics Act, 1940 and the rules made thereunder.

[855][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs

and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

3. Categories of drugs .....

Date..... Licence No.....

Licensing Authority.....

Conditions of Licence

1. This licence shall be displayed in a prominent place on the vehicle.

2. No drugs to which this licence applies shall be sold by wholesale or distributed unless the precautions as are published by the licensing authority from time to time in the Official Gazette have been observed throughout the period during which it has been in the possession of the licensee.

3. If the licensee wants to sell by wholesale or distribute during the currency of the licence additional categories of drugs listed in Schedule C and Schedule C(l) not included in this licence, he shall apply to the licensing authority for necessary permission. This licence shall be deemed to extend to the categories of drugs in respect of which such permission is given. This shall be endorsed on the licence by the licensing authority.

4. (i) No drug shall be sold by wholesale or distributed unless such drug is purchased under a cash or credit memo from a duly licensed manufacturer.

(ii) No sale by wholesale or distribution cf any drug shall be made for the purpose of resale to a person, not holding the requisite licence to sell, stock or exhibit for sale or distribute the drugs:

Provided that this condition shall not apply to the sale of any drug to—

(a) an officer or authority purchasing on behalf of the Government, or

(b) a hospital, medical, educational or research institution or a registered medical practitioner for the purpose of supply to his patients, or

(c) a manufacturer of hydrogenated vegetable oils, beverages, confectionery and other non-medicinal products, where such drugs are required for processing their products.

5. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

6. The licensee shall inform the licensing authority in writing in the event of any change in the ownership of the vehicle specified in this licence within seven days of such change.]

FORM 21C [856][***]

FORM 21CC [857][***]

FORM 22 [858][***]

FORM 23 [858][***]

FORM 24

(See rule 69)

APPLICATION FOR THE GRANT [859][***] OF A [860][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS OTHER THAN THOSE SPECIFIED IN [861][SCHEDULES C, C(l) AND X]

1. I/We,....., of.....hereby apply for the [862][grant] of a licence to manufacture on the premises situated at .....the following drugs being drugs other than those specified in [860][Schedules C, C(l) and X] to the Drugs and Cosmetics Rules, 1945.

2. Name of drugs categorized according to Schedule M.

3. Names, qualifications and experience of technical staff employed for manufacture and testing.

4. A fee of rupees.....has been credited to Government under the head of account.....

Date..... Signature.....
Note.—The application should be accompanied by a plant of the premises.

FORM 24A

(See rule 69A)

APPLICATION FOR GRANT [859][***] OF A LOAN [860][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS OTHER THAN THOSE SPECIFIED IN [861][SCHEDULES C, C(l) AND X]

1. I/We*,..... of[!] .....hereby apply for the [862][grant] of a licence to manufacture on the premises situated at .....C/o[#] .....the undermentioned drugs, other than those specified in [861][Schedules C, C(1) and X] to the Drugs and Cosmetics Rules, 1945.

Names of drugs (each substance to be separately specified).

2. The names, qualifications and experience of the expert staff actually connected with the manufacture and testing of the specified products in the manufacturing premises.

3. I/We enclose

(a) A true copy of a letter from me/us to the manufacturing concern whose manufacturing capacity is intended to be utilised by me/us.

(b) A true copy of a letter from the manufacturing concern that they agree to lend the services of their expert staff, equipment and premises for the manufacture of each item required by me/us and that they will analyse every batch of finished product and maintain the register of raw materials, finished products and reports of analysis separately in this behalf.

(c) Specimens of labels, cartons of the products proposed to be manufactured.

(4) A fee of rupees.....has been credited to Government under the head of account.....

Date..... Signature.....

* Enter here the name of the proprietor, partners or Managing Director as the case may be.

! Enter here the name of the applicant firm and the address or the principal place of business

Enter here the name and address of the manufacturing concern where the manufacture will be actually carried out and also the licence number under which the latter operates.

[863]**[FORM 24B**

(*See* rule 69)

APPLICATION FOR GRANT [864][***] OF A LICENCE TO REPACK FOR SALE OR DISTRIBUTION OF DRUGS, BEING DRUGS OTHER THAN THOSE SPECIFIED IN SCHEDULES C AND C(l) [865][EXCLUDING THOSE SPECIFIED IN SCHEDULE X]

1. I/We, ..., of.....hereby apply for [866][grant] of a licence to repack the following drugs at the premises situated at.....

2. Names of the drugs to be repacked.

3. Name, qualification and experience of competent staff.....

4. A fee of rupees forty has been credited to Government under the head of

account.....

Date..... .Signature of applicant.....]

Note.—The application shall be accompanied by a plan of the premises.

[867]**[FORM 24C**

(See rule 85B**)**

APPLICATION FOR GRANT [868][OR RENEWAL] OF A [869][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] HOMOEOPATHIC MEDICINES OR A LICENCE TO MANUFACTURE POTENTISED PREPARATIONS FROM BACK POTENCIES BY LICENSEES HOLDING LICENCE IN FORM 20C

[870][1. I/We, ..., of.....holder of licence No.....in Form 20C hereby apply for [871][grant or renewal] of licence to manufacture the undermentioned Homoeopathic Mother Tincture/Potentised and other preparations on the premises situated at.....

Names of the Homoeopathic preparations.....

(Each item to be separately specified).

2. Names, qualifications and experience of technical staff employed for manufacture and testing of Homoeopathic medicines.

3. A fee of rupees.....has been credited to Government under head of account.....

Date..... Signature.....]

Note.—(1) Delete whichever portion is not applicable.

(2) The application should be accompanied by a plan of the premises.

[872][FORM 24D

(See rule 153)

APPLICATION FOR THE GRANT OF A LICENCE TO MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA OR UNANI DRUGS

1. I/W e ..... of .....hereby apply for the grant of a licence to manufacture Ayurvedic, Siddha or Unani drugs on the premises situated at.....

2. Names of drugs categorized according to Schedule T to be manufactured (with details)

3. Names, qualifications and experience of technical staff employed for manufacture and testing of Ayurvedic, Siddha or Unani drugs.....

4. A fee of rupees ..... has been credited to the Government under the head of account ..... and the relevant Treasury Challan/online transaction slip is enclosed herewith.

Date..... Signature.....

(Applicant)

Note.—The application should be accompanied by a Plan of the premises.]

[873]**[FORM 24E**

(See rule 153A)

APPLICATION FOR THE GRANT OF A LOAN LICENCE TO MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA OR UNANI DRUGS

1. I/We* ....., of ..... hereby apply for the grant of a loan licence to manufacture Ayurvedic, Siddha or Unani drugs on the premises situated at.....C/o[#].....

2. Names of drugs categorized according to Schedule T to be manufactured (with details).

3. The names, qualifications and experience of technical staff actually connected with the manufacture and testing of Ayurvedic, Siddha or Unani drugs in the manufacturing premises.

4. I/We* enclose.

(a) A true copy of a letter from me/us to the manufacturing concern whose manufacturing capacity is intended to be utilized by me/us.

(b) A true copy of a letter from the manufacturing concern that they agree to lend the services of their competent technical staff, equipment and premises for the manufacture of each item required by me/us and

that they shall maintain the registers of raw materials and finished products separately in this behalf.

(c) Specimen of labels, cartons of the drugs proposed to be manufactured.

5. A fee of Rs.....has been credited to Government under the head of account ..... and the relevant Treasury Challan/online transaction slip is enclosed herewith.

Date..... Signature.....

* Enter here the name of the proprietor, partners or Managing Director as the case may be. ! Enter here the name of the applicant firm and the address or the principal place of
business.
Enter here the name and address of the manufacturing concern where the manufacture will be actually carried out and also the licence number under which the latter operates.]

[874][FORM 24E-1

(See rule 153B)

APPLICATION FOR THE CERTIFICATE OF GOOD MANUFACTURING PRACTICES FOR AYURVEDIC, SIDDHA OR UNANI DRUGS MANUFACTURING UNITS

l.I/We.....of.....hereby apply for the grant of a Certificate of Good Manufacturing Practices for Ayurvedic, Siddha or Unani drugs manufacturing on the premises situated at.....

2. A fee of rupees ..... has been credited to the Government under the head of account ..... and the relevant Treasury Challan/online transaction slip is enclosed herewith.

Date..... Signature.....

(Applicant)

Note.—The application should be accompanied by a Plan of the premises.]

[875][FORM 24F

(See rule 69)

APPLICATION FOR THE GRANT [876]]***] OF A [877][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS SPECIFIED IN SCHEDULE X AND NOT SPECIFIED IN SCHEDULES C AND C(l)

1. I/We, ..., of.....hereby apply for the [878][grant] of licence to manufacture on premises situated at .....the undermentioned drugs, specified in Schedule X to the Drugs and Cosmetics Rules, 1945.

2. Names of drugs.

3. Names, qualifications and experience of technical staff employed for manufacture and testing.

4. A fee of rupees.....has been credited to Government account under the head of account.....

Date.....Signature.....

Designation.....]

FORM 25

(See rule 70)

[877]LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS OTHER THAN THOSE SPECIFIED IN [879][SCHEDULES C, C(1) AND X]

Number of licence and date of issue.....

I.....is hereby licensed to manufacture the following categories of drugs being drugs other than those specified in [879][Schedules C, C(l) and X] to the Drugs Rules, 1945, on the premises situated at.....under the direction and supervision of the following [880][Competent Technical Staff]:—

(a) [880][Competent Technical Staff] (Names).....

(b) Names of Drugs (each item to be separately specified).....

2. The licence authorises the sale by way of wholesale dealing and storage for sale by the licensee of the drugs manufactured under the licence, subject to the conditions applicable to licence for sale.

[881][3. The licence unless sooner suspended or cancelled shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

4. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date..... Signature.....

Designation.....

[882][*Licencing Authority/ "Central Licence Approving.]

* Delete whichever is not applicable.

Conditions of Licence

1. This licence [883][***] shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the [884][Competent Technical Staff] named in the licence shall be forthwith reported to the licensing authority.

3. If the licensee wants to manufacture for sale additional items of drugs not included above, he should apply to the licensing authority for the necessary endorsement as provided in rule 69(5). This licence will be deemed to extend to the categories so endorsed.

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

FORM 25A

(See rule 70A*)*

LOAN [885][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS OTHER THAN THOSE SPECIFIED IN [886][SCHEDULES C, C(l) AND X]

1. Number of licence and date of issue.....

2.....of.....is hereby granted a loan licence to manufacture the following drugs being drugs other than those specified in [886][Schedules C, C(l) and X] to the Drugs and Cosmetics Rules, 1945, on the premises situated at .....C/o .....under the direction and supervision of the following [887][Competent Technical Staff]:—

(a) [887][Competent Technical Staff] (Names).....

(b) Names of drugs .....

3. The licence authorises the sale by way of wholesale dealing by the licensee and storage for sale by the licensee of the drug manufactured under the licence subject to the conditions applicable to licences for sale.

[888][4. The licence, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

5. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under Drugs and Cosmetics Act, 1940.

Date..... Signature.....

Designation.....

Conditions of Licence

1. This licence and [889][***] shall be kept on the approved premises and shall be produced on the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the [887][Competent Technical Staff] named in the licence shall be forthwith reported to the licensing authority.

3. If the licensee wants to undertake during the currency of the licence to manufacture for sale additional drugs he should apply to the licensing authority for the necessary endorsement to the licence as provided in Rule 69A. This licence will be deemed to extend to the drugs so endorsed.

4. The licensee shall inform the licensing authority in writing in the event of any changes in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

[890][FORM 25B

(See rule 70)

LICENCE TO REPACK FOR SALE OR DISTRIBUTION OF DRUGS BEING DRUGS OTHER THAN THOSE SPECIFIED IN SCHEDULES C AND C(l) [891][EXCLUDING THOSE SPECIFIED IN SCHEDULE X]

Number of licence and date of issue.....

1.....of.....is hereby granted a licence to repack the following drugs for sale or distribution on the premises situated at.....under the supervision of the following competent staff :

(a) Name of drugs to be repacked.

(b) Names of competent staff.

[892][2. The licence unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

3. The licence authorises the sale by way of wholesale dealing by the licensee and storage for sale by the licensee of the drugs repacked under the licence subject to conditions applicable to licence for sale.

4. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date..... Signature.....

Conditions of Licence

1. This licence [893][***] shall be kept on the licensed premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the competent staff named in the licence shall be forthwith reported to the licensing authority.

3. If the licensee wants to repack for sale or distribution additional items he should apply to the licensing authority for the necessary endorsement to this licence. The licence shall be deemed to extend to only those items so endorsed.

4. The drugs repacked under this licence shall bear on their label, apart from other particulars required by these Rules, the name and address of the licensee and the number of the licence under which the drug is repacked preceded by the words 'Rpg. Lic. No.'

5. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in tire name of the firm with the changed constitution.]

[894][FORM 25C

(*See* rule 85D)

[895][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] HOMOEOPATHIC MEDICINES

Number of licence and date of issue.....

1.[896][I, ..., of ..... *who holds a licence in Form 20C is hereby licensed to manufacture the under mentioned Homoeopathic Mother Tincture/potentised and other preparations on the premises situated at..... under the direction and supervision of following technical staff:—

Names of the Homoeopathic preparations.

(Each item to be separately specified)

Names of the Technical Staff.....]

2. The licence shall be in force from..... to.....

3. The licence is subject to the conditions stated below and to such other conditions as may be specified in the rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date..... Signature.....

Designation.....

* Delete the words 'who holds a licence in Form 20C' in the case this is not applicable.

Conditions of Licence

1. This licence and any certificate of renewal in force shall be kept on the premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the technical staff named in the licence shall be forthwith reported to the licensing authority.

[897][3. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]]

[898][FORM 25D

(See rule 154)

LICENCE TO MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA OR UNANI DRUGS

No. of Licence and date of issue.....

1..... is/are hereby licenced to manufacture the following Ayurvedic, Siddha or Unani drugs on the premises situated at..... ..... under the direction and supervision of the following competent technical staff:—

(a) Competent Technical staff (Names).

(b) Names of drugs categorized as per Schedule T (each item to be separately specified) with specific Product Code/QR Code for each approved drug.

2. The licence shall be in force from.....

3. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date ..... Signature.....

Designation.....

Conditions of Licence

1. Any change in the Technical staff named in the licence shall be forthwith reported to the Licensing Authority.

2. This licence shall be deemed to extend to such additional items as the licencee may intimate to the Licensing Authority from time to time, and as may be endorsed by the Licensing Authority.

3. The licencee shall inform the Licensing Authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the Licensing Authority in the name of the firm with the changed constitution.

4. The licence unless sooner suspended or cancelled shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act 1940 (23 of 1940) and the Drugs Rules, 1945 shall be assessed not less than once in five years or as needed as per risk based approach.

5. The licence is issued only after fulfillment of the requirements of Good Manufacturing Practices (GMP) of Ayurveda, Siddha or Unani drugs as laid down in Schedule T of the Drugs Rules, 1945.]

[899][FORM 25E

(See rule 154A)

LOAN LICENCE TO MANUFACTURE FOR SALE AYURVEDIC, SIDDHA OR UNANI DRUGS

1. Number of Licence.....date of issue.....

2..... of..... is hereby granted a loan licence to manufacture for sale Ayurvedic, Siddha, or Unani drugs, on the premises situated at ..... C/o.....under the direction and supervision of the following expert technical staff:

(a) Expert Technical staff (Names).....

(b) Names of drugs categorized as per Schedule T (each item to be separately specified) with specific Product Code/QR Code for each approved drug.

3. The licence shall be in force from.....

4. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date…… Designation……

Signature .....

Conditions of Licence

1. Any change in the technical staff named in the licence shall be forthwith reported to the Licensing Authority.

2. This licence shall be deemed to extend to such additional items as the licencee may intimate to the Licensing Authority from time to time, and as may be endorsed by the Licensing Authority.

3. The licencee shall inform the Licensing Authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall

be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the Licensing Authority in the name of the firm with the changed constitution.

4. The licence unless sooner suspended or cancelled shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act 1940 (23 of 1940) and the Drugs Rules, 1945 shall be assessed not less than once in five years or as needed as per risk based approach.]

[900][FORM 25F

(See rule 70)

[901][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS SPECIFIED IN SCHEDULE X AND NOT SPECIFIED IN SCHEDULES C AND C(l)

1.....of.....is hereby licensed to manufacture at the premises situated at.....the following drugs specified in Schedule X to the Drugs Rules, 1945.

2. Name of drugs.

3. Names of approved [902][Competent Technical Staff].

4. The licence authorises the sale by way of wholesale dealing and storage for sale by the licensee of the drugs manufactured under the licence subject to the conditions applicable to licence for sale.

5. The licence shall be in force from.....to.....

6. The licence is subject to the conditions stated below and to other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date of issue……..... Signature.....

Licence No…….. Designation……

[903] [Licensing Authority.....]

*Central Licence Approving Authority]

* Delete whichever is not applicable.

Conditions of Licence

1. This licence [904][***] shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. If the licensee wishes to undertake during the currency of the licence the manufacture of any drug specified in Schedule X not included above, he should apply to the licensing authority for the necessary endorsement to this licence. This licence shall be deemed to extend to only those so endorsed.

3. Any change in the [905][Competent Technical Staff] shall be forthwith reported to the licensing authority.

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

[906][5. The licence, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

6. The licensee shall not manufacture drugs covered by this licence for use as 'Physician's Samples'.]

FORM 26 [907][***]

FORM 26A [908][***]

FORM 26B [909][***]

FORM 26C

(See rule 85G)

CERTIFICATE OF RENEWAL OF LICENCE TO MANUFACTURE FOR SALE OF HOMOEOPATHIC MEDICINES

1. Certified that licence No.....granted on the.....to..... for the manufacture for sale of the Homoeopathic mother tinctures/potentised preparations at the premises situated at.....has been renewed for a period from the .....to.....

2. Names of technical staff.....

[910][3. Names of the drugs (each item to be separately specified).....

Date.....Signature .....

Designation.....

[911]**[FORM 26D**

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[913]**[FORM 26E**

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[914]**[FORM 26E-I**

(See rule 157B)

CERTIFICATE OF GOOD MANUFACTURING PRACTICES (GMP) TO MANUFACTURER OF AYURVEDA, SIDDHA OR UNANI DRUGS

Certified that manufacturing unit licensee, namely..... situated at.....State..... Licence No..... comply with the requirements of Good Manufacturing Practices of Ayurveda-

Siddha-Unani drugs as laid down in Schedule T of the Drugs and Cosmetics Rules, 1945.

This certificate is valid for a [915][period of five years and the Good Manufacturing Practices (GMP) is valid for the various dosage forms or Rasaushadhis, as follows:]

Dated..... Signature.....

Place..... Designation.....

Licensing Authority for
Ayurveda/ Siddha/Unani Drugs.]

[916][FORM 26E2-I

(See rule 158C)

State Drug Controller or Licensing Authority for Ayurveda, Siddha and Unani Medicines Name of the State or Union territory.....

Free Sale Certificate

It is certified that M/s.....(Name of the company).....situated at.....(Address) .....is holding valid Ayurvedic/Siddha/Unani Drug Manufacturing Licence Number.....and certificate of Good Manufacturing Practices for the State or Union territory of .....

It is also certified that the manufacturing plant situated at.....(Address)..... in which the Ayurvedic or Unani or Sidhha products are manufactured, conforms to the requirement of Good Manufacturing Practices and is subjected to inspection as per rules.

The firm has been permitted under Licence Number.....to manufacture and market the following products (attach list of products, if multiple) freely for sale in India under the provisions of the Drugs and Cosemtics Act, 1940 and the rules thereunder.

(i) .....

(ii) .....

(iii) .....

Date :.....

(Seal of issuing Officer) .....
(Signature and Name)
State Drug Controller/Licensing Authority
Address.....
Name of State or Union territory.....]

[917]**[FORM 26E2-II**

(See rule 158C)

State Drug Controller or Licensing Authority for Ayurveda, Siddha and Unani Medicines Name of the State or Union territory.....

Free Sale Certificate

It is certified that M/s.....(Name of the company).....situated at.....(Address) ..... is holding valid Ayurvedic/Siddha/Unani Drug Manufacturing Loan Licence Number ..... and the valid certificate of Good Manufacturing Practices for the State or Union territory of.....

It is also certified that the manufacturing plant situated at.....(Address)..... in which the Ayurvedic or Unani or Sidhha products are manufactured, conforms to the requirement of Good Manufacturing Practices and is subjected to inspection as per rules.

The firm has been permitted under Loan Licence Number.....to manufacture and market the following products (attach list of products, if multiple) freely for sale in India under the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the rules thereunder.

(i) .....

(ii) .....

(iii) .....

Date:..... (Seal of issuing Officer):.....

(Signature and Name)

State Drug Controller/Licensing Authority

Address.....

Name of State or Union territory.....]

[918][**FORM 26 E3**

(See rule 158C)

State Drug Controller or Licensing Authority for Ayurveda, Siddha and Unani Medicines Name of the State or Union territory.....

Non-Conviction Certificate

It is certified that M/s..... (Name of the company).....situated at ..... (Registered Address) ..... is holding valid Ayurvedic/Siddha/Unani Drug Manufacturing Licence Number.....in Form 25D/25E and valid certificate of Good Manufacturing Practices/valid Good Manufacturing Practices certificate of principal or original manufacturer for the State or Union territory of.....

As per the records of the State Drug Controller or Licensing Authority, as it may be, and affidavit (Annexure I) given by the company, the firm has not been convicted under the Drugs and Cosmetics Act, 1940 (23 of 1940) and the rules thereunder in the State or Union territory of....., during the last three years of the issuing of this certificate.

This certificate shall be valid only for one year from the date of issue.

Date :..... (Seal of issuing Officer) .....

(Signature and Name)

State Drug Controller/Licensing Authority for
Ayurveda, Siddha and Unani Medicines.
Address .....
Name of State or Union territory.....

ANNEXURE-1

(Proforma of Affidavit to be executed on appropriate non-judicial stamp paper of minimum value and attested by Notary Public)

I, ... S/O ..... age ..... working as ..... of ..... (Name and address of the company) ..... from ..... to ..... do hereby solemnly affirm and declare as under:

1. That I, in the capacity of Authorized Signatory of ..... (name and address of the company) ....., am duly competent to depose and verify the present affidavit.

2. That I apply for Non-conviction Certificate on behalf of M/s .....

3. That I declare that I am aware of the details of my organization and day to day activities from .....to .....

4. That I hereby undertake that the Non-Conviction Certificate, if issued, will be utilized for the bona fide purpose only.

5. I declare that the aforesaid firm is not convicted under the Drugs and Cosmetics Act, 1940 and rules thereunder during the last three years.

6. That it is my true statement.

Signature of Deponent

Verification

Verified at ..... (Place and State) .....today on this ..... day of ..... (month)....(Year) ..... that the contents of the above affidavit are true to my Knowledge and belief and no part of it is false and nothing has been concealed there from.

Signature of Deponent

Witness with Address

1.....

2……..

[919][FORM 26 E4]

1345.[*****]

[920][FORM 26 E5]

1345.**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**[*****]

FORM 26F [921][***]

[922][FORM 26G

(*See* rule 122F)

CERTIFICATE OF RENEWAL OF LICENCE TO OPERATE A [923][BLOOD CENTRE] FOR PROCESSING OF WHOLE HUMAN BLOOD AND/OR* FOR PREPARATION FOR SALE OR DISTRIBUTION OF ITS COMPONENTS

1. Certified that licence No.....granted on .....to M/s.....for the operation of a [924][Blood Centre] for processing of whole human blood

and/or for preparation of its components at the premises situated at .....is hereby renewed with effect from.....to.....

2. Name(s) of items:

1.....
2.....
3. Name(s) of Competent Technical staff.....
1.....
2.....

Date..... Signature .....

Name and Designation.....
Licensing Authority/
Central Licence Approving Authority.....]

* Delete, whichever is not applicable

FORM 26H [925]**[***]**

[926]**[FORM 26-I**

(See rule 122-1)

CERTIFICATE OF RENEWAL OF LICENCE FOR MANUFACTURE OF BLOOD PRODUCTS

Certified that licence No.....granted on .....to M/s..... for manufacture of blood products at the premises situated at .....is hereby renewed with effect from.....to.....

2. Name(s) of item(s):

1.....
2.....
3. Name(s) of Competent Technical staff.....

(a) responsible for manufacturing (b) responsible for testing

1..... 1.....
2..... 2.....

Date..... Signature.....

Name and Designation.....
Licensing Authority/
Central Licence Approving Authority]

[927][FORM 26J

[See rules 122G, 122H, 122-1, 122P]

CERTIFICATE OF RENEWAL OF LICENCE FOR COLLECTION, PROCESSING, TESTING, STORAGE, BANKING AND RELEASE OF UMBILICAL CORD BLOOD STEM CELLS

Certified that licence number.....granted on.....to M/s.....for collection, processing, testing, storage, banking and release of umbilical cord blood stem cells at the premises situated at.....is hereby renewed with effect from ..... to .....

1. Name(s) of competent Technical Staff:

1…….
2……..
3…….

Signature.....
Designation.....
Licensing Authority

Date..

……
Central Licence Approving Authority]

FORM 26J

[928] [***]

FORM 27

APPLICATION FOR GRANT [929][***] OF A [930][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS

SPECIFIED IN SCHEDULES C AND C(l) [931][EXCLUDING THOSE SPECIFIED IN [932][PART XB AND] SCHEDULE X]

1. I/We, ... hereby apply for the [933][grant] of a licence to manufacture on the premises situated at .....the undermentioned drugs, being drugs specified in Schedules C and C(l), [931][excluding those specified in [931][Part XB and] Schedule X] to the Drugs Rules, 1945,

Name of drugs.....(each item to be separately specified).

2. The names, qualifications and experience of the expert staff responsible for the manufacture and testing of the above-mentioned drugs:

(a) Name(s) of staff responsible for test.....

(b) Name(s) of staff responsible for manufacture.....

3. The premises and plan are ready for inspection/will be ready for inspection on.....

4. A fee of rupees .....and an inspection fee of rupees .....has been credited to Government under the head of account.....

Date.....Signature.....

Designation.....

Note.—The application shall be accompanied by a plan of the premises.

FORM 27A

(See rule 75 A)

APPLICATION FOR GRANT [929][***] OF A LOAN [930][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS SPECIFIED IN SCHEDULES C AND C(l) [931][EXCLUDING THOSE SPECIFIED IN [932][PART XB AND] SCHEDULE X]

1. I/We*, ..., of .....hereby apply for the [933][grant] of loan licence to manufacture on the premises situated at ..... C/o# ..... the undermentioned drugs, being drugs specified in Schedules C and C(l) [931][excluding v those specified in [932][Part XB and] Schedule X] to the Drugs Rules, 1945.

Name of drugs (each substance to be separately specified).

2. The names, qualifications and experience of the expert staff actually connected with the manufacture and testing the specified products in the manufacturing premises.

(a) Name(s) of expert staff responsible for manufacture .....

(b) Name(s) of expert staff responsible for testing.....

3. I/We enclose

(a) A true copy of a letter from me/us to the manufacturing concern whose manufacturing capacity is intended to be utilised by me/us.

(b) A true copy of a letter from the manufacturing concern that they agree to lend the services of their expert staff, equipment and premises for the manufacture of each item required by me/us and that they will analyse ever}' batch of finished products and maintain the registers of raw materials, finished products and reports of analysis separately on this behalf.

(c) Specimens of labels, cartons of the products proposed to be manufactured.

4. A fee of rupees.....has been credited to Government under the head of account.....

Date.....Signature.....

* Enter here name of the proprietor, partners or Managing Director as the case may be.

! Enter here name of the applicant firm and the address of the principal place of business.

Enter here the name and address of the manufacturing concern where the manufacture will be actually carried out and also the licence number under which the letter operates.

[934][FORM 27B

APPLICATION FOR GRANT [935][***] OF A [936][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS SPECIFIED IN SCHEDULES C, C(l) AND X

1. I/We, ..., of.....hereby apply for the [937][***] of a licence to manufacture on the premises situated at .....the undermentioned drugs, specified in Schedules C, C(l) and X to the Drugs Rules, 1945.

2. Names of drags.

3. The names, qualifications and experience of the expert staff responsible for the manufacture and testing of the abovementioned drugs.

(a) Name(s) of staff responsible for test.

(b) Name(s) of staff responsible for manufacture.

4. The premises and plant* are ready for inspection/will be ready for inspection on.....

5. A fee of rupees.....and an inspection fee of rupees.....has been credited to the Government under the head of account.....

Date.....Signature.....

The application shall be accompanied by a plan of the premises.]

* Delete whichever is not applicable.

[938][FORM 27C

(See rule 122F)

APPLICATION FOR GRANT/RENEWAL* OF LICENCE FOR THE OPERATION OF A [939][BLOOD CENTRE] FOR PROCESSING OF WHOLE BLOOD AND/OR* PREPARATION OF BLOOD COMPONENTS

1. I/We,....., of M/s.....hereby apply for the grant of licence/ renewal of licence number.....dated.....to operate a [940][Blood Centre], for processing of whole blood and /or* for preparation of its components on the premises situated at.....

2. Name(s) of the item(s) :

1.

2.

3. The name(s), qualification and experience of competent Technical Staff are as under:

(a) Name(s) of Medical Officer.

(b) Name(s) of Technical Supervisor.

(c) Name(s) of Registered Nurse.

(d) Name(s) of [941][Blood Centre] Technician.

4. The premises and plant are ready for inspection/will be ready for inspection on.....

5. A licence fee of rupees.....and an inspection fee of rupees.....has been credited to the Government under the Head of Account.....(receipt enclosed).

Signature.....

Dated..... Name and Designation.....

* Delete whichever is not applicable.

Note 1. The application shall be accompanied by a plan of the premises, list of machinery and equipment for collection, processing, storage and testing of whole blood and its components, memorandum of association/constitution of the firm, copies of certificate relating to educational qualifications and experience of the competent technical staff and documents relating to ownership or tenancy of the premises.

Note 2. A copy of the application together with the relevant enclosures shall also be sent to the Central Licence Approving Authority and to the concerned Zonal/ Sub-Zonal Officers of the Central Drugs Standard Control Organisation.]

[942][FORM 27D

(See rule 75)

APPLICATION FOR GRANT [943][***] OF A LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF [944][LARGE VOLUME PARENTERALS/ SERA AND VACCINE/RECOMBINANT DNA (R-DNA) DERIVED DRUGS] EXCLUDING THOSE SPECIFIED IN SCHEDULE X

1. I/We,..... of.....hereby apply for the [945][grant] of a licence to manufacture for sale or distribution on the premises situated at ....., the undermentioned [4][Large Volume Parenterals/Sera and Vaccine/Recombinant DNA (r-DNA) derived drugs], specified in Schedules C and C(l) to the Drugs Rules, 1945.

2. Name(s) of drug(s).....(each item to be separately specified).

3. The name(s), qualifications and experience of the competent technical staff responsible for the manufacture of the above mentioned drugs.

(a) Name(s) of staff responsible for testing.....

(b) Name(s) of staff responsible for manufacture.....

4. The premises and plant are ready for inspection/will be ready for inspection on.....:

5. A fee or rupees.....and an inspection fee of rupees.....has been credited to the Government under the Head of Account.....

Signature.....

Date.....Designation.....

Notes 1. The application is to be accompanied by a plan of the premises; list of equipments and machinery to be employed for manufacture and testing;

memorandum of association/constitution of the firm; copies of qualification and experience of competent technical staff and documents relating to ownership or tenancy of the premises.

Notes 2. A copy of the application together with relevant enclosure shall also be sent each to Central Licence Approving Authority and concerned Zonal/Sub-Zonal Officers of Central Drugs Standard Control Organisation.]

[946][FORM 27DA

(See rule 75A)

APPLICATION FOR GRANT [947][*1 OF A LOAN LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF LARGE VOLUME PARENTERALS/SERA AND VACCINE/ RECOMBINANT DNA (R-DNA) DERIVED DRUGS EXCLUDING THOSE SPECIFIED UNDER SCHEDULE X**

1. I/We*,.....of #.....hereby apply for the [948][grant] of a loan licence to manufacture on the premises situated at c/o @..... ..... the under-mentioned drugs being Large Volume Parenterals/Sera and Vaccine/ Recombinant DNA (r-DNA) derived drugs specified in Schedules C, C(1), excluding those specified in Schedule X to the Drugs Rules, 1945.

2. Name(s) of drugs..... (each item to be separately specified).

3. The name(s), qualifications and experience of the competent technical staff responsible for the manufacture of the above-mentioned drugs.

(a) Name(s) of competent technical staff responsible for testing.....

(b) Name(s) of competent technical staff responsible for manufacture.....

4. I/we enclose:

(a) A true copy of a letter from letter from me/us to manufacturing concern whose manufacturing capacity is intended to be utilized by me/us.

(b) A true copy of a letter from the manufacturing concern that they agree to lend the services of their competent technical staff, equipment and premises for the manufacture of each item required by me/us and they will analyse every batch of finished product and maintain the registers of raw materials, finished products and reports of analysis separately on this behalf.

(c) Specimens of labels, cartons of the drugs proposed to be manufactured.

5. A fee of rupees.....has been credited to Government under the head of account.....]

Date..... Signature.....

Designation.....

* Entre here name of the proprietor, partners or Managing Director, as may be.

Enter here name of the applicant firm and the address of the principal place of business.

@ Enter here the name and address of the manufacturing concern where the manufacture will be actually carried out and also the licence number under which the latter operates".

[949][FORM 27E

(See rule 122F)

APPLICATION FOR GRANT/RENEWAL OF LICENCE TO MANUFACTURE BLOOD PRODUCTS FOR SALE OR DISTRIBUTION

1. I/We,..... of M/s.....hereby apply for the grant of licence/renewal of licence number..... dated..... to manufacture blood products on the premises situated at.....

2. Name(s) of item(s):

1.

2.

3. The name(s), qualification and experience of Competent Technical Staff as under:

(a) responsible for manufacturing	(b) responsible for testing
1.	1.
2.	2.

4. The premises and plant are ready for inspection/will be ready for inspection on.....

5. A licence fee of rupees .....and an inspection fee of rupees ..... has been credited to the Government under the Head of Account .....(receipt enclosed).

Dated.....Signature.....

Name and Designation.....

* Delete whichever is not applicable.

Note 1. The application shall be accompanied by a plant of the premises, list of machinery and equipment for manufacture of blood products, memorandum of association/constitution of the firm, copies of certificate relating to educational qualifications and experience of the competent technical staff and documents relating to ownership or tenancy of the said premises.

Note 2. A copy of the application together with the relevant enclosures shall also be sent to the Central Licence Approving Authority and to the concerned Zonal/ Sub-Zonal Officers of the Central Drugs Standard Control Organisation.]

[950][FORM 27F

(See rule 122F)

APPLICATION FOR GRANT/RENEWAL* OF LICENCE FOR COLLECTION, PROCESSING, TESTING, STORAGE, BANKING AND RELEASE OF UMBILICAL CORD BLOOD STEM CELLS

I/We.....of M/s..... hereby apply for the grant of licence/renewal* of licence number..... dated..... for collection, processing, testing, storage, banking and release of umbilical cord blood stem cells on the premises situated at.....

2. Name(s), qualification and experience of competent Technical Staff are as under:

1. Medical Director
2. Laboratory In-charge
3. Technical Supervisor
4. Cord Blood Bank Technician(s)

3. The premises and plant are ready for inspection/will be ready for inspection on.....

4. A licence fee of rupees..... and an inspection fee of rupees..... has been credited to the Government under the Head of Account..... (receipt enclosed)

Signature.....

Dated.....Name & Designation.....

"Delete whichever is not applicable.

Note.—1. The application shall be accompanied by a plan of the premises, list of machinery and equipment for collection, processing, testing, storage, banking and release of umbilical cord blood stem cells, memorandum of association/ constitution of the Firm, copies of certificate relating to educational qualification and experience of the competent technical staff and documents relating to ownership or tenancy of the premises.

2. A copy of the application together with the relevant enclosure shall also be sent to the Central Licence Approving Authority and to the Zonal/Sub-Zonal Officers concerned of the Central Drugs Standard Control Organization.]

FORM 28

(See rule 76)

[951][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS SPECIFIED IN SCHEDULES C AND C(l) [952][EXCLUDING THOSE SPECIFIED IN SCHEDULE X]

Number of licence and date of issue.....

1.....is hereby licensed to manufacture at the premises situated at the .....the following drugs, being drugs specified in Schedules C and C(l) [952][excluding those specified in Schedule X] to the Drugs and Cosmetics Rules, 1945.

Names of drugs.....

2. Names of approved [953][Competent Technical Staff].....

3. The licence authorises the sale by way of wholesale dealing and storage for sale by the licensee of the drugs manufactured under the licence subject to the condition application to licence for sale.

[954][4. The licence, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

5. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date of issue..... Signature.....

Designation.....

[955][*Licensing Authority/Central Licence Approving Authority]

* Delete whichever is not applicable.

Conditions of Licence

1. This licence [956][***] shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. If the licensee wishes to undertake during the currency of the licence the manufacture of any drug specified in Schedules C and C(l) [957][excluding those specified in Schedule X] not included above, he should apply to the licensing authority for the necessary endorsement as provided in rule 75(3). This licence will be deemed to extend to the items so endorsed.

3. Any change in the [958][Competent Technical Staff] shall be forthwith reported to the licensing authority.

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

FORM 28A

(*See* rule 76A)

LOAN [959][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS SPECIFIED IN SCHEDULE C AND C(l) [960][EXCLUDING THOSE SPECIFIED IN SCHEDULE X]

1. Number of licence and date of issue.....

2.....of.....is hereby granted a loan licence to manufacture on the premises situated at ..... C/o ..... the following drugs being drugs specified in Schedules C and C(l) [961][excluding those specified in Schedule X] to the Drugs Rules, 1945.

Names of drugs .....

3. Names of approved [962][Competent Technical Staff] .....

[963][3A. The licence, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

4. The licence authorises the sale by way of wholesale dealing by the licensee and storage for sale by the licensee of the drugs manufactured under the licence subject to the conditions applicable to licence for sale.

5. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date of issue.....Signature.....

Designation.....

Conditions of Licence

1. This licence [964][***] shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. If the licensee wishes to undertake during the currency of the licence to manufacture any drug specified in Schedules C and/or C (1) [964][excluding those specified in Schedule X] not included above, he should apply to the licensing authority for the necessary endorsement as provided in rule 75A. This licence will be deemed to extend to the items so endorsed.

3. Any change in the [962][Competent Technical Staff] shall be forthwith reported to the licensing authority.

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

[965][FORM 28B

[*See* rule 76)]

[966][LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF] DRUGS SPECIFIED IN SCHEDULES C, C(l) AND X

No. of licence.....

1.....is hereby licensed to manufacture at the premises situated at.....the following drugs specified in Schedules C, C(l) and X to the Drugs Rules, 1945.

Name of drugs.....

2. Names of approved expert staff.

3. The licence authorises the sale by way of wholesale dealing and storage for sale by the licensee of the drugs manufactured under the licence subject to the conditions applicable to licence for sale.

[967][4. The licence, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

5. The licence is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date..... Signature.....

Designation.....

[968][*Licensing Authority/*Central Licence Approving Authority]

* Delete whichever is not applicable.

Conditions of Licence

1. The licence [969][***] shall be kept at the approved premises and shall be produced at the request of the Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. If the licensee wishes to undertake during the currency of the licence the manufacture of any drug specified in Schedule X not included above, he should apply to the licensing authority for the necessary endorsement as provided in rule 75(4). This licence will be deemed to be applicable to the items so endorsed.

3. Any change in the expert staff shall be forthwith reported to the licensing authority.

4. The licensee shall inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.

5. The licensee shall furnish to the licensing authority copies of invoices of sales made to dealers.

6. The licensee shall not manufacture drugs specified in Schedule X covered by this licence for use as "Physician's Samples".]

[970]**[FORM 28C**

(*See* rule 122C)

LICENCE TO OPERATE A [971][BLOOD CENTRE] FOR COLLECTION, STORAGE AND PROCESSING OF WHOLE HUMAN BLOOD AND/OR* ITS COMPONENTS FOR SALE OR DISTRIBUTION

1. Number of Licence.....date of issue.....at the premises situated at.....

2. M/s ..... is hereby licensed to collect, store process and distribute whole blood and/or its components.

3. Name(s) of the item(s) :

1.

2.

4. Name(s) of Competent Technical Staff :

1.

2.

5. The licence authorises licensee to collect, store, distribute, and processing of whole blood and/or blood components subject to the conditions applicable to this licence.

6. The licence shall be in force from..... to .....

7. The licence shall be subject to the conditions stated below and to such other conditions as may be specified from time to time in the Rules made under the Drugs and Cosmetics Act, 1940.

Dated.....Signature.....

Name and Designation.....

*Licensing Authority/

*Central Licence Approving Authority

* Delete, whichever is not applicable.

Conditions of Licence

1. The licensee shall neither collect blood from any professional donor or paid donor nor shall he prepare blood components from the blood collected from such a donor.

2. The licence and any certificate of renewal in force shall be displayed on the approved premises and the original shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

3. Any change in the technical staff shall be forthwith reported to the licensing authority and/or Central Licence Approving Authority.

4. The licensee shall inform the licensing authority and/or Central Licence Approving Authority in writing in the event of any change in tbe constitution of the firm operating under the licence. Where any change in the constitution of

the firm takes place, the current licence shall be deemed to be valid for maximum period of three months from the date on which the change has taken place unless, in the meantime, a fresh licence has been taken from the licensing authority and /or Central Licence Approving Authority in the name of the firm with the changed constitution.]

[972][FORM 28D

(See rule 76)

LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF [973][LARGE VOLUME PARENTERALS/SERA AND VACCINE/RECOMBINANT DNA (R-DNA) DERIVED DRUGS] SPECIFIED IN SCHEDULE C AND C(l) EXCLUDING THOSE SPECIFIED IN SCHEDULE X

Number of licence.....and Date of issue.....

1.....is hereby licensed to manufacture at the premises situated at..... the following [973][Large Volume Parenterals/Sera and Vaccine/Recombinant DNA (r-DNA) derived drugs] specified in Schedule C and C(l) excluding those specified in Schedule X to the Drugs and Cosmetics Rules, 1945.

2. Name(s) of drug(s) (each item to be separately specified).....

3. Name(s) of competent technical staff.....

(a) responsible for manufacturing	(b) responsible for testing
1.	1.
2.	2.

4. The licence authorises the sale by way of wholesale dealing and storage for sale by the licensee of the drugs manufactured under the licence, subject to the conditions applicable to licence for sale.

[974][5. The licence, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs

Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

6. The licence shall be subject to the conditions stated below and to such other conditions as shall be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Signature.....

Designation.....

Licensing Authority/Central Licence Approving Authority

Date.....

Conditions of Licence

1. The licence [975][***] shall be kept on the approved premises and shall be produced at the request of an inspector appointed under the Drugs and Cosmetics Act, 1940.

2. If the licensee wishes to undertake during the currency of the licence to manufacture any drug specified in Schedule C and/or C(l) excluding those specified in Schedule X not included above, he should apply to the licensing authority and/or Central Licence Approving Authority for the necessary endorsement as provided in the Rules. This licence shall be deemed to extend to the items so endorsed.

3. Any change in the competent technical staff named in the licence shall be forthwith reported to the licensing authority and/or Central Licence Approving Authority.

4. The Licensee shall inform the licensing authority and/or Central Licence Approving Authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been applied for alongwith prescribed fee and necessary documents to the licensing authority and/or

Central Licence Approving Authority in the name of the firm with the changed constitution.]

[976][FORM 28DA

(See rules 76A, 78A, 83AA)

LOAN LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF LARGE VOLUME PARENTERALS/SERA AND VACCINE/RECOMBINANT DNA (R-DNA) DERIVED DRUGS EXCLUDING THOSE SPECIFIED UNDER SCHEDULE X

Number of licence.....and date of issue.....

1..... of..... is hereby granted a loan licence to manufacture on the premises situated at..... c/o..... the following drugs being Large Volume Parenterals/Scra and Vaccine/Recombinant DNA (r-DNA) derived drugs specified in Schedules C, C(l), excluding those specified in Schedule X to the Drugs and Cosmetics Rules, 1945.

1. Names of drugs.....

2. Name (s) of competent technical staff.....

[977][3. The licence unless sooner suspended or cancelled shall remain valid perpetually. However, the compliance with the conditions of licence and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

4. The licence authorizes the sale by way of wholesale dealing by the licensee and storage for sale by the licensee of the drugs manufactured under the licence subject to the conditions applicable to licence for sale.

5. The licence is subject to the conditions stated below and to such other conditions as may be specified in the rules for time being in force under the Drugs and Cosmetics Act, 1940.

Date.....

Signature.....
Designation.....
Licensing/ Authority.....
Central Licence Approving Authority

Conditions of licence

1. This licence [978][***] shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the competent technical staff shall be forthwith reported to the Licensing Authority and Central Licence Approving authority.

3. If the licensee wants, during the currency of the licence, to manufacture for sale additional items of drugs not included above, he should apply to the Licensing Authority and/or Central Licence Approving Authority for the necessary endorsement as provided in the rules. This licence will be deemed to extend to the items so endorsed.

4. The licensee shall inform the Licensing Authority and/or Central Licence Approving Authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing Authority and/or Central Licence Approving Authority in the name of the firm with the changed constitution.]

[979][FORM 28E

(See rule 122G)

LICENCE TO MANUFACTURE AND STORE BLOOD PRODUCTS FOR SALE OR DISTRIBUTION

1. Number of licence.....date of issue.....at the premises situated at.....

2. M/s.....is hereby licensed to manufacture, store, sell or distribute the following blood products:—

3. Name(s) of the item(s):

1.
2.

3.
4.
5.

4. Name(s) of Competent Technical Staff:

(a) responsible for manufacturing	(b) responsible for testing
1.	1.
2.	2.
3.	3.

5. The licence authorises the licensee to manufacture, store, sell or distribute the blood products, subject to the conditions applicable to this licence.

6. The licence shall be in force from.....to .....

7. The licence shall be subject to the conditions stated below and to such other conditions as may be specified from time to time in the Rules made under the Drugs and Cosmetics Act, 1940.

Signature .....
Name and Designation.....
Date.....
*Licensing Authority/ *Central Licence Approving Authority

Conditions of Licence

1. The licensee shall not manufacture blood products from the blood drawn from any professional donor or paid donor.

2. This licence and any certificate of renewal in force shall be displayed on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

3. Any change in the technical staff shall be forthwith reported to the licensing authority and/or Central Licence Approving Authority.

4. The licensee shall inform the licensing authority and/or Central Licence Approving Authority in writing any change in the constitution of the firm

operating under the licence. In the event of any change in the constitution of the firm, the licence shall be deemed to be valid for a period of three months from the date on which the change takes place unless, a fresh licence has been taken from the licensing authority and/or Central Licence Approving Authority in the name of the firm with changed constitution.]

[980][FORM 28F

(See rules 122F to 122-1, 122.K, 122P)

LICENCE TO COLLECT, PROCESS, TEST, STORE, BANKING AND RELEASE OF UMBILICAL CORD BLOOD STEM CELLS

1. Number of licence.....date of issue.....at the premises situated at.....

2. M/s.....is hereby licensed to collect, process, test, store, banking and release of umbilical cord blood stem cells.

3. Name(s) of competent Technical Staff:

1.
2.
3.
4.
5.

4. The licence authorises licensee to collect, process, test, store, banking and release of umbilical cord blood stem cells subject to the conditions applicable to this licence.

5. The licence shall be in force from.....to.....

6. The licence shall be subject to the conditions stated below and to such other conditions as may be specified from time-to-time in the Rules made tinder the Drugs and Cosmetics Act, 1940.

Signature.....
Name & Designation.....
Licensing Authority.....
Central Licence Approving Authority

Dated.....

Conditions of Licence

1. Umbilical cord blood specific for an individual will be collected after signing an agreement with the parent(s), whose child's Umbilical cord blood is to be collected, and the cord blood bank.

2. Umbilical cord blood shall be collected from hospitals, nursing homes, birthing centers and from any other place where a consenting mother delivers, under the supervision of the qualified Registered Medical Practitioner responsible for the delivery.

3. The licence and any certificate of renewal in force shall be displayed on the approved premises and the original shall be produced at the request of an inspector appointed under the Drugs and Cosmetics Act, 1940.

4. Any change in the technical staff shall be forthwith reported to the Licensing Authority and/or Central Licence Approving Authority.

5. The licensee shall inform the Licensing Authority and/or Central Licence Approving Authority in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for maximum period of three months from the date on which the change has taken place unless, in the meantime, a fresh licence has been taken from the Licensing Authority and/or Central Licence Approving Authority in the name of the firm with the changed constitution.]

FORM 29

(See rule 89)

LICENCE TO MANUFACTURE DRUGS FOR PURPOSES OF EXAMINATION, TEST OR ANALYSIS

1.....|..... of ..... is hereby licensed to manufacture the drugs specified below for purposes of examination, test or analysis at.....

2. This licence is subject to the conditions prescribed in Part VIII of the Drugs and Cosmetics Rules, 1945.

3. This licence shall be in force for [981][three years] from the date specified below.

Name of drugs

Date..... Licensing Authority.....

FORM 30

(See rule 90**)**

APPLICATION FOR LICENCE TO MANUFACTURE DRUGS FOR PURPOSES OF EXAMINATION, TEST OR ANALYSIS

I, ..., of ..... by occupation ..... hereby apply for a licence to manufacture the drugs specified below for purposes of examination, test or analysis at ..... and I undertake to comply with the conditions applicable to the licence.

Names of drugs

Date.....Signature.....

FORM 31

[982][***]

FORM 31A

[983][***]

FORM 32

[984][***]

FORM 32A

[985][***]

FORM 33

[986][***]

FORM 33A

[987][***]

FORM 34

[988][***]

[989][FORM 35

[990][See rules 65, 67G, 74, 74A, 74B, 78, 78A, 85H, 122P, 142, 142B, 150E, 158 and 158A]

FORM IN WHICH THE INSPECTION BOOK SHALL BE MAINTAINED

(A) The cover of the Inspection Book shall contain the following particulars, namely:—

1. The name and address of the licensee.....

2. Licence number and the date up to which the licence is valid .....

(B) (i) The pages of the Inspection Book shall be serially numbered and duly stamped by the licensing authority. The pages, other than the first and the last pages, shall have the following particulars:—

Name and designation of the Inspector who inspects the premises of the licensee.....

Date of Inspection.....

Observations of the Inspector.....

Signature of the Inspector

(ii) The first and last pages of the Inspection Book shall be endorsed by the licensing authority with the following words, namely:—

'Inspection Book maintained by M/s.....situated at.....for licence number .....in Form..... under Drugs Rules, 1945.

Seal and Signature of the Licensing Authority

Notes.—(i) Printed copy of the inspection Book may be obtained by the licensee from the licensing authority on payment.

(ii) The Inspection Book shall be maintained at the premises of the licensee.

(iii) The observation^ made by the Drugs Inspector shall be in triplicate. The original copy shall be retained in the Inspection Book to be maintained in the premises of the licensee. The duplicate copy shall be sent to the licensing authority. The triplicate copy shall be taken as record by the Inspector.]

[991][FORM 36

(See rule 150 B)

APPLICATION FOR GRANT [992][***] OF APPROVAL FOR CARRYING OUT TESTS ON DRUGS/[993][***] OR RAW MATERIALS USED IN THE MANUFACTURE THEREOF ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF DRUGS/[993][***] [994][OR FOR AN INDIVIDUAL OR ORGANISATION OR PROCUREMENT AGENCY]

(1) I/We, ..., of..... hereby apply for the grant [995][***] of approval for carrying out tests of identity, purity, quality and strength on the following categories of drugs/[996][***] or raw materials used in the manufacture thereof on behalf of licensees from manufacture for sale of drugs/[993][***][994][or for an individual or organisation or procurement agency].

(2) *Categories of drugs, [996][***]:—

(a) Drugs other than those specified in Schedules C and C(l) and also excluding Homoeopathic Drugs:—

1. Crude vegetable drugs.

2. Mechanical contraceptives.

3. Surgical dressings.

4. Drugs requiring the use of ultraviolet/Infra Red Spectro-photometer or Chromatography.

5. Disinfectants.

6. Other drugs.

(b) Drugs specified in Schedules C and C(l):

1. Sera, Vaccines, Antigens, Toxins, Antitoxins, Toxoids, Bacteriophages and similar Immunological Products.

2. Antibiotics.

3. Vitamins.

4. Parenteral preparations.

5. Sterilised surgical ligature/suture.

6. Drugs requiring the use of animals for their test.

7. Drugs requiring microbiological tests.

8. Drugs requiring the use of Ultraviolet/Infra Red Spectro-photometer or Chromatography.

9. Homoeopathic drugs.

(c) Homoeopathic drugs.

(d) [997][***]

(3) Names, qualifications and experience of expert staff employed for testing and the person-in-charge of testing.

(4) List of testing equipment provided.

(5) I/We enclose a plan of the testing premises showing the location and area of the different sections thereof.

(6) An inspection fee of rupees.....has been credited to Government under the head of account.....

Dated.....Signature.....]

* Delete whichever is not applicable.

[998][FORM 37

(See rule 150C)

APPROVAL FOR CARRYING OUT TESTS ON DRUGS/[997][***] AND RAW MATERIALS USED IN THEIR MANUFACTURE ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF DRUGS/[997][***] [999][OR FOR AN INDIVIDUAL OR ORGANISATION OR PROCUREMENT AGENCY]]

Number of approval and date of issue.....

(1) Approval is hereby granted to.....for carrying out tests for identity, purity, quality and strength on the following categories of drugs/[1001][***] and the raw materials used in the manufacture thereof on the premises situated at.....

Categories of drugs/[1001][***].

(2) Names of approved [1000][Competent Technical Staff] employed for testing and person-in-charge of testing.

[1002][(3) The approval, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of approval and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and [997][***] Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach.]

4. The approval is subject to the conditions stated below and such other conditions as may be specified in the Rules for the time being in force under the Act.

Date..... Signature.....

Designation.....

Conditions of Approval

(1) This approval [1003][***] shall be kept in the approved premises and shall be produced at the request of the Inspector appointed under the Act.

(2) If the approved institution wishes to undertake during the currency of the approval the testing of any other category of drugs [1004][***] it should apply to the approving authority for necessary endorsement as provided in Rule 150B. This approval will be deemed to extend to the items so endorsed.

(3) Any change in the analytical staff or in the person-in-charge of the testing shall be forthwith reported to the approving authority.

[1005][(4) The approved institution shall inform the approving authority in writing in the event of any change of the constitution of the institution operating under this Form. Where any change in the constitution of the institution takes place, the current approval shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless in the meantime, a fresh approval has been taken from the approving authority in the name of the institution with the changed constitution.]]

FORM 38 [1006][***]

[1007][**FORM 39**

[See rule 150E(f)]

REPORT OF TEST OR ANALYSIS BY APPROVED INSTITUTION

(1) Name of manufacture from whom sample received together with his manufacturing licence number under the Act and under the rules made thereunder.

(2) Reference number and date of the letter from the manufacturer under which the sample was forwarded.

(3) Date of receipt of the sample.

(4) Name of drug/[1008][***]/raw material purporting to be contained in the sample.

(5) Details of raw material/final product (in bulk)/final product (in finished pack)* as obtained from the manufacturer:

(a) Original manufacturer's name in the case of raw materials and drugs repacked.

(b) Batch number.

(c) [1009][Batch size as represented by sample.]

(d) Date of manufacture, if any.

(e) Date of expiry, if any.

(6) Results of test or analysis with protocols of test analysis applied.

In the opinion of the undersigned, the sample referred to above is of standard quality/is not of standard quality as defined in the Act and the Rules made thereunder for the reasons given below.

Date.....Signature of person-in-charge of testing]

Note : Final product includes repacked material.

* Delete whichever is not applicable.

[1010]**[FORM 39A**

[See sub-rule (f) of rule 150E]

REPORT OF TEST OR ANALYSIS BY APPROVED INSTITUTION FOR AN INDIVIDUAL OR ORGANISATION OR PROCUREMENT AGENCY

(1) Name of individual or organisation or procurement agency from whom sample is received.....

(2) Serial number and date of sender's memorandum.....

(3) Number of samples.....

(4) Date of receipt of the sample..... .....

(5) Name of drug or cosmetics or raw material purporting to be contained in the sample..... ....

(6) Details of raw material or final product in bulk or final product in finished pack* as obtained by sender:

(a) Name and address of the Manufacturer and Licence number mentioned on the label..... ....

(b) Name of original Manufacturer in the case of raw materials and re-packed drugs ....

(c) Batch number..... .....

(d) Date of manufacture, if any..... .....

(e) Date of expiry, if any..... .....

(7) Results of test or analysis with protocols of test or analysis applied.

In the opinion of the undersigned, the sample referred to above is *of standard quality/is not of standard quality as defined in the Act and the rules made thereunder for the reasons given below.

Date.....Signature of Person-in-charge of testing

Note : Final product includes repacked material.

* Delete whichever is not applicable.]

[1011][FORM 40

(See rule 24A)

APPLICATION FOR ISSUE OF REGISTRATION CERTIFICATE FOR IMPORT OF DRUGS INTO INDIA UNDER THE DRUGS AND COSMETICS RULES, 1945

I/We*,.....(name and full address) hereby apply for the grant of Registration Certificate to the manufacturer M/s..... .....(full address with telephone, fax and E-mail address of the foreign manufacturer) for his premises, and manufactured drugs meant for import into India.

1. Name of Drugs for registration.

[1012][***]

2. I/We* enclose herewith the information and undertakings specified in Schedule D(I) and Schedule D(II) duly signed by the manufacturer for grant of Registration Certificate for the premises stated below.

3. A fee of.....for registration of premises, the particulars of which are given below, of the manufacturer has been credited to the Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs Rules, 1945—Central *vide* Challan No..... dated..... (attached in original).

4. A fee of.....for registration of the drugs for import as specified at Serial No.2 above has been credited to the Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs Rules, 1945—Central *vide* Challan No....., dated..... (attached in original)

5. Particulars of premises to be registered where manufacture is carried on:

Address(es).....

Telephone.....

Fax.....

E-mail.....

I/we undertake to comply with all the terms and conditions required to obtain Registration Certificate and to keep it valid during its validity period.

Place.....

Date..... Name.....

Signature..... .....

Designation.....

Seal/Stamp of manufacturer or his authorised agent in India.

(Note.—In case the applicant is an authorised agent of the manufacturer in India, the Power of Attorney is to be enclosed).

*Delete whichever is not applicable.]

[1013][FORM 41

(See rule 27A)

REGISTRATION CERTIFICATE REGISTRATION CERTIFICATE TO BE ISSUED FOR IMPORT OF DRUGS INTO INDIA UNDER THE DRUGS RULES, 1945

Registration Certificate No..... Date..... M/s..... ..... (Name and full Address of registered office) .....having factory premises at.....(full address) has been registered under rule 27A as a manufacturer and is hereby issued this Registration Certificate.

2. Name(s) of drugs which may be imported under this Registration Certificate.

[1014][***]

3. This Registration Certificate shall be in force from.....to..... unless it is sooner suspended or cancelled under the rules.

4. This Registration Certificate is issued through the office of the manufacturer or his authorised agent in India M/s (name and full address).....who will be responsible for the business activities of the manufacturer, in India in all respects.

5. This Registration Certificate is subject to the conditions, stated below and to such other conditions as may be specified in the Act and the rules, from time to time.

Place..... .. Licensing Authority

Date..... ..... Seal/Stamp

Conditions of the Registration Certificate

1. The Registration Certificate shall be displayed at a prominent place by the authorised agent.

2. No drug shall be registered unless it has a free sale approval in the country of origin, and/or in other major countries.

3. The manufacturer or liis authorised agent in India shall comply with the conditions of the import licence issued under the Drugs Rules, 1945.

4. The manufacturer or his authorised agent in India shall inform the licensing authority forthwith in the event of any administrative action taken due to adverse reaction, *viz.* market withdrawal, regulatory restrictions, or cancellation of authorisation, and/or not of standard quality report of any drug pertaining to this Registration Certificate declared by the Regulatory Authority of the country of origin or by any Regulatory Authority of any other country, where the drug is marketed/sold or distributed. The despatch and marketing of the drug in such cases shall be stopped immediately, and the licensing authority shall be informed immediately. Further action in respect of such stopped marketing of drug shall be followed as per the direction of the licensing authority. In such cases, action equivalent to that taken with reference to the concerned drug in the country of origin or in the country of marketing shall be followed in India also, in consultation with the licensing authority. The licensing authority may, however, direct any further modification to this course of action, including the withdrawal of the drug from Indian market within 48 hours time period .

5. The manufacturer or his authorised agent in India shall inform the licensing authority within 30 days in writing in the event of any change in manufacturing process, or in packaging, or in labelling or in testing, or in documentation of any of the drug pertaining to this Registration Certificate.

In such cases, where there shall be any major change/modification in manufacturing, or in processing or in testing, or in documentation as the case may be, at the discretion of the licensing authority, the manufacturer or his authorised agent in India shall obtain necessary approval within 30 days by submitting a separate application along with the registration fee, as specified in clause (ii) of sub-rule (3) of rule 24A.

6. The manufacturer or his authorised agent in India shall inform the licensing authority immediately in writing in the event of any change in the constitution of the firm and/or address of the registered office/factory premises operating under this Registration Certificate. Where any such change in the constitution of the firm and/or address takes place, the current Registration Certificate shall be deemed to be valid for a maximum period of three months from the date on which the change has taken place unless, in the meantime, a fresh Registration Certificate has been taken from the licensing authority in the name of the firm with the changed constitution of the firm and/or changed address of the registered office or factory premises.]

FORM 42

[1015][***]

FORM 43

[1016][***]

[1017][FORM 44

(See rules 122A, 122B, 122D and 122DA)

APPLICATION FOR GRANT OF PERMISSION TO IMPORT OR MANUFACTURE A NEW DRUG OR TO UNDERTAKE CLINICAL TRIAL

I/we.....of M/s..... (address) hereby apply for grant of permission for import of and/or clinical trial or for approval to manufacture a new drug or fixed dose combination or subsequent permission for already approved new drug. The necessary information/data is given below:

1. Particulars of new drug:

(1) Name of the drug:
(2) dosage form:
(3) Composition of the formulation:
(4) Test specification:
  (i) active ingredients:
  (ii) inactive ingredients
(5) Pharmacological classification of the drug:
(6) Indication for which proposed to be used:

(7) Manufacture of the raw material (bulk drug substances): [1018][***]

2. Data submitted along with the application (as per Schedule Y with indexing and page nos.)

A. Permission to market a new drug:

(1) Chemical and Pharmaceutical information
(2) Animal pharmacology
(3) Animal Toxicology
(4) Human/Clinical Pharmacology (Phase 1)
(5) Exploratory Clinical Trials (Phase II)
(6) Confirmatory Clinical Trials (Phase III) (including published review articles)
(7) Bio-availability, dissolution and stability study Data
(8) Regulatory status in other countries
(9) Marketing information:
  (a) Proposed product monograph
  (b) Drafts of label and cartoons
(10) Application for test license
[1019][(11) New Chemical Entity and Global Clinical Trial—
  (a) Assessment of risk versus benefit to the patients
  (b) Innovation *vis-à-vis* existing therapeutic option
  (c) Unmet medical need in the country.]

B. Subsequent approval/permission for manufacture of already approved new drug:—

(a) Formulation:

(1) Bio-availability/bio-equivalence protocol
(2) Name of the investigator/centre
(3) Source of raw material (bulk drug substances) and stability study data.

(b) Raw material (bulk drug substances)

(1) Manufacturing method

(2) Quality control parameters and or analytical specification, stability report.

(3) Animal toxicity data.

C. Approval/permission for fixed dose combination:

(1) Therapeutic Justification. (authentic literature in [1020][peer-reviewed journals]/text books)

(2) Data on pharmacokinetics/pharmacodynamics combination.

(3) Any other data generated by the application on the safety and efficacy of the combination.

D. Subsequent approval or approval for new indication—new dosage form:

(1) Number and date of approval/permission already granted.

(2) Therapeutic Justification for new claim/modified dosage form.

(3) Data generated on safety or quality parameters.

A total fee of rupees..... (in words) ..... has been credited to the government under the head of account..... (Photocopy of receipt is enclosed).

Dated..... Signature.....

Designation.....

Note.—Delete, whichever is not applicable.

[1021][FORM 45

(See rule 122A, 122D, 122DA)

PERMISSION TO IMPORT FINISHED FORMULATION OF A NEW DRUG

Number of the permission and date of issue.....

M/s.....of ..... (address) is hereby permitted to import the following new drug formulation under rule 122A/122D/ 122DA of the Drugs Rules, 1945.

(1) Name of the New drug:

(2) Dosage from:
(3) Composition:
(4) Indication

ated..... Signature.....

Name and Designation of Licensing Authority.....

Condition for grant of approval/permission

(1) The formulation shall confirm to the specification approved by the Licensing Authority.

[1022][(2) The proper name of the drug or fixed dose combination drug other than fixed dose combinations of vitamin and other fixed dose combinations containing three or more drugs, shall be printed or written in a conspicuous manner which shall be at least two font size larger than the brand name or the trade name, if any, and in other cases the brand name or the trade name, if any, shall be written below or after the proper name on the label of the innermost container of the drug or every other covering in which the container is packed.]

(3) The label of the innermost container of the drug and every other covering in which the container is packed shall bear a [1023][caution or warning, as applicable, depending on whether the drug is covered under Schedule G or Schedule H or Schedule HI or Schedule X, as specified in rule 97, in legible black coloured font size in a completely red rectangular box] without disturbing the other condition printed on the label to depict it is prescription drug.

(4) The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING: To be sold by the retail on the prescription of a.....only."

[1024][(5) As Post Marketing Surveillance, the applicant shall submit Periodic Safety Update Reports every six months for the first two years. For subsequent two years, the Periodic Safety Update Reports shall be submitted annually.]

(6) All reported adverse reaction related to the drug shall be intimated to the drugs Controller, India and Licensing Authority and regulatory action resulting from their review should be complied with.

(7) No claims except those mentioned above shall be made for the drug without the prior approval of the Licensing Authority.

(8) Specimen of the cartoon, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Licensing Authority before the drug is marketed.

(9) Each consignment of imported drug shall be accompanied by a test/analyse report.

[1025][FORM 45A

(See rules 122A and 122DA)

PERMISSION TO IMPORT RAW MATERIAL (NEW BULK DRUG SUBSTANCE)

Number of the permission and date of issue.....

M/s.....of .....(address) hereby permitted to import the following raw material (new bulk drug substances) under ride 122A/122DA of the Drugs Rules, 1945, namely:—

Name of the raw material (new bulk drug substances):

(1) .....
(2) .....
(3) .....

Dated..... Signature.....

Name and Designation of the Licensing Authority.....

Conditions for Grant of Approval/Permission

(1) The raw material (new bulk drug substance) shall conform to the test specifications as approved by the Licensing Authority.

(2) For manufacture of raw material (new bulk drug substance) or its formulation in the country, separate approval under rule 122B shall be obtained from the Licensing Authority.

(3) The permission to import shall not be used to convey or imply that the raw material (new bulk drug) is categorized as "life saving or essential drug".]

[1026][FORM 46

(See rule 122B, 122D, 122DA)

PERMISSION/APPROVAL FOR MANUFACTURE OF A NEW DRUG FORMULATION

Number of the permission and date of issue.....

M/s.....of ..... (address) is hereby granted Permission/Approval to manufacture following new drug formulation under rule 122B/122D/122DA of the Drugs and Cosmetics Rules, 1945, namely:—

(1) Name of the formulation:

(2) Dosage form:

(3) Composition:

(4) Indications:

Dated……. Signature……..

Name and Designation of Licensing Authority.

Conditions for grant of approval/permission

(1) The formulation shall confirm to the specification approved by the Licensing Authority.

[1027][(2) The proper name of the drug or fixed dose combination drug other than fixed dose combinations of vitamin and other fixed dose combinations containing three or more drugs, shall be printed or written in a conspicuous manner which shall be at least two font size larger than the brand name or the trade name, if any, and in other cases the brand name or the trade name, if any, shall be written below or after the proper name on the label of the innermost container of the drug or every other covering in which the container is packed.]

(3) The label of the innermost container of the drug and every other covering in which the container is packed shall bear a [1028][caution or warning, as applicable, depending on whether the drug is covered under Schedule G or Schedule H or Schedule HI or Schedule X, as specified in rule 97, in legible black coloured font size in a completely red rectangular box] without disturbing the other condition printed on the label to depict it is prescription drug.

(4) The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING: To be sold by the retail on the prescription of a.....only."

[1029][(5) As Post Marketing Surveillance, the applicant shall submit Periodic Safety Update Reports every six months for the first two years. For subsequent two years, the Periodic Safety Update Reports shall be submitted annually.]

(6) All reported adverse reaction related to the drug shall be intimated to the Drugs Controller, India and Licensing Authority and regulatory action resulting from their review should be complied with.

(7) No claims except those mentioned above shall be made for the drug without the prior approval of the Licensing Authority.

(8) Specimen of the cartoon, labels, package insert that will be adopted for marketing the drug in the country, shall be get approved from the Licensing Authority before the drug is marketed.

[1030][FORM 46A

(See rules 122B and 122DA)

PERMISSION/APPROVAL FOR MANUFACTURE OF RAW MATERIAL (NEW BULK DRUG SUBSTANCE)

Number of the permission and date of issue.....

M/s……of…….(address) is hereby granted Permission/Approval to manufacture the following raw material (new bulk drug substances) under rule 122B/122DA of the Drugs Rules, 1945:—

Name of the raw material (new bulk drug substance):

(1) .....

(2).....

(3) .....

Dated..... Signature.....

Name and Designation of the Licensing Authority.....

Conditions for Grant of Permission/Approval

(1) The raw material (new bulk drug substance) shall confirm to the specifications approved by the Licensing Authority.

(2) The raw material (new bulk drug substance) can be sold to only those manufacturers who have permission, in writing, from Licensing Authority, either to use the drug for development purpose/clinical trial/bio-equivalence study or to manufacture the formulation.

(3) For manufacture of the formulation in the country, separate approval under rule 122B shall be obtained from the Licensing Authority.]

[1031][FORM 47

(See rule 160 A)

APPLICATION FOR GRANT OR RENEWAL OF APPROVAL FOR CARRYING OUT TESTS ON AYURVEDIC, SIDDHA AND UNANI DRUGS OR RAW MATERIALS USED IN THE MANUFACTURE THEREOF ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA AND UNANI DRUGS

1. *I/We..... of ..... hereby apply for the grant/renewal of approval for carrying out tests of identity, purity, quality and strength on the following categories of Ayurvedic, Siddha and Unani drugs or raw materials used in the manufacture thereof on behalf of licensee for manufacture for sale of Ayurvedic, Siddha and Unani drugs.

2. *Categories of Ayurvedic, Siddha and Unani drugs other than those specified in the First Schedule to this Act for which testing will be carried out:

AYURVEDA AND SIDDHA	UNANI
1. Asava and Arista	1.Nabeez, Khal (Sirka)
2.Arka-Tinir	2.Majoon and its sub-categories Itrifal, Jawarish, Khameera, Laooq, Halwar
3.Avaleha and Paka-Ilakam	3.Sufoof, Zuroor, Sunoon.
4. Kavatha Curna-Kutinir Curanam	4.Namak, Khar
5. Guggulu	5. Raughan
6. Ghrita-Ney	6. Zimad
7. Chuma-Curanam	7. Habb (Pill)
8. Taila-Tailam	8. Shiyaf
9. Dravaka-Tiravakam	9. Qutoor(drops)
10. Lavana-Uppu	10. Kohal (Surma), Kajal
11. Kshara-Saram	11. Satt, Usara
12. Lepa-Pacai	12. Kushta
13. Vati, Gutika-Kulikai	13. Joshanda (single drugs)
14. Vartti	14. Sharbat Sikanjabeen
15. Netrabindu (Aschyotan)	15. Sayyal, Arq (Distillates)
16. Anjana-Kanmai	16. Qurs (Tablet)
17. Sattva-Sattu	17. Marham, Qairooti
18. Kupipakva Rasayana -Kuppi Centuram	18. Humool, Furzaja
19. Parpati	19. Bakhoor
20. Pishti	20. Nabati Advia
21. Bhasma-Parpam	21. Maadni Advia
22. Mandura-Atai Kutinir	22. Ajsad Advia
23. Rasayoga-Centuram	23. Haiwani Advia

24. Lauha	24. Jauhar
25. Ghana Sattva	25. Natool
26. Kvath Pravahi-Kutinir	26. Nashooq, Naswar
27. Panak (Syrup)-Manappaku	27. Shamoom
28. Tablet-Mattirai	28. Saoot (Nasal drops)
29. Capsule	29. Mazoogh 30 Tila
30. Ointment-Kalimapu	31. Lashooq
31. Phalavarti	32. Gulqand
32. Dhoomravarti/Doopan	33. Fateela
33. Kshar Sutra/Kshar Varti	34. Ghaza, Ubtan, Sabhgh
34. Single drugs:	
(a) Plant based	
(b) Mineral based	
(c) Metal based	
(d) Animal based	
(e) Synthetic	
(f) Any other Ayurvedic, Siddha, Unani formulation.	
35. Pushp (Phool)	35. Capsule
36. Nasya	36. Huqna
37. Swarasa (Fresh juice)	37. Naurah
38. Kama Bindu (Ear drops)	38. Latookh
39. Any other dosage form of Patent and Proprietary and Ayurvedic, Siddha, Unani Drug.	39. Vajoor (Throat pain)
	40. Mazmazah (Mouth washer)

(3) Names, qualifications and experience of experts employed for testing and the person-in-charge of testing.

(4) List of testing equipment provided.

(5) *I/We enclose a plan of the testing premises showing the location and area of the different sections thereof.

(6) An inspection fee of rupees ..... .has been credited to Government under the head of account…….

Dated.....

Signature.....

Full address of the Applicant

* Delete whichever is not applicable

[1032][FORM 48

(See rule 160B)

APPROVAL FOR CARRYING OUT TESTS OR ANALYSIS ON AYURVEDIC, SIDDHA AND UNANI DRUGS OR RAW MATERIALS USED IN THE MANUFACTURE THEREOF ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA AND UNANI DRUGS

Number of approval and date of issue:

(1) Approval is hereby granted to.....for carrying out tests for identity, purity, quality and strength on the following categories of Ayurvedic, Siddha or Unani drugs and the raw materials used in the manufacture thereof on the premises situated at..... Categories of Ayurvedic, Siddha and Unani drugs.

(2) Name of experts employed for testing and the person-in-charge of testing..... (experts) and ..... (person-in-charge)

(3) The approval shall be in force from.....to.....

(4) The approval is subject to the conditions stated below and such other conditions as may be specified in the rules for the time being in force under the Act.

Date.....Signature.....

Place.....Designation.....

Seal of State Licensing Authority

Conditions of Approval

(1) This approval and any certificate of renewal in Form 42 shall be displayed in the approved premises and shall be produced at the request of the Inspectors appointed under the Act.

(2) If the applicant wishes to undertake during the currency of the approval the testing of any other category of Ayurvedic, Siddha or Unani drugs it should

apply to the approving authority for necessary endorsement as provided in rule 160A. This approval will be deemed to extend to the items so endorsed.

(3) Any change in the experts or in the person-in-charge of the testing shall be forthwith reported to the approving authority.

(4) The applicant shall inform the approving authority in writing in the event of any change of the constitution of the laboratory operating under this Form. Where any change in the constitution of the laboratory takes place, the current approval shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless in the meantime, a fresh approval has been taken from the approving authority in the name of the laboratory with the changed constitution.]

[1033][FORM 49

(See rule 160-1)

CERTIFICATE OF RENEWAL FOR CARRYING OUT TESTS OR ANALYSIS ON AYURVEDIC, SIDDHA OR UNANI DRUGS OR RAW MATERIALS USED IN THE MANUFACTURE THEREOF ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA OR UNANI DRUGS

(1) Certified that approval number ..... granted on the ..... day of..... 2001 for carrying out tests of identity, purity, quality and strength on the following categories of Ayurvedic, Siddha or Unani drugs and the raw materials used in the manufacture thereof at the premises situated at.....has been renewed from.....to..... (Date).

Categories of Ayurvedic, Siddha or Unani drugs.

……

……

(2) Names of experts and the person-in-charge of testing..... (experts) and .....(person-in-charge).

Date..... .Signature.....

Place..... Designation.....

Seal of State Licensing Authority]

[1034] [FORM 50

[See rule 160 D(f)]

REPORT OF TEST OR ANALYSIS BY APPROVED LABORATORY

(1) Name of manufacturer from whom sample received together with his manufacturing license number under the Act or the rules made thereunder……..

(2) Reference number and date of the letter from the manufacturer under which the same was forwarded……..

(3) Date of receipt of the sample……

(4) Name of Ayurvedic, Siddha and Unani drug or raw material purporting to be contained in the sample……..

(5) Details of raw material of final product (in bulk finished pack)* as obtained from the manufacturer:

(a) Original manufacturer's name in the case of raw materials and drugs repacked …….

(b) Batch number.....

(c) Batch size as represented by sample.....

(d) Date of manufacture, if any.....

(e) Date of expiry, if any.....

(6) Results of test or analysis with protocols of test or analysis applied or as per Ayurvedic, Siddha or Unani Pharmacopoeial standards.

(7) Other specific tests for identity, purity, quality and strength of Patent and Proprietary drugs.

In the opinion of the undersigned, the sample referred to above is of standard Equality/is not of standards quality as defined in the Act or the rules made thereunder for the reasons given below:

(Signature of the person-in-charge of testing)

Date..... (F.No.....)

Place..... Name and Designation and Seal

Name and Address of the Laboratory.....

Licence No.....

Note.—Final product includes repacked material.

"Delete whichever is not applicable.]

[1035][FORM 51

[See rules 71(9), 71A(5), 71B(v), 76(11) and 76A(v)]

FORM OF UNDERTAKING TO THE LICENSING AUTHORITY FOR MARKETING A DRUG UNDER A BRAND NAME OR TRADE NAME

(1) I ..... of..... intend to market the drug specified below under a brand name or trade name— .....

(i) Name of the drug:

(ii) Dosage form:

(iii) Composition:

(2) I hereby give this undertaking that to the best of my knowledge based on search in trade marks registry, central data base for brand name or trade name of drugs maintained by Central Drugs Standard Control Organisation, literature and reference books on details of drug formulations in India, and internet, such or similar brand name or trade name is not already in existence

with respect to any drug in the country and the proposed brand name or trade name shall not lead to any confusion or deception in the market.

Place..... .....

Date.....[Signature, Name, Designation Seal/Stamp of manufacturer or on behalf of the manufacturer]]

[1036][SCHEDULE B

(*See* rules 7 and 48)

FEES FOR TEST OR ANALYSIS BY THE CENTRAL DRUGS LABORATORIES OR STATE DRUGS LABORATORIES

1. Fees for test and assay of Drugs requiring use of animals—

	Rupees
Adrenocorticotrophic hormone assay	1000
Gonadotrophic hormone for LH activity	1000
FSH activity	1000
Posterior pituitary extract or its Synthetic substitute for oxytocin activity	400
Vasopressor activity	400
Insulin and insulin in combination for hypogloycaemic activity	2000
Hyaluronidase	500
Glucagon	2000
Heparin for anticoagulant activity	600
Protamine sulphate	300
Depressor or Histamine like substance	300
Pyrogen test	500
Antigened ty or foreign protein test	300
Abnormal or undue toxicity or safety test	200
Determination of Lethal doses, LD10 or LDM| in mice	800
Skin sensitivity/eye irritation	250
Implantation test	2000
2. Microbiological tests and assays—	
Bioassay of Antibiotic	400
Microbiological assay of vitamins	300
Phenol coefficient	300
Preservative-Microbial Challenge test	2000
Sterility test-Parenteral preparations	100
Surgical dressings	200
Syringes and needles	300
Transfusion and infusion sets or assemblies	400
Other sterile devices	

3. Identification tests—	
(a) Chemical Methods	50
(b) Microscopical	50
(c) IR Spectroscopy	150
(d) UV Spectroscopy	100
(e) Chromatography	
(i) Paper	100
(ii) Thin layer	150
(iii) Column	100
(iv) GLC	250
(v) HPLC	500
(vi) Gel filtration	300
(f) Electrophoresis	
(i) Paper and cellulose acetate	200
(ii) Polyacrylamide Gel, starch gel, agar gel	300 each
Physical tests—	
(a) Optical rotation, specific gravity, refractive index, weight, per ml, fluorescence	75 each
(b) Viscocity	100
(c) Ph, solubility, loss on drying, net content, ash, sulphated ash etc.	20 each
(d) Absorbancy, wt/unit area (surgical) foreign matter, extractive value, thread count etc.	30 each
(e) Uniformity of weight	
(i) Tablets	15
(ii) Capsules	20
(f) Acid value, iodine value, peroxide value, saponification value, acetyl value.	100 each
(g) Disintegration tests—	
(i) Ordinary tablets	20
(ii) Capsule	30
(iii) Sugar coated tablets	50
(iv) Enteric coated tablets	100
(h) Dissolution test	250
(i) Uniformity of content	500
(i) Wt. per unit area (powder), particle size, count, methoxy value	200 each
(k) Limit test for impurities	100 each
(1) Related substances (i) TLC method	
(A) Without reference standards	150
(B) With reference standards (ii) Gas Liquid Chromatography	250

(A) Without reference standards	250
(B) With reference standards	350
(iii) High Pressure Liquid Chromatography	500
(A) Without reference standards	500
(B) With reference standards	200

(m) Water (Karl Fisher)

(5) Assays—

(a) General chemical method	100 for each ingredient
(b) Non-aqueous/instrumental	200 for each ingredient
(c) Chromatography	
(i) TLC	250
(ii) Column	200
(iii) GLC	350
(iv) HPLC	500
(v) Gel filtration	400
(d) Nitrogen determination	200
(e) Medicinal gases	400
(6) Polymorph test—	300
(Content of polymorph A in chloramphenicol-palmitate)	
Surgical sutures (Depending on number of tests to be carried	200-500
Other miscellaneous tests	100-500

II. Fees for Sera and Vaccine—	
Sterility test	100
Abnormal toxicity test	400
Specific toxicity test	800
Inactivation test (Rabies)	200
Potency testing of rabies vaccine	2025
Potency testing of pertussis fraction of DPT vaccine	2025
Potency testing of tetanus fraction of DPT/DT/TT vaccine	2500
Potency testing of diphetheria fraction of DPT/DT vaccine	2700
Testing of antisera for the specific titre	1000
Potency testing of measles/Mumps/Rubella Vaccine	760 each
Testing of Oral Polio Vaccine (OPV)	400
Potency	4550
Indentity	1000
Stability	800
Potency testing of Japanese Encephalitis Vaccine	3900
Potency testing of Snake Venoms Serum	400 for each venom
Identity testing for vaccines / sera cell culture (Other than OPV) 400	
Other than cell culture	100
Estimation of volume/PH/total solids/No. of organisms/ Physical checking	50 each
Estimation of total proteins/aluminium content/	

phenol/formaldehyde/thiomersal/moisture	200 each
Pyrogen testing	500
Stability test for vaccines other than Oral Polio Vaccine	4550
IV. Rubber Condoms	1000

[1037][***]

V. [1038][***]

Notes.—1. For tests not listed in the Schedule, changes will be determined by the Director or the Government Analyst of the Laboratory/institute as the case may be.

2. [1039][***]]

[1040]**[SCHEDULE B(1)**

(See rule 163F)

FEES FOR THE TEST OR ANALYSIS BY THE PHARMACOPOEIA COMMISSION FOR INDIAN MEDICINE AND HOMOEOPATHY OR THE GOVERNMENT ANALYST

S.No.	Type of testing/analysis	Cost of testing or analysis in Rupees
	(1)	(2)
1.	Test for sterility	500.00
2.	Abnormal toxicity or undue toxicity or safety test	750.00
3.	Determination of lethal does LD50 to 10 on mice	2500.00
4.	Chemical test for each ingredient	500.00
5.	Disinfectants	1000.00
6.	Any other test requiring animal experimentation	500.00
7.	Microbiological assay	1000.00
8.	Microscopic examination of single drugs	500.00
9.	Microscopic examination of raw material of compound drug	100.00
10.	Chemical identification as per Pharmacopoeia	250.00

11.	Disintegration of tablets and capsules	
	(a) ordinary	200.00
	(b) sugarcoated	200.00
	(c) enteric coated	400.00
12.	Physiochemical Assays	300.00
13.	Test other than assay (limit tests for impurities ,ash Content, total solids, acid value, saponification value, loss ondrying etc.) for each test.	250.00
14.	Optical rotation	300.00
15.	Refractive index	250.00
16.	Arsenic testing	250.00
17.	Paper chromatography	250.00
18.	Thin layer chromatography	800.00
19.	Column chromatography	2500.00
20.	Gas liquid chromatography	2000.00
(1)	(2)	(3)
21.	HPTLC restricted to single drugs qualitative	2000.00
22.	Atomic absorption spectrophotometry for Hg, Pb, As, Cd and Biochemic drug	1000.00
23.	Cosmetics/tails/creams	500.00
24.	Identification test for raw material of plant origin(other than assay of constituents)	250.00
25.	Identification test for raw material of chemical origin (other than assay)	250.00
26.	Limit test for drug of chemical origin	200.00
27.	Assay of total alkaloids or of drugs of chemical origin	250.00
28.	Identification test for drugs of animal origins or Microbiological testing.	250.00
29.	Fees for testing of Mother tincture, lower potencies upto 3X or Equivalent, ointment, oils, Biochemic/ triturations/ homoeopathic formulations	500.00 for each test
30.	Other miscellaneous tests	1000.00

Note:—Sample testing charges shall be determined or revised by the Director, Pharmacopoeia Commission for Indian Medicine and Homoeopathy or Government Analyst of its Central Laboratory, as the case may be, in consultation with the Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH).]

[1041][*SCHEDULE C*

(*See* rules 23, 61 and 76 and Part X)

BIOLOGICAL AND SPECIAL PRODUCTS

1. Sera.
2. Solution of serum proteins intended for injection.
[1042][3. Vaccines for parenteral injections.]
4. Toxins.
5. Antigen.
6. Antitoxins.
7. Neo-arsphenamine and analogous substances used for the specific treatment of infective diseases.
8. Insulin.
9. Pituitary (Posterior Lobe) Extract.
10. Adrenalin and Solutions of Salts of Adrenaline.
[1043][11. Antibiotics and preparations thereof in a form to be administered parenterally.]
[1044][12. Any other preparation which is meant for parenteral administration as such or after being made up with a solvent or medium or any other sterile product and which—
(a) requires to be stored in a refrigerator; or
(b) does not require to be stored in a refrigerator.]
13. Sterilized surgical ligature and sterilized surgical suture.
[1045][14. Bacteriophages.]
[1046][15. Ophthalmic preparations.]
[1047][16. Sterile Disposable Devices for single use only.]]

[1048][SCHEDULE C(I)

(See rules 23, 61 and 76)

OTHER SPECIAL PRODUCTS

1. Drugs belonging to the Digitalis group and preparations containing drugs belonging to the Digitalis group not in a form to be administered parenterally.

2. Ergot and preparations containing Ergot not in a form to be administered parenterally.

3. Adrenaline and preparations containing Adrenaline not in a form to be administered parenterally.

4. Fish Liver Oil and preparations containing Fish Liver Oil.

5. Vitamins and preparations containing any vitamins not in a form to be administered parenterally.

6. Liver extract and preparations containing liver extract not in a form to be administered parenterally.

7. Hormones and preparations containing hormones not in a form to be administered parenterally.

8. Vaccine not in a form to be administered parenterally.

[1049][9. Antibiotics and preparations thereof not in a form to be administered parenterally.]]

[1050][10. In-vitro Blood Grouping Sera.

11. In-vitro Diagnostic Devices for HIV, HbsAg and HCV.]

SCHEDULE D

(See rule 43)

Class of drugs	*Extent and conditions of exemption*
1. [1051][Substances not intended for medicinal use excluding those intended to be used as drugs after further purification or rendering them sterile.]	All provisions of Chapter III of the Act and Rules thereunder subject to the condition that if the substance is imported in bulk, the importer shall certify that the substance is imported for non-medical uses, and if imported otherwise than in bulk, each container shall bear a label indicating that the substance is not intended for medicinal use or is intended for some purposes other than medicinal use or is of commercial quality. [1052][Further, permission from licensing authority as defined in clause (b) of rule 21 has to be obtained for import of the substance for non-medicinal use without registration and import licence.]
[1053][***] [1054][***]	
[1055][5. The following substances, which are used both as articles of food as well as	All the provisions of Chapter III of the

Class of drugs	Extent and conditions of exemption
drugs:— (i) all condensed or powdered milk whether pure, skimmed or malted, fortified with vitamins and minerals. (ii) Farex, Oats, Lactose and all other similar cereal preparations whether fortified with vitamins or otherwise excepting those for parenteral use. (iii) Virol, Bovril, Chicken essence and all other similar predigested food. (iv) Ginger, Pepper, Cumin, Cinnamon and all other similar spices and condiments unless they are specifically labelled as conforming to the standards in the [1056][Indian Pharmacopoeia or the official pharmacopoeias and the official compendia of drug standards prescribed under the Act and Rules made thereunder.]]	Act and Rules thereunder.
[1057][6. Drugs and cosmetics imported for manufacture and export by units situated in "Special Economic Zones" as notified by the Government of India from time to time.	The provisions of Chapter III of the Act and rules thereunder which require them to be covered by an import licence, import registration ana import through notified port of entry, subject to tne conditions that these drugs and [1058][***] shall not be diverted for sale in the country: Provided that such imported drugs and cosmetics may be permitted to the domestic area if they meet the requirements of standard procedure for import and registration as required under Chapter III of the Act and rules thereunder.] The provisions of Chapter III of the Act and rules thereunder which required them to be covered by an import licence, import registration and import through notified port of entry, subject to the conditions that these drugs and cosmetics shall not be diverted for sale in the country: Provided that such imported drugs

Class of drugs	*Extent and conditions of exemption*
	and cosmetics may be permitted to the domestic area if they meet the requirements of standard procedure for import and registration as required under Chapter III of the Act and rules thereunder.
[1059][7. Custom Made Devices	All provisions of Chapter III of the Act and the rules made thereunder, subject to the condition that the device is specifically made in accordance with a duly qualified medical practitioner's written prescription under his responsibility, in accordance with specific design characteristics and is intended for the sole use of a particular patient and the label should bear the word "custom made device." *Explanation.*—Mass produced devices which only need adoption to meet the specific requirements of the medical practitioner or any other professional user shall not be considered to be custom made devices.]

[1060][SCHEDULE D(I)

(See rule 21(d) and rule 24A)

INFORMATION AND UNDERTAKING REQUIRED TO BE SUBMITTED BY THE MANUFACTURER OR HIS AUTHORISED AGENT WITH THE APPLICATION FORM FOR A REGISTRATION CERTIFICATE

(The format shall be properly Filled in for each application in Form 40. The detailed information, secret in nature, may be furnished on a Computer Floppy)

1. Particulars of the manufacturer and manufacturing premises :—

1.1 Name and address of the manufacturing premises (Telephone No., Fax No., E-mail address) to be registered.

1.2 Name(s) and address(es) of the Proprietor/Partners/Directors.

1.3 Name and address of the authorised Agent in India, responsible for the business of the manufacturer.

1.4 A brief profile of the manufacturer's business activity, in domestic as well as global market.

1.5 A copy of Plant Master File (duly notarised).

1.6 A copy Plant registration/approval Certificate issued by the Ministry of Health/National Regulatory Authority of the foreign country concerned (duly notarised).

1.7 A brief profile of the manufacturer's research activity.

2. Particulars of the manufactured drugs to be registered under Registration Certificate:

2.1 Names of drugs (Bulk/Formulation/special product) to be registered meant for import into and use in India:

2.2 A copy of the approved list showing the bulk drugs/formulations/special products mentioned in 2.1 above are permitted for manufacturing/marketing m the country of origin, (duly notarised).

[1061][2.3 A copy of Good Manufacturing Practice (GMP) certificate as per WHO -GMP guidelines or Certificate of Pharmaceutical Products (CPP) or written confirmation for active substances exported to European Union which is equivalent to GMP certificate issued as per WHO - GMP guidelines, by the National Regulatory Authority of the country of origin or a copy of the certificate equivalent to GMP certificate as per WHO GMP guidelines issued by National Regulator of United States of America or Japan or Australia or Canada or the European Union for the purpose of marketing of the drugs in their country, in relation to bulk drugs or formulations or special product meant for import into India.]

2.4 The domestic prices of the drugs to be registered in India, in the currency of the country of origin;

2.5 The name(s) of the drug(s) which are original research products of the manufacturer.

3. Undertaking to declare that:

3.1 We shall comply with all the conditions imposed on the Registration Certificate read with rules 74 and 78 of the Drugs and Cosmetics Rules, 1945.

3.2 We declare that we are carrying on the manufacture of the drugs mentioned in this Schedule, at the premises specified above, and we shall from time to time report any change of premises on which manufacture will be carried on and in cases where manufacture is carried on in more than one factory any change the distribution of functions between the factories.

3.3 We shall comply with the provisions of Part IX of the Drugs and Cosmetics Rules, 1945;

3.4 Every drug manufactured by us for import under the Registration Certificate into India shall be as regard strength, quality and purity conforms with the provisions of Chapter III of Drugs and Cosmetics Act, 1940 and Part IV of the Drugs and Cosmetics Rules, 1945, and their amendments from time to time:

3.5 We shall from time to time import for any change or manufacturing process, or in packaging, or in labeling, or in testing, or in documentation of aiw of the drugs, pertaining to the Registration Certificate, to be granted to us. Where any change in respect of any of the drugs under the Registration Certificate has taken place, in respect of any of the above matters, we shall inform the same to the licensing authority, in writing within 30 days from the date of such changes. In such cases, where there will be any major change/modification in manufacturing or in processing or in testing, or in documentation, as the case may be, at the discretion of the licensing authority, we shall obtain necessary approval within 30 days

by submitting a separate application, alongwith the registration fee as specified in clause (ii) of sub rule (3) of rule 24A.

3.6 We shall from time to time report for any administrative action taken due adverse reaction, *viz.*, market withdrawal regulatory restriction, or cancellation of authorisation and/or "not of standard quality import" of any drug pertaining the Registration Certificate declared by any Regulatory Authority of any country where the drug is marketed/sold or distributed. The despatch and marketing of the drug in such cases, shall be stopped immediately and the licensing authority shall be informed immediately. Further action in respect of stop marketing of drug shall be taken as per the directions of the licensing authority. In such cases, action equivalent to that taken with reference to the concerned drug(s) in the country of origin or to the country of marketing will be followed in India also, in consultation with the licensing authority. The licensing authority may direct any further modification to this course of action, including the withdrawal of the drug from Indian market 48 hours time period.

3.7 We shall comply with such further requirements, if any, as may be specified, by the Government of India, under the Act and the rules, made thereunder.

3.8 We shall allow the licensing authority and/or any person authorised by him in that behalf to enter and inspect the manufacturing premises and to examine the process/procedure and documents in respect of any drug manufactured by us for which the application for Registration Certificate has been made.

3.9 We shall allow the licensing authority or any person authorised by him in that behalf to take samples of the drugs concerned for test, analysis or examination, if considered necessary by the licensing authority.

Place.....

Date..... .....

Signature of the manufacturer [1062][or his authorised agent] Seal/Stamp

SCHEDULE D(II)

(See rule 21(d) and rule 24A)

INFORMATION REQUIRED TO BE SUBMITTED BY THE MANUFACTURER OR HIS AUTHORISED AGENT WITH THE APPLICATION FORM FOR THE REGISTRATION OF A BULK DRUG/FORMULATION/SPECIAL PRODUCT FOR ITS IMPORT INTO INDIA

(The format shall be properly filled in and the detailed information, secret in nature, may be furnished on a Computer Floppy)

1. General

1.1 Name of the drug/formulation/special product, a brief description and the therapeutic class to which it belongs.

1.2 Regulatory status of the drug. Free Sale Certificate and/or Certificate of Pharmaceutical Products (CPP) issued by the Regulatory Authority of the country of origin. Free sale approval issued by the Regulatory Authorities of other major countries.

1.3 Drugs Master File (DMF) for the drug to be registered (duly notarised).

[1063][1.4 GMP certificate as per WHO - GMP format, or Certificate of Pharmaceutical Products (CPP), or written confirmation for active substances exported to the European Union which is equivalent to GMP certificate issued as per WHO - GMP guidelines, by the National Regulatory Authority of the country of origin or a duly notarised copy of the certificate equivalent to GMP certificate as per WHO - GMP guidelines issued by United States of America or Japan or Australia or Canada or the European Union for the purpose of marketing of the drug in their country.]

1.5 List of countries where marketing authorisation or import permission for the said drug is granted with date (respective authorisation shall be enclosed).

1.6 List of countries where marketing authorisation or import permission for the said drug is cancelled /withdrawn with date.

1.7 List of countries where marketing authorisation or import permission for the said drug is pending since (date).

1.8 Domestic price of the drug in the currency followed in the country of origin.

1.9 List of countries where the said drug is patented.

2. Chemical and Pharmaceutical information of Drugs

2.1 Chemical name Code name or number, if any Non-proprietary or generic name, if any Structure Physico-chemical properties.

2.2 Dosage form and its composition, Qualitative and Quantitative composition in terms of the active substance(s) and excipient(s). List of active substance(s) separately from the constituent(s) of excipient(s).

2.3 Specification of active and inactive ingredient(s) including pharmacopoeil references.

2.4 Sources of active ingredient(s), name and address.

2.5 Test for identification of active ingredient(s), Method of its assays and tests for impurity profile with reference standards for the impurities (Protocol to be submitted alongwith reference standards for the impurities) relative substances.

2.6 Outline method and flow chart of manufacture of the bulk drug or finished formulation or special product.

2.7 Detailed test protocol for the drug with pharmacopoeil reference or in-house specification as approved by the registration authority, in the country of origin.

2.8 Stability date including accelerated stability and real time stability analysis.

2.9 Documentation on pack size

2.10 Numerical expression or EAN bar code on the labels and cartons.

2.11 Safety documents on containers and closer.

2.12 Documentation on storage conditions.

2.13 Three samples of medical products/drug and outer packaging are to be submitted with batch certificates. Additional samples as well as reference substances with batch certificates including date of manufacture, shelf-life storage conditions of reference substance may be required both during registration procedure and during validity of registration decision.

2.14 Batch test reports/certificate of five consecutive production batches in details of the medicinal product are to be submitted for every site of manufacturing premises.

2.15 Manner of labelling as per rule 96 of the Drugs Rules, 1945.

2.16 Package insert.

2.17 Details of safety handling procedure of the drug

2.18 Detaild of PMS study report for marketing period not exceeding five years.

3. Biological and Biopharmaceutical Information of Drugs

3.1 Biological control tests applied on the starting material, if applicable.

3.2 Biological control tests applied on the intermediate products, if applicable.

3.3 Biological control tests applied on the finished medical products, if applicable.

3.4 Stability of the finished products in terms of biological potency of the drug, if applicable.

3.5 Sterility tests, if applicable, specification and protocol therein.

3.6 Pyrogen tests, if applicable specification and protocol therein.

3.7 Acute and sub-acute toxicity tests, if applicable specification and protocol therein.

3.8 Bio-availability studies and bio-equivalence data, if applicable.

3.9 Data relating to the environmental risk assessment for r-DNA products.

3.10 Other information relevant under the section.

4. Pharmacological and Toxicological Information of Drugs

Executive summary of the product is to be submitted mentioning the specific and general pharmacological actions of the drug and pharmacokinetic studies on absorption, metabolism, distribution and excretion. A separate note is to be given on acute and sub-acute toxicity studies and long term toxicity studies. Specific studies on reproductive toxicity, local toxicity and carcinogenic activity of the drug is to be elaborated, as far as possible.

5. Clinical Documentation

A new drug as defined under rule 122E of the Drugs and Cosmetics Rules, 1945 is required to be permitted separately by the licensing authority under rule 122A of the said rules prior to its registration. Such a new drug requires a brief summary on clinical documentation, along with permission under 122A of the said rules for its Registration Certificate.

6. Labelling and Packaging Information of Drugs

6.1 Lables should conform as per the specifications under the Drugs and Cosmetics Rules, 1945.

6.2 Package insert should be in English and shall indicate the following therapeutic indications:—

Posology and method of administration.
Contra-indications.
Special warnings and special precautions for use, if any.
Interaction with other medicaments and oilier forms of intention.
Pregnancy and lactation, if contra-indicated.
Effects of ability to drive and use machines, if contra-indicated.
Undesirable effects/side effects.
Antidote for overdosing.

6.3 Package insert should indicate the following pharmaceutical information:—

List of excipients.
Incompatibilities.
Shelf life in the medical product as packaged for sale.
Shelf life after dilution or reconstitution according to direction.
Shelf life after first opening the container.
Special precautions for storage.
Nature and specification of the container.
Instructions for use/handling.

7. Specific Information Required for the Special Products (to be supplied, separately in annexure, as 'A', ' B' and 'C')

The information submitted above is true to the best of my knowledge and belief. Place.....

Date..... Signature of the manufacturer

[1064][or his authorised agent] Seal/Stamp

NB.—1. Any change in the process of manufacture, method of testing, labelling, packaging, designing of the sale pack, medical literature and documentation is to be intimated to the licensing authority forthwith and permission to be obtained from him within 30 days time period.

2. Information relating to Serial No. 4 and Serial No. 5 are not applicable for drugs figuring in Indian Pharmacopoeia and also for the drugs figuring in United States of Pharmacopoeia, European Pharmacopoeia, and British Pharmacopoeia. Provided such drugs have already been approved for marketing in India for the applicant under rules 122A, 122B, 122C or 122D of the Drugs and Cosmetics Rules, 1945.

ANNEXURE A

[See Schedule D (II), item No. 7]

INFORMATION TO BE SUBMITTED IN SCHEDULE D (II)

Specific information required for the blood products

A product dossier showing the—

1. Details of source Plasma, its viral screening, storage and transport from Collection Centres to Fractionation Centre. Regulatory status of Collection Centres.

2. Details of Fractionation Centre, Regulatory Status, Method of Fractionation and Control Processes.

3. Details of viral inactivation process for enveloped and non-enveloped virus(es) and viral validation studies to assess the viral load of the product. Testing of viral screening at any stage is to be highlighted with the details of the Kits used with their respective sensitivity and specificity.

4. Bulk filtration prior to pharmaceutical packing giving the full details of Microfiltration or nano-filtration followed.

5. Complete details of pharmaceutical processing and unitization.

6. Test protocol of the product showing the specifications and Pharmacopoeial method followed for various testing parameters.

Specific batch test report for at least 3 batches showing the specifications of each testing parameter.

7. Pack size and labelling

8. Product Insert.

9. Specimen Batch Release Certificate issued by the National Regulatory Authority of the country of origin.

Specific processings like safe handling, material control, area control, pasteurization, stability studies, storage at quarantine stage and finished stage and packaging should be highlighted in the product dossier.

The information submitted above is true to the best of my knowledge and belief.

Place.....

Date..... ……

Signature of the manufacturer Seal /Stamp

NB.—1. Any change in the process of manufacturer, method of testing, labelling, packaging, designing of the sale pack, medical literature and documentation is to be intimated to the licensing authority forthwith and permission to be obtained from him within 30 days time period.

ANNEXURE B

[*See* Schedule D(II), item No. 7]

INFORMATION TO BE SUBMITTED IN SCHEDULE D(II)

Specific information required for the diagnostic kits

A product dossier showing the—

1. The details of source antigen or antibody as the case may be and characterisation of the same. Process control of coating of antigen or antibody on the base material like Nitrocellulose paper, strips or cards or ELISA wells etc.
Details composition of the kit and manufacturing flow chart process of the kit showing the specific flow diagram of individual components or source of the individual components.

2. Test protocol of the kit showing the specifications and method of testing. In house evaluation report of sensitivity, specificity and stability studies carried out by the manufacturer.

3. The report of evaluation in details conducted by the National Control Authority of country of origin.
Specimen batch test report for at least consecutive 3 batches showing specification of each testing parameter.

4. The detailed test report of all the components used/packed in the finished kit.

5. Pack size and labelling.

6. Product insert.

Specific evaluation report, if done by any laboratory in India showing the sensitivity and specificity of the kit.
Specific processing like safe handling, material control, area control, process control, stability studies, storage at quarantine stage and finished stage, packaging should be highlighted in the product dossier.

The information submitted above is true to the best of my knowledge and belief.

Place:.....

Date:.....

Signature of the manufacturer Seal/Stamp

NB.—1. Any change in the process of manufacture, method of testing, labelling, packaging, designing of the sale pack, medical literature and documentation is to be intimated to the licensing authority forthwith and permission to be obtained from him within 30 days time period.

ANNEXURE C

[See Schedule D(II), item No. 7]

INFORMATION TO BE SUBMITTED IN SCHEDULE D(II)

Specific information required for vaccines

A product dossier showing the—

1. History, source, date of receipt, storage, identity and characterisation of seed strain.

2. Detailed flow chart of manufacturing process showing all the details of in-process control on toxicity, potency study and stability data of the final bulk and the final finished product including the storage temperature.

3. Complete details of chemical and pharmaceutical data for the product. Composition and dosage form—method of manufacture with detailed flow chart—control of starting material—control tests on intermediate and finished products certificate of analysis of finished products validation of critical manufacturing steps.

4. Test protocol of the vaccines showing the specification and method of testing including Pharmacopoeial specification.

5. Specimen batch test report for at least consecutive three batches showing the specification of each testing parameter.

6. The detailed lest reports of all the components used/packed in the finished vaccine.

7. Pack-size and labelling.

8. Product insert.

9. Specimen batch release certificates issued by the National Regulatory Authority of the country of origin

10. Summary of pre-clinical and clinical data including:

(a) Prescribing information.

(b) Pharmacological and toxicological data pertaining to tests on animals characterisation of immune response and safety study in human use, in specific conditions.

Specific information on source of seed strain, its characterisation, inactivation etc. and processings like safe handling, material control, area

control, process control, stability studies, storage at quarantine stage and finished stage, packaging should be highlighted in the product dossier.

Specimen production and quality control protocols for at least three consecutive lots showing the specifications for each quality control parameter including Pharmacopoeial requirement shall be submitted for study.

The information submitted above is true to the best of my knowledge and belief.

Place.....

Date..... ……

Signature of the manufacturer Seal/Stamp

NB.—1. Any change in the process of manufacture, method of testing, labelling, packaging, designing of the sale pack, medical literature and documentation is to be intimated to the licensing authority forthwith and permission to be obtained from him within 30 days time period.

2. All vaccines shall be new drugs unless certified otherwise by the licensing authority approved under rule 21 of the Drugs and Cosmetics Rule, 1945. A copy of approval of the vaccine issued by the said licensing authority is to be enclosed, prior to issue of Registration Certificate of the said vaccines.]

SCHEDULE D(III)

[1065][***]

[1066][***]

[1067][SCHEDULE E(1)

[See rule 161(2)]

LIST OF POISONOUS SUBSTANCES UNDER THE AYURVEDIC (INCLUDING SIDDHA) AND UNANI SYSTEMS OF MEDICINE

A. AYURVEDIC SYSTEM

I. **DRUGS OF VEGETABLE**	**ORIGIN**
1. Ahipena (Except seeds)	
2. Arka	Papaver somniferum Linn. Except

3.	Bhallataka	seeds) Calotropis procera (Ait.) R. Br.
4.	Bhanga (Except seeds)	Semecarpus anacardium Linn. f.
5.	Danti	Cannabis sativa Linn. (Except seeds)
6.	Dhattura	Baliospermum montanum Mull. Arg.
7.	Gunja (Seed)	Datura metel Linn.
8.	Jaipala (Seed)	Abrus precatorius Linn. (Seed)
9.	Karaveera	Croton tiglium Linn.
10.	Langali	Nerium indicum Mill
11.	Parasika Yavani	Gloriosa superba Linn.
12.	Vatsanabha/	Hyoscyamus niger Linn.
	Shringivisha	Aconitum ferox, Wall, ex Ser.
	Holmes	Aconitum Chasmanthum Stapf. Ex
13.	Vishamushti	Stychnos nux vomica Linn.

II. DRUGS OF ANIMAL ORIGIN

14.	Sarpa Visha	Snake poison

III. DRUGS OF MINERAL ORIGIN

15.	Gauripashna	Arsenic
16.	Hartala	Arsenic trisulphide
17.	Manahashila	Arsenic disulphide
18.	Parada	Mercury
19.	Rasa karpura	Hydrargyri subchloridum
20.	Tuttha	Copper sulphate
21.	Hingula	Cinnabar

B. SIDDHA SYSTEM

1.	Abini (except seed)	Papaver somniferum Linn
2.	Alari	Nerium indicum Mill
3.	Attru thummatti	Citrullus colocynthis (L.) Schrad
4.	Umathai	Datura stramonium Linn.
5.	Etti	Stychnos nux vomica Linn
6.	Ganja (except seed)	Cannabis sativa Linn.
7.	Kalappaki Kizahangu	Gloriosa superba Linn.
8.	Kodikkalli (exempted for external use)	Euphorbia tirucalli Linn.

10. Kattu Thumatti	Cucumis trigonus Roxb.
11. Kunri (except root)	Arbus precatorius Linn.
12. Cheramkottai	Semecarpus anacardium Linn.f.
13. Thillai	Exoecoria agallocha Linn.
14. Nabi	Aconitum ferox Wall.
15. Nervalam	Croton tiglium Linn.
16. Pugaielai	Nicotiana tabacum Linn.
17. Mancevikkalli (exempted for external use)	Euphorbia species

C. UNANI MEDICINE

I. **DRUGS OF VEGETABLE**	**ORIGIN**
1. Afiyun (except seed)	Papaver somniferum Linn.
2. Bazur-ul-banj	Hyoscyamus niger Linn.
3. Bish	Aconitum chasmanthum Stapfex Holmes
4. Bhang (except seed)	Cannabis sativa Linn.
5. Charas (resin) (Except seed)	Cannabis sativa Linn.
6. Dhatura seeds	Datura metel Linn, (seeds)
7. Kuchla	Stychnos nux vomica Linn.
8. Shokran	Conium maculatum Linn.

II. DRUGS OF ANIMAL ORIGIN	
9. Sanp (head)	Snake (head)
10. Telni Makkhi	Mylabaris cichorii Linn. Mylabaris pustulata Thumb Mylabaris macilenta

III. DRUGS OF MINERAL ORIGIN	
11. Darachikna	Hydrargyri perchloridum
12. Hira	Diamond
13. Ras Kappor	Hydrargyri Subchloridum (calomel)
14. Shingruf	Hydrargyri bisulphuratum
15. Zangar	Cupri subacetas

16. Sammul-Far	(Abyaz, Asfar, Aswad and Ahmar (white, yellow, black and red, arsenic)
17. Tootiya	Copper Sulphate
18. Para	Hydrargyrum
19. Hartal	Arsenic trisulphite (yellow)

*Arka used for Bhawna before making Bhasma is exempted.]

SCHEDULE F

(*See* rule 78 and Part X)

[1068][***]

[1069][PART XII B
REQUIREMENTS FOR THE FUNCTIONING AND OPERATION OF A BLOOD BANK AND/OR FOR PREPARATION OF BLOOD COMPONENTS

I. BLOOD BANKS/BLOOD COMPONENTS

A. General

1. *Location and Surroundings*—The blood bank shall be located at a place which shall be away from open sewage, drain, public lavatory or similar unhygienic surroundings.

2. *Building*—The building(s) used for operation of a blood bank and/or preparation of blood components shall be constructed in such a manner so as to permit the operation of the blood bank and preparation of blood components under hygienic conditions and shall avoid the entry of insects, rodents and flies. It shall be well lighted, ventilated and screened (mesh), wherever necessary. The walls and floors of the rooms, where collection of blood or preparation of blood components of blood products is carried out shall be smooth, washable and capable of being kept clean. Drains shall be of adequate size and where connected directly to a sewer, shall be equipped with traps to prevent back siphonage.

3. *Health, clothing and sanitation of staff*—The employees shall be free from contagious or infectious diseases. They shall be provided with clean overalls, headgear, foot-wears and gloves, wherever, required. There shall be adequate, clean and convenient hand washing and toilet facilities.

B. Accommodation for a Blood Bank

A blood bank shall have an area of 100 square metres for its operations and an additional area of 50 square metres for preparation of blood components. It shall be consisting of a room each for—

(1) Registration and medical examination with adequate furniture and facilities for registration and selection of donors;

(2) Blood collection (air-conditioned);

(3) Blood component preparation. (This shall be air-conditioned to maintain Temperature between 20 degree centigrade to 25 degree centigrade);

(4) Laboratory for blood group serology (air conditioned);

(5) Laboratory for blood transmissible diseases like Hepatitis, Syphilis, Malaria, HIV-antibodies (air-conditioned);

(6) Sterilization-cum-washing;

(7) Refreshment-cum-rest room (air-conditioned);

(8) Store-cum-records.

Notes.—

(1) The above requirements as to accommodation and area may be relaxed, in respect of testing laboratories and sterilization-cum-washing room, for reasons to be recorded in writing by the licensing authority and/or the Central Licence approving Authority, in respect of blood banks operating in hospitals, provided the hospital concerned has a pathological laboratory and a sterilization-cum-washing room common with other departments in the said hospital.

(2) Refreshments to the donor after phlebotomy shall be served so that he is kept under observation in the Blood Bank.

C. Personnel

Every blood bank shall have following categories of whole time competent technical staff:—

(a) Medical Officer, possessing the qualifications specified in condition (i) of rule 122G.

(b) Blood Bank Technician(s), possessing:—

(i) Degree in Medical Laboratory Technology (M.L.T.) with six months' experience in the testing of blood and/or its components; or

(ii) Diploma in Medical Laboratory Technology (M.L.T.) with one year's experience in the testing of blood and/or its components, the degree or diploma being from a University/Institution recognised by the Central Government or State Government.

(c) Registered Nurse(s).

(d) Technical supervisor (where blood components are manufactured), possessing—

(i) Degree in Medical Laboratory Technology (M.L.T.) with six month's experience in the preparation of blood components; or

(ii) Diploma in Medical Laboratory Technology (M.L.T.) with one year's experience in the preparation of blood components,

the degree or diploma being from a University/Institution recognised by the Central Government or State Government.

Notes.—

(1) The requirements of qualification and experience in respect of Technical Supervisor and Blood Bank Technician shall apply in the cases of persons who are approved by the licensing authority and/or Central Licence

Approving Authority after the commencement of the Drugs and Cosmetics (Amendment) Rules, 1999*[1070].

(2) As regards, the number of whole time competent technical personnel, the blood bank shall comply with the requirements laid down in the Directorate General of Health Services Manual.

(3) It shall be the responsibility of the licensee to ensure through maintenance of records and other latest techniques used in blood banking system that the personnel involved in blood banking activities for collection, storage, testing and distribution are adequately trained in the current Good Manufacturing Practices/Standard Operating Procedures for the tasks undertaken by each personnel. The personnel shall be made aware of the principles of Good Manufacturing Practices/Standard Operating Procedures that affect them and receive initial and continuing training relevant to their needs.

D. Maintenance

The premises shall be maintained in a clean and proper manner to ensure adequate cleaning and maintenance of proper operations. The facilities shall include—

(1) Privacy and thorough examination of individuals to determine their suitability as donors.

(2) Collection of blood from donors with minimal risk of contamination or exposure to activities and equipment unrelated to blood collection.

(3) Storage of blood or blood components pending completion of tests.

(4) Provision for quarantine, storage of blood and blood components in a designated location, pending repetition of those tests that initially give questionable serological results.

(5) Provision for quarantine, storage, handling and disposal of products and reagents not suitable for use.

(6) Storage of finished products prior to distribution or issue.

(7) Proper collection, processing, compatibility testing, storage and distribution of blood and blood components to prevent contamination.

(8) Adequate and proper performance of all procedures relating to plasmapheresis, plateletpheresis and leucapheresis.

(9) Proper conduct of all packaging, labelling and other finishing operations.

(10) Provision for safe and sanitary disposal of—

(i) Blood and/or blood components not suitable for use, distribution or sale.

(ii) Trash and items used during the collection, processing and compatibility testing of blood and/or blood components.

E. Equipment

Equipment used in the collection, processing, testing, storage and sale/distribution of blood and its components shall be maintained in a clean and proper manner and so placed as to facilitate cleaning and maintenance. The equipment shall be observed standardised and calibrated on a regularly scheduled basis as described in the Standard Operating Procedures Manual and shall operate in the manner for which it was designed so as to ensure compliance with the official requirements (the equipments) as stated below for blood and its components.

Equipment that shall be observed, standardised and calibrated with at least the following frequencies:—

	Equipment	***Performance***	***Frequency***	***Frequency of Calibration***
1.	Temperature recorder	Compare against thermometer	Daily	As often as necessary
2.	Refrigerated centrifuge	Observe speed and temperature	Each day of use	As often as necessary
3	Hematocrit Centrifuge	----------	--------	Standardize before initial use, after repair or adjustments, and annually

	Equipment	*Performance*	*Frequency*	*Frequency of Calibration*
4.	General lab. Centrifuge	----------	----------	Tachometer every 6 months
5.	Automated Blood typing	Observe controls for correct results	Each day of use	----------
6.	Haemoglo-binometer	Standardize against cyanamethemoglobulin standard	Each day of use	----------
7.`	Refractometer	Standardize against distilled water	—ditto—	----------
8.	Blood container weighing device	Standardize against container of known weight	—ditto—	As often as necessary
9.	Water Bath	Observe temperature	—ditto—	—ditto—
10.	Rh view box (wherever necessary)	—ditto—	—ditto—	—ditto—
11.	Autoclave	—ditto—	Each day of use	—ditto—
12.	Serologic rotators	Observe controls for correct results	Each day of use	Speed as often as necessary
13.	Laboratory thermometers	----------	----------	Before initial use
14.	Electronic thermometers	----------	Monthly	----------
15.	Blood agitator	Observe weight of the first container of blood filled for correct results.	Each day of use	Standardize with container of known mass or volume before initial use, and after repairs or adjustments

F. Supplies and Reagents

All supplies and reagents used in the collection, processing, compatibility, testing, storage and distribution of blood and blood components shall be stored at proper temperature in a safe and hygienic place, in a proper manner and in particular—

(a) All supplies coming in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product.

(b) Supplies and reagents that do not bear an expiry date shall be stored in a manner that the oldest is used first.

(c) Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

(d) All final containers and closures for blood and blood components not intended for transfusion shall be clean and free of surface solids and other contaminants.

(e) Each blood collecting container and its satellite container(s), if any, shall be examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination shall include inspection for breakage of seals, when indicated and abnormal discoloration. Where any defect is observed, the container shall not be used of if detected after filling, shall be properly discarded.

(f) Representative samples of each lot of the following reagents and/or solutions shall be tested regularly on a scheduled basis by methods described in the Standard Operating Procedures Manual to determine their capacity to perform as required.

Reagents and solutions	*Frequency of testing alongwith controls*
Anti-human serum	Each day of use
Blood grouping serums	Each day of use
Lectin	Each day of use
Antibody screening and reverse grouping cells.	Each day of use
Hepatitis test reagents	Each run
Syphilis serology reagents	Each run
Enzymes	Each day of use
HIV I and II reagents	Each run
Normal saline (LISS and PBS)	Each day of use
Bovine Albumin	Each day of use

G. Good Manufacturing Practices (GMPs)/Standard Operating Procedures (SOPs)

Written Standard Operating Procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage and sale or distribution of blood and/or preparation of blood components for homologous transfusion, autologous transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the concerned areas. The Standard Operating Procedures shall *inter alia* include:—•

1. (a) Criteria used to determine donor suitability;

(b) methods of performing donor qualifying tests and measurements including minimum and maximum values for a test or procedure, when a factor in determining acceptability;

(c) solutions and methods used to prepare the site of phlebotomy so as to give maximum assurance of a sterile container of blood;

(d) method of accurately relating the product(s) to the donor;

(e) blood collection procedure, including in-process precautions taken to measure accurately the quantity of blood drawn from the donor;

(f) methods of component preparation including, any time restrictions for specific steps in processing;

(g) all tests and repeat tests performed on blood and blood components during processing;

(h) pre-transfusion testing, wherever applicable, including precautions to be taken to identify accurately the recipient blood components during processing;

(i) procedures of managing adverse reactions in donor and recipient reactions;

(j) storage temperatures and methods of controlling storage temperatures for blood and its components and reagents;

(k) length of expiry dates, if any, assigned for all final products;

(1) criteria for determining whether returned blood is suitable for reissue;

(m) procedures used for relating a unit of blood or blood component from the donor to its final disposal;

(n) quality control procedures for supplies and reagents employed in blood collection, processing and re-transfusion testing;

(o) schedules and procedures for equipment maintenance and calibration;

(p) labelling procedures to safeguard its mix-ups, receipt, issue, rejected and inhand;

(q) procedures of plasmapheresis, plateletpheresis and leucapheresis if performed, including precautions to be taken to ensure re-infusion of donor's own cells;

(r) procedures for preparing recovered (salvaged) plasma if performed, including details of separation, pooling, labelling, storage and distribution;

(s) all records pertinent to the lot or unit maintained pursuant to these regulations shall be reviewed before the release or distribution of a lot or unit of final product. The review or portions of the review may be performed at appropriate periods during or after blood collection, processing, testing and storage. A thorough investigation, including the conclusions and follow-up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specification shall be made and recorded.

2. A licensee may utilise current Standard Operating Procedures, such as the manuals of the following organisations, so long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part, namely:—

(i) Directorate General of Health Services Manual.

(ii) Other Organisations or individual blood bank's manuals, subject to the approval of State licensing authority and Central Licence Approving Authority.

H. Criteria for Blood Donation

Conditions for donation of blood:

(1) *General*—No person shall donate blood and no blood bank shall draw blood from a person, more than once in three months. The donor shall be in good health, mentally alert and physically fit and shall not be inmates of jail, persons having multiple sex partners and drug-addicts. The donors shall fulfil the following requirements, namely:—

[1071][(a) the donor shall be in the age group of 18 to 65 years;]

(b) the donor shall not be less than 45 kilograms;

(c) temperature and pulse of the donor shall be normal;

(d) the systolic and diastolic blood pressures are within normal limits without medication;

(e) haemoglobin which shall not be less than 12.5 grams;

(f) the donor shall be free from acute respiratory diseases;

(g) the donor shall be free from any skin diseases at the site of phlebotomy;

(h) the donor shall be free from any disease transmissible by blood transfusion, insofar as can be determined by history and examination indicated above;

(i) the arms and forearms of the donor shall be free from skin punctures or scars indicative of professional blood donors or addiction of self injected narcotics.

(2) *Additional qualifications of a donor*—No person shall donate blood, and no blood bank shall draw blood from a donor, in the conditions mentioned in column (1) of the Table given below before the expiry of the period of deferment mentioned in the column (2) of the said Table.

Table: Deferment of blood donation

S. No.	Conditions	Period of Deferment
(1)	(2)	(3)
(a)	Abortions	6 months
(b)	History of Blood transfusion	6 months
(c)	Surgery	12 months
(d)	Typhoid	12 months after recovery
(e)	History of Malaria and duly treated	3 months (endemic) 3 years (non endemic area)
(f)	Tatto	6 months
(g)	Breast feeding	12 months after delivery
(h)	Immunization (Cholera), Typhoid, Diphtheria Tetanus, Plague, Gammaglobulin	15 days
(i)	Rabies vaccination	1 year after vaccination
(i)	History of Hepatitis in family of close contact	12 months
(k)	Immunoglobulin	12 months

(3) No person shall donate blood and no blood bank shall draw blood from a person, suffering from any of the diseases mentioned below, namely:—

(a) Cancer
(b) Heart disease
(c) Abnormal bleeding tendencies
(d) Unexplained weight loss
(e) Diabetes-controlled on Insulin
[1072][(f) Hepatitis infection]
(g) Chronic nephritis
(h) Signs and symptoms, suggestive of AIDS
(i) Liver disease
(j) Tuberculosis
(k) Polycythemia Vera
(1) Asthma
(m) Epilepsy
(n) Leprosy
(o) Schizophrenia
(p) Endocrine disorders

I. General Equipments and Instruments

1. For blood collection room:

(i) Donor beds, chairs and tables : These shall be suitably and comfortably cushioned and shall be of appropriate size.

(ii) Bedside table.

(iii) Sphygmomanometer and Stethoscope.

(iv) Recovery beds for donors.

(v) Refrigerators, for storing separately tested and untested blood, maintaining temperature between 2 to 6 degree centigrade with digital dial thermometer, recording thermograph and alarm device, with provision for continuous power supply.

(vi) Weighing devices for donor and blood containers.

2. For haemoglobin determination :

(i) Copper sulphate solution (specific gravity 1.053)

(ii) Sterile lancet and impregnated alcohol swabs.

(iii) Capillary tube (1.3 x 1.4 x 96 mm or pasteur pipettes)

(iv) Rubber bulbs for capillary tubings.

(v) Sahli's haemoglobinometer/Colorimeteric method.

3. For temperature and pulse determination:

(i) Clinical thermometers.

(ii) Watch (fitted with a seconds-hand) and a stop-watch.

4. For blood containers:

(a) Only disposable PVC blood bags shall be used (closed system) as per the specifications of IP/UPS/BP.

(b) Anti-coagulants: The anti-coagulant solution shall be sterile, pyrogen-free and of the following composition that will ensure

satisfactory safety and efficacy of the whole blood and/or for all the separated blood components.

(i) Citrate Phosphate Dextrose Adenine solution (CPDA) or Citrate Phosphate Dextrose Adenine -1 (CPDA-1) — 14 ml. solution shall be required for 100 ml of blood**.**

Note 1.—(i) In case of single/double/triple/quadruple blood collection bags used for blood component preparations, CPDA blood collection bags may be used.

(ii) Acid Citrate Dextrose solution (A.C.D. with Formula-A), I.P. —15 ml solution shall be required for 100 ml of blood.

(iii) Additive solutions such as SAGM, ADSOL, NUTRICEL may be used for storing and retaining Red Blood Corpuscles upto 42 days.

Note 2.—The licensee shall ensure that the anti-coagulant solutions are of a licensed manufacturer and the blood bags in which the said solutions are contained have a certificate of analysis of the said manufacturer.

5. Emergency equipments/items:

(i) Oxygen cylinder with mask, gauge and pressure regulator.

(ii) 5 per cent. Glucose or Normal Saline.

(iii) Disposable sterile syringes and needles of various sizes.

(iv) Disposable sterile I.V. infusion sets.

(v) Ampoules of Adrenaline, Noradrenaline, Mephentin, Betamethasone or Dexamethasone, Metoclorpropamide injections.

(vi) Aspirin.

6. Accessories:

(i) Such as blankets, emesis basins, haemostats, set clamps, sponge forceps, gauze, dressing jars, solution jars, waste cans.

(ii) Medium cotton balls, 1.25 cm. adhesive tapes.

(iii) Denatured spirit, Tincture iodine, green soap or liquid soap.

(iv) Paper napkins or towels.

(v) Autoclave with temperature and pressure indicator.

(vi) Incinerator

(vii) Stand-by generator.

7. Laboratory equipment:

(i) Refrigerators, for storing diagnostic kits and reagents, maintaining a temperature between 4 to 6 degree centigrade (plus/minus 2 degree centigrade) with digital dial thermometer having provision for continuous power supply.

(ii) Compound Microscope with low and high power objectives.

(iii) Centrifuge Table Model

(iv) Water bath : having range between 37 degree centigrade to 56 degree centigrade

(v) Rh viewing box in case of slide technique.

(vi) Incubator with thermostatic control.

(vii) Mechanical shakers for serological tests for Syphilis.

(viii) Hand-lens for observing tests conducted in tubes.

(ix) Serological graduated pipettes of various sizes.

(x) Pipettes (Pasteur)

(xi) Glass slides

(xii) Test tubes of various sizes/micrometer plates (U or V type)

(xiii) Precipitating tubes 6 mm x 50 mm of different sizes and glass beakers of different sizes.

(xiv) Test tube racks of different specifications.

(xv) Interval timer electric or spring wound.

(xvi) Equipment and materials for cleaning glass wares adequately.

(xvii) Insulated containers for transporting blood, between 2 degree centigrade to 10 degree centigrade temperatures, to wards and hospitals.

(xviii) Wash bottles

(xix) Filter papers

(xx) Dielectric tube sealer.

(xxi) Plain and EDTA vials

(xxii) Chemical balance (wherever necessary)

(xxiii) ELISA reader with printer, washer and micropipettes.

J. Special Reagents

(1) Standard blood grouping sera Anti A, Anti B and Anti D with known controls. Rh typing sera shall be in double quantity and each of different brand or if from the same supplier each supply shall be of different lot numbers.

(2) Reagents for serological tests of syphilis and positive sera for controls.

(3) Anti Human Globulin Serum (Coomb's serum)

(4) Bovine Albumin 22 per cent Enzyme reagents for incomplete antibodies.

[1073][(5) ELISA or Rapid RPHA test kits for Hepatitis and HIV I & II.]

(6) Detergent and other agents for cleaning laboratory glass wares.

K. Testing of whole Blood

(1) It shall be responsibility of the licensee to ensure that the whole blood collected, processed and supplied conforms to the standards laid down in the Indian Pharmacopoeia and other tests published, if any, by the Government.

(2) Freedom from HIV antibodies (AIDS) Tests-Every licensee shall get samples of every blood unit tested, before use, for freedom from HIV I and HIV II antibodies either from laboratories specified for the purpose by the Central Government or in his own laboratory. The results of such testing shall be recorded on the label of the container.

(3) Each blood unit shall also be tested for freedom from [1074][Hepatitis B surface antigen and Hepatitis C virus antibody], VDRL and malarial parasite and results of such testing shall be recorded on the label of the container.

Note.—(a) Blood samples of donors in pilot tube and the blood samples of the recipient shall be preserved for 7 days after issue.

(b) The blood intended for transfusion shall not be frozen at any stage.

(c) Blood containers shall not come directly in contact with ice at any stage.

L. Records

The records which the licensee is required to maintain shall include *inter alia* the following particulars, namely:—

(1) *Blood donor record:*—It shall indicate serial number, date of bleeding, name, address and signature of donor with other particulars of age, weight, haemoglobin, blood grouping, blood pressure, medical examination, bag number and patient's detail for whom donated in case of replacement donation,

category of donation (voluntary/replacement) and deferral records and signature of Medical Officer Incharge.

(2) *Master records for blood and its components:*—It shall indicate bag serial number, date of collection, date of expiry, quantity in ml. ABO/Rh Group, results for testing of HIV I and HIV II antibodies, Malaria, V.D.R.L., [2][Hepatitis B surface antigen and Hepatitis C virus antibody] and irregular antibodies (if any), name and address of the donor with particulars, utilisation issue number, components prepared or discarded and signature of the Medical Officer Incharge.

(3) *Issue register:*—It shall indicate serial number, date and time of issue, bag serial number, ABO/Rh Group, total quantity in ml. name and address of the recipient, group of recipient, unit/institution, details of cross-matching report, indication for transfusion.

(4) *Records of components supplied:*—quantity supplied; compatibility report, details of recipient and signature of issuing person.

(5) Records of A.C.D./C.P.D/CPD-A/SAGM bags giving details of manufacturer, batch number, date of supply, and results of testing.

(6) *Register for diagnostic kits and reagents used:*—name of the kits/reagents, details of batch number, date of expiry and date of use.

(7) Blood bank must issue the cross matching report of the blood to the patient together with the blood unit.

(8) Transfusion adverse reaction records.

(9) Records of purchase, use and stock in hand of disposable needles, syringes, blood bags, shall be maintained.

Note.—The above said records shall be kept by the licensee for a period of five years.

M. Labels

The labels on every bag containing blood and/or component shall contain the following particulars, namely:—

(1) The proper name of the product in a prominent place and in bold letters on the bag.

(2) Name and address of the blood bank

(3) Licence number

(4) Serial number

(5) The date on which the blood is drawn and the date of expiry as prescribed under Schedule P to these rules.

(6) A coloured label shall be put on every bag containing blood. The following colour scheme for the said labels shall be used for different groups of blood:

Blood Group	*Colour of the label*
O	Blue
A	Yellow
B	Pink
AB	White

(7) The results of the tests of [1075][Hepatitis B surface antigen and Hepatitis C virus antibody], syphilis, freedom from HIV I and HIV II antibodies and malarial parasite.

(8) The Rh group.

(9) Total volume of blood, the preparation of blood, nature and percentage of anti-coagulant.

(10) Keep continuously temperature at 2 degree centigrade to 6 degree centigrade for whole human blood and/or components as contained under III of Part XIIB.

(11) Disposable transfusion sets with filter shall be used in administration equipment.

(12) Appropriate compatible cross matched blood without a typical antibody in recipient shall be used.

(13) The contents of the bag shall not be used if there is any visible evidence of deterioration like haemolysis, clotting or discoloration.

(14) The label shall indicate the appropriate donor classification like "Voluntary Donor" or "Replacement Donor" in no less prominence than the proper name.

Notes.—1. In the case of blood components, particulars of the blood from which such components have been prepared shall be given against item numbers (5), (7), (8), (9) and (14).

2. The blood and/or its components shall be distributed on the prescription of a Registered Medical Practitioner.

II. BLOOD DONATION CAMPS

A blood donation camp may be organised by—

(a) a licensed designated Regional Blood Transfusion Centre; or

(b) a licensed Government blood bank; or

(c) the Indian Red Cross Society

[1076][(d) a licensed blood bank run by registered voluntary or charitable organization recognized by State or Union territory Blood Transfusion Council; or

(e) a private hospital blood bank.]

Notes.—(i) "Designated Regional Blood Transfusion Centre" shall be a centre approved and designated by a Blood Transfusion Council constituted by a State Government to collect, process and distribute blood and its components to cater to the needs of the region and that centre has also been licensed and approved by the Licensing Authority and Central Licence Approving Authority for the purpose.

(ii) The designated Regional Blood Transfusion Centre, Government blood bank and Indian Red Cross Society shall intimate within a period of seven days, the venue where blood camp was held and details of group wise blood units

collected in the said camp to the Licensing Authority and Central Licence Approving Authority.

For holding a blood donation camp, the following requirements shall be fulfilled/ complied with, namely:—

(A) Premises, Personnel etc.

(a) Premises under the blood donation camp shall have sufficient area and the location shall be hygienic so as to allow proper operation, maintenance and cleaning.

(b) All information regarding the personnel working, equipment used and facilities available at such a Camp shall be well documented and made available for inspection, if required, and ensuring—

(i) continuous and uninterrupted electrical supply for equipment used in the Camp;

(ii) adequate lighting for all the required activities;

(iii) hand-washing facilities for staff;

(iv) reliable communication system to the central office of the Controller/ Organiser of the Camp;

(v) furniture and equipment arranged within the available place;

(vi) refreshment facilities for donors and staff;

(vii) facilities for medical examination of the donors;

(viii) proper disposal of waste.

(B) Personnel for Out-door Blood Donation Camp

To collect blood from 50 to 70 donors in about 3 hours or from 100 to 120 donors in 5 hours, the following requirements shall be fulfilled/complied with:—

(i) One medical Officer and two nurses or phlebotomists for managing 6-8 donor tables;

(ii) two medico social workers;

(iii) three blood bank technicians;
(iv) two attendants;
(v) vehicle having a capacity to seat 8-10 persons, with provision for carriage of donation goods including facilities to conduct a blood donation camp.

C. Equipments

1. BP apparatus.
2. Stethoscope.
3. Blood bags (single, double, triple, quadruple)
4. Donor questionnaire.
5. Weighing device for donors.
6. Weighing device for blood bags.
7. Artery forceps, scissors.
8. Stripper for blood tubing.
9. Bed sheets, blankets/mattress.
10. Lancets, swab stick/tooth picks.
11. Glass slides.
12. Portable Hb meter/copper sulphate.
13. Test tube (big) and 12x100 mm (small)
14. Test tube stand.
15. Anti-A, Anti-B and Anti-AB, Antisera and Anti-D
16. Test tube sealer film.
17. Medicated adhesive tape.
18. Plastic waste basket
19. Donor cards and refreshment for donors.
20. Emergency medical kit.
21. Insulated blood bag containers with provisions for storing between 2 degree centigrade to 10 degree centigrade.
22. Dielectric sealer or portable tube sealer.

23. Needle destroyer (wherever necessary).

III. PROCESSING OF BLOOD COMPONENTS FROM WHOLE BLOOD BY A BLOOD BANK

The blood components shall be prepared by blood banks as a part of the blood Bank services. The conditions for grant or renewal of licence to prepare blood components shall be as follows:—

(A) Accommodation

(1) Rooms with adequate area and other specifications, for preparing blood components depending on quantum of work load shall be as specified in item B under the heading "I. BLOOD BANKS/BLOOD COMPONENTS" of this Part.

(2) Preparation of blood components shall be carried out only under closed system using single, double, triple or quadruple plastic bags except for preparation of Red Blood Cells Concentrates, where single bags may be used with transfer bags.

(B) Equipment

(i) Air conditioner;

(ii) Laminar air flow bench;

(iii) Suitable refrigerated centrifuge;

(iv) Plasma expresser;

(v) Clipper and clips and or dielectric sealer;

(vi) Weighing device;

(vii) Dry rubber balancing material;

(viii) Artery forceps, scissors;

(ix) Refrigerator maintaining a temperature between 2 degree centigrade to 6 degree centigrade, a digital dial thermometer with recording thermograph and alarm device, with provision for continuous power supply;

(x) Platelet agitator with incubator (wherever necessary);

(xi) Deep freezers maintaining a temperature between minus 30 degree centigrade to minus 40 degree centigrade and minus 75 degree centigrade to minus 80 degree centigrade;

(xii) Refrigerated Water bath for Plasma Thawing;

(xiii) Insulated blood bag containers with provisions for storing at appropriate temperature for transport purposes

(C) Personnel

The whole time competent technical staff meant for processing of Blood Components (that is Medical Officer, Technical Supervisor, Blood Bank Technician and Registered Nurse) shall be as specified in item C, under the heading 'I. BLOOD BANKS /BLOOD COMPONENTS' or this Part.

(D) Testing Facilities

General: Facilities for A, B, AB and O groups and Rli(D) grouping. [1077][Hepatitis B surface antigen and Hepatitis C virus antibody], VDRL, HIV I and HIV II antibodies and malarial parasites shall be mandatory for every blood unit before it is used for the preparation of blood components. The results of such testing shall be indicated on the label.

(E) Categories of Blood Components

(1) Concentrated Human Red Blood Corpuscles :

The product shall be known as "Packed Red Blood Cells" that is Packed Red Blood Cells remaining after separating plasma from human blood.

General Requirements:

(a) *Storage*—Immediately after processing, the Packed Red Blood Cells shall be kept at a temperature maintained between 2 degree centigrade to 6 degree centigrade.

(b) *Inspection*—The component shall be inspected immediately after separation of the plasma, during storage and again at the time of issue. The product shall not be issued if there is any abnormality in colour or physical appearance or any indication of microbial contamination.

(c) *Suitability of Donor*—The source blood for Packed Red Blood Cells shall be obtained from a donor who meets the criteria for blood donation as specified in item H under the heading "I. BLOOD BANKS/BLOOD COMPONENTS" of this Part.

(d) *Testing of Whole Blood*— Blood from which Packed Red Blood Cells are prepared shall be tested as specified in item K relating to testing of whole blood under the heading "I. BLOOD BANKS/BLOOD COMPONENTS" of this Part .

(e) *Pilot Samples*— Pilot samples collected in integral tubing or in separate pilot tubes shall meet the following specifications:—

(i) one or more pilot samples of either the original blood or of the Packed Red Blood Cells being processed shall be preserved with each unit of Packed Red Blood Cells which is issued.

(ii) Before they are filled, all pilot sample tubes shall be marked or identified so as to relate them to the donor of that Unit or Packed Red Blood Cells.

(iii) Before the final container is filled or at the time the final product is prepared, the pilot sample tubes accompanying a unit of Packed Red Blood Cells, shall be attached in a tamper-proof manner that shall conspicuously identify removal and re-attachment.

(iv) All pilot sample tubes, accompanying a unit of Packed Red Blood Cells, shall be filled immediately after the blood is collected or at the time the final product is prepared, in each case, by the person who performs the collection of preparation.

(f) *Processing*—

(i) *Separation*—Packed Red Blood Cells shall be separated from the whole blood—

(a) if the whole blood is stored in ACD solution within 21 days, and

(b) if the whole blood is stored in CPDA-1 solution, within 35 days, from the date of collection. Packed Red Blood Cells may be prepared either by centrifugation done in a manner that shall not tend to increase the temperature of the blood or by normal undisturbed sedimentation method. A portion of the plasma, sufficient to ensure optimal cell preservation, shall be left with the Packed Red Blood Cells.

(ii) *Packed Red Blood Cells Frozen*—Cryophylactic substance may be added to the Packed Red Blood Cells for extended manufacturer's storage not warmer than minus 65 degree centigrade provided the manufacturer submits data to the satisfaction of the licensing authority and Central Licence Approving Authority, as adequately demonstrating through in-vivo cells survival and other appropriate tests that the addition of the substance, the material used and the processing methods results in a final product meets the required standards of safety, purity and potency for Packed Red Blood Cells, and that the frozen product shall maintain those properties for the specified expiry period.

(iii) *Testing*—Packed Red Blood Cells shall conform to the standards as laid down in the Indian Pharmacopoeia.

(2) *Platelets Concentrates*—

The product shall be known as "Platelets Concentrates" that is platelets collected from one unit of blood and re-suspended in an appropriate volume of original plasma.

General Requirements:

(i) *Source*—The source material for platelets shall be platelet-rich plasma or buffy coat which may be obtained from the whole blood or by plateletpheresis.

(ii) *Processing*—

(a) Separation of buffy-coat or platelet-rich plasma and platelets and re-suspension of the platelets shall be in a closed system by centrifugal method with appropriate speed, force and time.

(b) Immediately after collection, the whole blood or plasma shall be held in storage between 20 degree centigrade to 24 degree centigrade. When it is to be transported from the venue of blood collection to the processing laboratory, during such transport action, the temperature as close as possible to a range between 20 degree centigrade to 24 degree centigrade shall be ensured. The platelet concentrates shall be separated within 6 hours after the time of collection of the unit of whole blood or plasma.

(c) The time and speed of centrifugation shall be demonstrated to produce an unclamped product, without visible haemolysis, that yields a count of not less than $3.5 \times IO^{10}$ (3.5 x 10 raised to the power of 10) and $4.5 \times IO^{10}$ (4.5x10 raised to the power of ten) i.e. platelets per unit from a unit of 350 ml. and 450 ml. blood respectively. One percent of total platelets prepared * shall be tested of which 75 per cent of the units shall conform to the above said platelet count. ,

(d) The volume of original plasma used for resuspension of the platelets shall be determined by the maintenance of the pH of not less than 6 during the storage period. The pH shall be measured on a sample of platelets which has been stored for the permissible maximum expiry period at 20 degree centigrade to 24 degree centigrade.

(e) Final containers used for platelets shall be colourless and transparent to permit visual inspection of the contents. The caps selected shall maintain a hermetic seal to prevent contamination of the contents. The container material shall not interact with the contents, under the normal conditions of the storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, or efficacy of the product. At the time of filing, the final container shall be marked or identified by number so as to relate it to the donor.

(iii) *Storage*—Immediately after re-suspension, platelets shall be placed in storage not exceeding for a period of 5 days, between 20 degree centigrade to 24 degree centigrade, with continuous gentle agitation of the platelet concentrates maintained through such storage.

(iv) *Testing*—The units prepared from different donors shall be tested at the end of the storage period for—

(a) Platelet count;

(b) pH of not less than 6 measured at the storage temperature of the unit;

(c) measurement of actual plasma volume;

(d) one per cent of the total platelets prepared shall be tested for sterility;

(e) the tests for functional viability of the platelets shall be done by swirling movement before issue;

(f) if the results of the testing indicate that the product does not meet the specified requirements, immediate corrective action shall be taken and records maintained.

(v) *Compatibility Test*:—Compatible transfusion for the purpose of variable number of Red Blood Cells, A, B, AB and O grouping shall be done if the platelets concentrate is contaminated with red blood cells.

(3) *Granulocyte Concentrates—*

(i) *Storage:*—It shall be kept between 20 degree centigrade to 24 degree centigrade for a maximum period of 24 hours.

(ii) Unit of granulocytes shall not be less than 1×10^{10} (i.e. 1x10 raised to the power of 10) when prepared on cell separator.

(iii) Group specific tests/HLA test wherever required shall be carried out.

(4) *Fresh Frozen Plasma—-*

Plasma frozen within 6 hours after blood collection and stored at a temperature not warmer than minus 30 degree centigrade, shall be preserved for a period of not more than one year.

(5) *Cryoprecipitate—*

Concentrate of anti-hemophiliac factor shall be prepared by thawing of the fresh plasma frozen stored at minus 30 degree centigrade.

(a) *Storage*—Cryoprecipitate shall be preserved at a temperature not higher than minus 30 degree centigrade and may be preserved for a period of not more than one year from the date of collection.

(b) *Activity*—Anti-hemophiliac factor activity in the final product shall be not less than 80 units per bag. One per cent of the total cryoprecipitate prepared shall be tested of which seventy five per cent of the unit shall conform to the said specification.

F. *Plasmapheresis, Plateletpheresis, Leucapheresis using A Cell Separator*

An area of 10 square metres shall be provided for apheresis in the blood bank. The blood banks specifically permitted to undertake the said apheresis on the donor shall observe the criteria as specified in item H relating to criteria for blood donation under the heading "I. BLOOD BANKS/BLOOD COMPONENTS" of the Part. The written consent of the donor shall be taken and the donor must be explained, the hazards of apheresis. The Medical Officer shall certify that donor is fit for apheresis and it shall be carried out by a trained person under supervision of the Medical Officer.

(A) Plasmapheresis, Platelet Pheresis and Leucapheresis

The donors subjected to plasmapheresis, plateletpheresis and leucopheresis shall, in addition to the criteria specified in item H relating to the criteria for blood donation, under the heading "I. BLOOD BANKS/BLOOD COMPONENTS" of this part being observed, be also subjected to protein

estimation on post-pheresis/first sitting whose results shall be taken as a reference for subsequent pheresis/sitting. It shall also be necessary that the total plasma obtained from such donor and periodicity of Plasmapheresis shall be according to the standards described under validated Standard Operating Procedures.

Notes.—(i) At least 48 hours must elapse between successive apheresis and not more than twice in a week.

(ii) Extracoporeal blood volume shall not exceed 15% of donor's estimated blood volume.

(iii) Platelet pheresis shall not be carried out on donors who have taken medication containing Aspirin within 3 days prior to donation.

(iv) If during plateletpheresis or leucapheresis, RBCs cannot be re-transfused then at least 12 weeks shall elapse before a second cytapheresis procedure is conducted.

(C) Monitoring For Apheresis

Before starting apheresis procedure, haemoglobin or heamatocrit shall be done. Platelet count, WBC counts, differential count may be carried out. In repeated plasmapheresis, the serum protein shall be 6 gm./lOO ml.

(D) Collection of Plasma

The quantity of plasma separated from the blood of a donor shall not exceed 500 ml. per sitting and once in a fortnight or shall not exceed 1000 ml. per month.

PART XII C

I. REQUIREMENTS FOR MANUFACTURE OF BLOOD PRODUCTS

The blood products shall be manufactured in a separate premises other than that meant for blood bank. The requirements that are essential for grant or renewal of licence to manufacture blood products such as Albumin, Plasma Protein Fraction, Immunoglobins and Coagulation Factor Concentrates, shall be as follows, namely:—

A. General Requirements

1. *Location and surroundings, buildings and water supply*—The requirements as regards location and surrounding, buildings and water supply as contained in paragraphs 1.1.1, 1.1.2, 1.1.3 of Part I of Schedule M shall apply *mutatis mutandis* to the manufacture of blood products.

2. *Disposal of waste and infectious materials*—

(i) The requirement as regards disposal of waste and infectious materials as contained in paragraph 1.1.4 of Part I of Schedule M shall apply *mutatis mutandis* to the manufacture of blood products.

(ii) Proper facility shall also be provided for potentially infectious materials, particularly HIV I and II, [1078][Hepatitis B surface antigen and Hepatitis C virus antibody] through autoclaving, incineration or any other suitable validated methods.

3. *Health, clothing and sanitation of personal*:—

(i) The requirement as contained in paragraph 3 of Part I of Schedule M shall be complied with.

(ii) The personnel working in the manufacturing areas shall be vaccinated against Hepatitis B virus and other infectious transmitting diseases.

4. *Requirements for manufacturing area for Blood Products*—

(i) For the manufacture of blood products, separate enclosed areas specifically designed for the purpose shall be provided. These areas be provided with air locks for entry and shall be essentially dust free and ventilated with an air supply for manufacturing area shall be filtered through bacteria retaining filters (HEPA Filters) and shall be at a pressure higher than in the adjacent areas. The filters shall be checked for performance on installation and periodically thereafter, and records thereof shall be maintained.

(ii) Interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks, they shall not shed matter and shall permit easy cleaning and disinfection. Drains shall be excluded from aseptic areas.

Routine microbial count of the manufacturing area shall be carried out during manufacturing operations. The results of such counts shall be checked against well documented in-house standards and records maintained.

Access to the manufacturing areas shall be restricted to a minimum number of authorised personnel. Special procedures for entering and leaving of the manufacturing areas shall be prominently displayed.

(iii) Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material such as stainless steel, without an overflow, and be supplied with water of potable quality. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents and airborne dissemination of pathogenic microorganisms.

(iv) Lighting, air-conditioning, ventilation shall be designed to maintain a satisfactory temperature and relative humidity to minimise contamination and to take account of the comfort of personnels working with protective clothing.

(v) Premises used for the manufacture of blood products shall be suitably designed and constructed to facilitate good sanitation.

(vi) Premises shall be carefully maintained and it shall be ensured that repair and maintenance operations do not present any hazard to the quality of products. Premises shall be cleaned and, where applicable, disinfected according to detailed written validated procedures.

(vii) Adequate facilities and equipments shall be used for the manufacture of blood products derived from blood plasma.

(viii) All containers of blood products, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross contamination shall be prevented by adoption of the following measures, namely:—

(a) processing and filling shall be in segregated areas;

(b) manufacture of different products at the same time shall be avoided;

(c) simultaneous filling of the different products shall be avoided;

(d) ensure transfer, containers/materials by means of airlocks, air extraction, clothing change and careful washing and decontamination of equipment;

(e) protecting containers/materials against the risk of contamination caused by re-circulation of untreated air or by accidental re-entry of extracted air;

(f) using containers that are sterilised or are of documented low "bioburden".

(ix) Positive pressure area shall be dedicated to the processing area concerned;

(x) Air-handling units shall be dedicated to the processing area concerned;

(xi) Pipe work, valves and vent filters shall be properly designed to facilitate cleaning and sterilisation. Valves on fractionation/reacting vessels shall be completely steam-sterilisable. Air vent filters shall be hydrophobic and shall be validated for their designated use.

5. *Ancillary Areas*—

(i) Rest and refreshment rooms shall be separated from other areas.

(ii) Facilities for changing and storing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the number of users. Toilets shall not be connected directly with production or storage areas.

(iii) Maintenance workshops shall be separated from production areas. Wherever parts and tools are stored in the production area, they shall be kept in rooms or lockers reserved for that use.

(iv) Animals houses shall be well isolated from other areas, with separate entrance.

B. Collection and Storage of Plasma for Fractionation

(a) *Collection*—

(1) Plasma shall be collected from the licensed blood banks through a cold chain process and stored in frozen condition not warmer than minus twenty degree centigrade.

(2) Individual plasma shall remain in quarantine till it is tested for [1079][Hepatitis B surface antigen and Hepatitis C virus antibody] HIV I and HIV II.

(3) A sample from pooled lot plasma of about 10-12 units of different donors shall be tested of [1079][Hepatitis B surface antigen and Hepatitis C virus antibody] , HIV I and HIV II and if the sample found negative, only then it shall be taken up for fractionation.

(b) *Storage Area*—

(1) Storage areas shall be of sufficient space and capacity to allow orderly storage of the various categories of materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned, or recalled products.

(2) Storage areas shall be designed or adopted to ensure good storage conditions. In particular, they shall be clean, dry and maintained within temperature required for such storage and where special storage conditions are required *(e.g.* temperature, humidity), these shall be provided, checked and monitored.

(3) Receiving and dispatch bays shall protect materials and products from the weather and shall be designed and equipped to allow containers of incoming materials to be cleaned, if necessary, before storage.

(4) Where quarantine status is ensured by storage in separate areas, these areas shall be clearly marked and their access restricted only to authorised personnel.

(5) There shall be separate sampling area for raw materials. If sampling is performed in the storage area, it shall be conducted in such a way so as to prevent contamination or cross-contamination.

(6) Segregation shall be provided for the storage of rejected, recalled, or returned materials or products.

(7) Adequate facility shall be provided for supply of ancillary material, such as ethanol, water, salts and polyethylene glycol. Separate facilities shall be provided for the recovery of organic solvents used in fractionation.

C. Personnel—

(1) *Manufacture*—The manufacture of blood products shall be conducted under the active direction and personal supervision of competent technical staff, consisting of at least one person who shall be a whole time employee, with one year practical experience in the manufacture of blood products/plasma fractionation and process—

(a) Post-graduate degree in Medicine - M.D. (Microbiology / Pathology / Bacteriology / Immunology / Biochemistry); or

(b) Post-graduate degree in Science (Microbiology); or

(c) Post-graduate degree in Pharmacy (Microbiology), from a recognised University or Institution.

2. *Testing*—The head of the testing unit shall be independent of the manufacturing unit and testing shall be conducted under the active direction and personal supervision of competent technical staff consisting at least one person who shall be a whole time employee. The Head of the testing unit shall have eighteen months practical experience in the testing of drugs, especially the blood products and possesses—

(a) Post-graduate degree in Pharmacy or Science - (Chemistry/Microbiology/ Bio-chemistry); or

(b) Post-graduate degree in Medicine - M.D. (Microbiology/Pathology/ Biochemistry); from a recognised University or Institution.

D. Production Control

(1) The production area and the viral inactivation room shall be centrally air-conditioned and fitted with HEPA Filters having Grade C (Class 10,000) environment as given in the Table below.

(2) The filling and sealing shall be carried out under aseptic conditions in centrally air-conditioned areas fitted with HEPA Filters having Grade A or, as the case may be, grade B (Class 100) environment given in the said Table.

Table—Air Classification system for Manufacture of Sterile Products

Grade	Maximum number of particles permitted per m^3		Maximum Number of Viable Micro-organism permitted per m^3
	0.5-5 *micron*	*Less than 5 micron*	
A (Class 100) (Laminar-Air flow workstation)	3500	None	Less than 1
B (Class 100)	3500	None	Less than 5
C (Class 10000)	3,50,000	2,000	Less than 100

(3) The physical and chemical operations used for the manufacture of plasma fractionation shall maintain high yield of safe and effective protein.

(4) The fractionation procedure used shall give a good yield of products meeting the in-house quality requirements as approved by the licensing authority and Central Licence Approving Authority reducing the risk of microbiological contamination and protein denaturation to the minimum.

(5) The procedure adopted shall not affect the antibody activity and biological half-life or biological characteristics of the products.

E. Viral Inactivation Process

The procedure used by the licensee to inactivate the pathogenic organisms such as enveloped and non-enveloped virus, especially infectivity from HIV I & HIV II, [1080][Hepatitis B surface antigen and Hepatitis C virus antibody] the viral inactivation and validation methods adopted by the licensee, shall be submitted

for approval to the licensing authority and Central Licence Approving Authority.

Notes.—(1) No preservative (except stabiliser to prevent - protein denaturation such as glycine, sodium chloride or sodium caprylate) shall be added to Albumin, Plasma Protein Fraction, Intravenous Immunoglobulins or Coagulation Factor Concentrates without the prior approval of licensing authority and Central Licence Approving Authority.

(2) The licensee shall ensure that the said stabilisers do not have deleterial effect on the final product in the quantity present so as not to cause any untoward or adverse reaction in human beings.

F. Quality Control

Separate facilities shall be provided for Quality Control such as Hematological, Bio-chemical, Physico-chemical, Microbiological, Pyrogens, Instrumental and Safely testing. The Quality Control Department shall have *inter alia* the following principal duties, namely:—

(1) To prepare detailed instructions, in writing for carrying out test and analysis.

(2) To approve or reject raw material, components, containers, closures, in-process materials, packaging material, labelling and finished products.

(3) To release or reject batch of finished products which are ready for distribution.

(4) To evaluate the adequacy of the conditions under which raw materials, semi-finished products and finished products are stored.

(5) To evaluate the quality and stability to finished products and when necessary of raw materials and semi-finished products.

(6) To review production records to ensure that no errors have occurred or if errors have occurred that they have been fully investigated.

(7) To approve or reject all procedures or specifications impacting on the identity, strength, quality and purity of the product.

(8) To establish shelf-life and storage requirements on the basis of stability tests related to storage conditions.

(9) To establish and when necessary revise, control procedures and specifications.

(10) To review complaints, recalls, returned or salvaged products and investigations conducted thereunder for each product.

(11) To review Master Formula Records/Cards periodically.

G. Testing of Blood Products

The products manufactured shall conform to the standards specified in the Indian Pharmacopoeia and where standard of any product is not specified in the Pharmacopoeia, the standard for such product shall conform to the standard specified in the United States Pharmacopoeia or the British Pharmacopoeia. The final products shall be tested for freedom from HIV I and HIV II antibodies, [1081][Hepatitis B surface antigen and Hepatitis C virus antibody].

H. Storage of Finished Product

(i) The final products shall be stored between two degree centigrade to eight degree centigrade, unless otherwise specified by the Central Licence Approving Authority.

(ii) The shelf-life assigned to the products by the licensee shall be submitted for approval to the licensing authority and Central Licence Approving Authority.

I. Labelling

The products manufactured shall be labelled as specified in the Indian Pharmacopoeia, the British Pharmacopoeia or the United States' Pharmacopoeia which shall be in addition to any other requirement stated under part IX or Part X of these rules. The labels shall indicate the results of tests for [1082][Hepatitis B surface antigen and Hepatitis C virus antibody] freedom from HIV I and HIV II antibodies.

J. Records

The licensee shall maintain records as per Schedule U and also comply with Batch manufacturing records as specified in Paragraph 9 of Part I of Schedule M and any other requirement as may be directed by licensing authority and Central Licence Approving Authority.

K. Master Formula Records

The licensee shall maintain Master Formula Records relating to all manufacturing and quality control procedures for each product, which shall be prepared and endorsed by the competent Technical Staff, *i.e.* Head of the manufacturing unit. The Master Formula Records shall contain—

(i) the patent or proprietary name of the product alongwith the generic name if any, strength and the dosage form;

(ii) a description or identification of the final containers, packing materials, labels and closures to be used;

(iii) the identity, quantity and quality of each raw material to be used irrespective of whether or not it appears in the finished product. The permissible overage that may be included in a formulated batch shall be indicated;

(iv) a description of all vessels and equipments and the sizes used in the process.

(v) manufacturing and control instructions along with parameters for critical steps such as mixing, drying, blending, sieving and sterilising the product;

(vi) the theoretical yield to be expected from the formulation at different stages of manufacture and permissible yield limits;

(vii) detailed instructions on precautions to be taken in the manufacture and storage of drugs and of semi-finished products; and

(viii) the requirements in-process quality control tests and analysis to be carried out during each stage of manufacture including the designation of persons or departments responsible for the execution of such tests and analysis.

II. REQUIREMENTS FOR MANUFACTURE OF BLOOD PRODUCTS FROM BULK FINISHED PRODUCTS

Where the blood products, such as Albumin, Plasma Protein Fraction, Immunoglobulins and Coagulation Factor Concentrates are manufactured through the manufacturing activities of filling and sealing the blood products from bulk powder or solution or both, the requirements as they apply to the manufacture of blood products from whole blood shall apply *mutatis mutandis* to such manufacture of blood products, unless other requirements have been approved by the Central Licence Approving Authority.]

[1083][PART XIID

REQUIREMENTS FOR COLLECTION, PROCESSING, TESTING, STORAGE, BANKING AND RELEASE OF UMBILICAL CORD BLOOD DERIVED STEM CELLS

A. GENERAL REQUIREMENTS

1. *Location, Surroundings and Building:*The building(s) for storage of Umbilical cord blood shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produces disagreeable or obnoxious odour or fumes, excessive soot, smoke, chemical or biological emissions.

2. *Building*and *premises:*(1) The premises used for processing and storage shall be designed, constructed and adapted and maintained to ensure that the above operations and other ancillary functions are performed smoothly under hygienic conditions and in sterile areas wherever required. They shall also conform to the conditions, laid down in the Factories Act, 1948 (63 of 1948).

The premises shall be:

(a) adequately provided with working space to allow orderly and logical placement of equipment, material and movement of personnel so as to maintain safe operations and prevent contamination;

(b) designed/constructed/maintained to prevent entry of insects, pests, birds, vermins and rodents. Interior surfaces (walls, floors, ceilings and

doors) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection, and in aseptic areas the surfaces shall be impervious, nonshedding, non-flaking and non-cracking;

(c) flooring shall be unbroken and provided with a cove both at the junction between the wall and the floor as well as the wall and the ceiling;

(d) provided with light fittings and grills which shall flush with the walls and not hanging from the ceiling to prevent contamination;

(e) if provided with fire escapes, these shall be suitably installed in the walls without any gaps;

(f) provided with the furniture in a septic areas which is smooth, washable and made of stainless steel or any other appropriate non-shedding material other than wood;

(g) provided with separate areas for processing and storage of products to prevent mix-ups, product contaminations and cross-contamination;

(h) provided with defined environmental conditions for temperature, humidity, ventilation, and air filtration. Classifications shall be defined and, if appropriate, monitored.

(2) A periodical record of cleaning and renovating of the premises shall be maintained.

3. *Disposal of waste and infectious materials:*

(a) waste materials awaiting disposal shall be stored safely;

(b) the disposal of sewage and effluents from the facility shall be in conformity with the requirements of the Pollution Control Board;

(c) all bio-medical waste shall be dealt with in accordance with the provisions of the Bio-medical Waste (Management and Handling) Rules, 1996.

4. Health, Clothing and Sanitation of personnel:

(a) all personnel shall undergo medical examination prior to employment and shall be free from infectious and contagious diseases and thereafter they should be medically examined periodically at least once a year and for this purpose records shall be maintained thereof;

(b) all personnel, prior to and during employment, shall be trained in practices which ensure personal hygiene and a high level of personal hygiene shall be observed by all those engaged in the collection, processing, banking of umbilical cord blood;

(c) all persons shall wear clean body coverings appropriate for their duties before entering the Processing Zone and the Change Rooms with adequate facilities shall be provided prior to entry into any specific zone;

(d) smoking, eating, drinking, is prohibited inside the Laboratory;

(e) all personnel working in the Laboratory shall be protected against virus infections.

5. *Requirements for Processing, Testing and Storage Areas for Umbilical cord blood stem cells:*

(a) separate dedicated areas specifically designed for the purpose and the workload shall be provided;

(b) there shall be separate areas for designated work purposes, namely:—

(i) *Cord blood Reception:*Cord blood reception area with space for transient storage of units and physical examination shall have adequate facilities for registration, data entry and generation of bar-coded labels. Air condition area of at least 10.00 Sq. meters shall be provided;

(ii) *Cord blood processing area:*The room shall be clean and have an air handling System to provide a Class 10,000 environment. Entry to this area shall be through air lock. The room will house Class 100 biological safety cabinets for Umbilical cord blood processing. The temperature of the clean room shall be maintained 20 to 25°C and with a positive differential pressure of

10-15 pascals and Relative humidity of 50 - 60% Minimum area shall be 10.00 Sq. meters for the activity;

(iii) *Haematotogy and Serology Laboratory:*The laboratory shall be equipped and utilized for the purpose of independently testing of Umbilical Cord Blood for ABO grouping and Rh Typing, Total Nucleated Cell Count, Progenitor Cell Count and viability test. The room shall be air-conditioned and area of at least 10.00 Sq. meters shall be provided.

(iv) *Transfusion Transmissible Disease Screening Laboratory:*The Laboratory shall be equipped and utilized for screening tests on maternal blood for infectious diseases viz. HIV I & II; Hepatitis B & C virus, syphilis, malaria, CMV and HTLV. The room shall be air-conditioned and area of at least 10.00 Sq. meters shall be provided.

(v) *Sterility Testing Laboratory:*The laboratory shall be used for performing Sterility tests on Umbilical cord blood unit. The premises may be classified depending on the testing method used. The room shall be air-conditioned with adequate and ancillary area for media preparation, sterilization, incubation and decontamination. Area of at least 10.00 Sq. meters shall be provided.

(vi) *HLA Typing Laboratory:*The Umbilical cord blood Unit shall have arrangements for HLA typing and genetic disease testing. Inhouse testing can be done by providing a well demarcated Laboratory from the processing area for evaluation of possible genetic disease and HLA typing. The area shall have Class 100,000 environment and air conditioned and area of at least 10.00 Sq. meters shall be provided.

(vii) *Sterilization-cum-washing:*Appropriate facility shall be provided within the premises for proper washing and sterilization. This facility would be optional for Laboratories using entirely disposable items.

(viii) *Records and Store Rooms:*There shall be designated record room(s) and store room(s) of at least 10.00 Sq. meters each. The access to record room shall be permitted only to authorized persons. The room will have adequate protective facilities as the documents and records are to be preserved for long years.

(ix) *Cryogenic Storage room:*A minimum spate of 20.00 sq. meters shall be provided by the Licensee. The cryogenic storage room shall have provision for temperature monitoring of storage vessels, liquid nitrogen level in storage vessels and oxygen meter. The service space between each liquid nitrogen storage vessel, supply cylinders and connecting hose should be minimum 1.00 sqr. meters. Separate storage space for other accessories required shall be provided. The room shall be air-conditioned.

(x) *General Storage area:*General storage area shall be provided to store all the consumables, under conditions deemed optimum for storage by manufacturers.

B. COLLECTION AND STORAGE OF PROCESSES UMBILICAL CORD BLOOD COMPONENT

1. *Collection:*

(a) umbilical cord Wood specific for an individual will be collected after signing an agreement with the parents, whose child's umbilical cord blood is to be collected, and the cord blood bank. Private and Public Umbilical Cord Blood Banking to have different agreements;

(b) umbilical cord blood shall be collected from hospitals, nursing homes, birthing centers and from any other place where a consenting mother delivers, under the supervision of the qualified Registered Medical Practitioner responsible for the delivery;

(c) the cord blood shall be collected aseptically in a disposable PVC bag, containing adequate quantity of sterile, pyrogen free anti-coagulant and sealed effectively and such PVC Bags shall be procured from licensed manufacturer;

(d) the Umbilical cord blood would be collected from a premises operating in hygienic condition to allow proper operation, maintenance and cleaning.

2. *Transportation:*

(a) umbilical cord blood shall be transported from the birthing center to the designated laboratory under end as per procedure prescribed by the cord blood bank;

(b) the transportation procedure shall be validated to ensure optimum survival of the Stem Cells;

(c) the transportation temperature should be between 18 to 28°C;

(d) the time period between collection and processing shall not exceed 72 hours.

3. *Storage:*

(a) the Umbilical cord blood shall be stored at room temperature, between 20 to 25°C in the reception area prior to processing;

(b) samples pending tests for specific transfusion transmittable infectious diseases shall be stored in a segregated manner.

Note.—Temperature range between 4 to 37 degrees Celsius, for the whole time period of transit may be allowed beyond the 18°C to 28°C in exceptional cases. The effects of deviation of transit temperature from the optimum, on the product shall be adequately explained by the licensee in the client education booklet.

C. PERSONNEL

Cord blood bank shall have following categories of whole time competent technical staff, namely:—

1. *Medical Director:*The operation of cord blood bank shall be conducted under the active directions and supervision of a Medical Director who is a whole time employee and is possessing a Post Graduate degree in Medicine -

MD (Pathalogy/ Transfusion Medicine/Microbiology) and has experience/training in cord blood processing and Cryogenic Storage.

2. *Laboratory In-charge:*The laboratory in-charge shall have Post-Graduate qualification in Physiology or Botany or Zoology or Cell Biology or Microbiology or Biochemistry or Life Sciences, or Graduate in Pharmacy and one year working experience in pathological laboratory licensed by the local health authority or any microbiology laboratory of a licensed drug manufacturing/testing unit and or experience/training in cord blood processing and cryogenic storage.

3. *Technical Supervisor (cord blood processing):*The technical supervisor shall have a:

(a) Degree in Physiology or Botany or Zoology, Pharmacy or Cell Biology or Bio Sciences or Microbiology or Biochemistry or Medical Laboratory Technology (M.L.T.) with minimum of three years of experience in the preparation of blood components and/or experience or training in cord blood processing and Cryogenic Storage; or

(b) Diploma in Medical Laboratory Technology (M.L.T) with five years' experience in the preparation of blood components and experience or training in cord blood processing and Cryogenic Storage shall be essential.

4. *Cord Blood Bank Technicians):*The technicians employed shall have a:

(a) A Degree in Physiology or Botany or Zoology or Pharmacy or Cell Biology or Bio Science or Microbiology or Biochemistry or Medical Laboratory Technology (M.L.T.) with six months experience and or training in cord blood processing and cryogenic storage; or

(b) Diploma in Medical Laboratory Technology (MLT) with one year experience in the testing of blood and/or its components and/or experience or training in cord blood processing and Cryogenic Storage.

D. AIR HANDLING SYSTEMS

1. Air handling for sterile areas shall be different from those for other areas. The filter configuration in the air handling system shall be suitably designed to

achieve the grade of air as given in the Table I. The environmental microbiological monitoring of clean areas shall be in accordance to the recommended limits given in Table II.

2. The Processing area shall have HVAC system and fitted with HEPA Filters having Grade C (Class 10,000) environment as given in Table I.

3. The entire processing shall be done conforming to Grade A (Class 100) Standard of air quality.

TABLE I

AIR BORNE PARTICULATE CLASSIFICATIONS FOR MANUFACTURE OF STERILE PRODUCTS

Grade	Maximum number of permitted particles per cubic meter equal to or above			
	At rest (b)		In Operation (a)	
	0.5 µm	5 µm	0.5 µm	5µm
A	3,500	0	3,500	0
B(a)	3,500	0	3,50,000	2000
C(a)	3,50,000	2000	35,00,000	20,000
D(a)	35,00,000	20,000	Not defined	Not defined

Notes.—

(a) In order to reach the B, C and D air grades, the number of air changes shall be related to the size of the room and the equipment and personnel present in the room. The air system shall be provided with the appropriate filters such as HEPA for Grades A, B and C. The maximum permitted number of particles in the "at rest" condition shall approximately be as under:

[Grade A and B corresponds with class 100 or M 3.5 or class 5]; Grade C with Class 10,000 or M 5.5 or ISO Class 7; Grade D with Class 1,00,000 or M 6.5 or ISO Class 8.

(b) The requirement and limit for the area shall depend on the nature of the operation carried out.

TABLE II

RECOMMENDED LIMITS FOR MICROBIOLOGICAL MONITORING OF CLEAN AREAS "IN OPERATION"

Grade	Air Sample Cfu/ m^3	Settle Plates (dia 90 mm) cfu/2 hrs.	Contact plates (dia 55 mm) cfu per plate	Glove points (five fingers) cfu per glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	500	100	50	-

Notes.—

(a) These are average values.

(b) Individual settle plates may be exposed for not less than two hours in Grade B, C and D areas and for not less than thirty minutes in Grade A area.

E. QUALITY CONTROL

1. Facilities shall be provided for Quality Control such as Haematological, Microbiological and Instrumental testing.

2. Following duties shall be performed under the function of quality control:

(a) to prepare detailed instructions for carrying out such tests and analysis;

(b) to approve or reject raw materials and consumables, used in any step, on the basis of approved specifications;

(c) Haematological Tests like Total Nucleated Cell Counts, Mononuclear Cell Count, Enumeration of the population of Stem Cells, Stem Cell viability shall be performed on samples of processed umbilical cord blood Unit;

(d) microbiological Tests shall be done on Maternal Blood samples for freedom from Hepatitis B Surface Antigen, Hepatitis C Virus antibody, HIV I and II antibodies'. Syphilis, Malaria, CMV and HTLV. Bacterial and Fungal Culture shall be done on the umbilical cord blood Samples;

(e) instruments which would be used to process test and store the UCB unit would be validated before commissioning and calibrated from time to time to check their conformity to specific standards according to an approved and valid protocol;

(f) the environmental monitoring of the clean rooms would be done at periodic intervals according to an accepted and validated protocol;

(g) all tests Mentioned above shall be done in house except tests under item numbers (e), (f) and test for enumeration of Stem Cell Population, HLA typing and "Genetic Disease Testing which may be outsourced to a competent third party approved by the licensing authority.

F. SCREENING TESTS

1. The maternal Blood sample shall be tested for

(a) Hepatitis B;
(b) Hepatitis C;
(c) HIV 1 & 2;
(d) Syphilis;
(e) Malaria;
(f) CMV;
(g) HTLV.

2. The Umbilical Cord Blood shall be tested for

(a) Total Nucleated Cell Count;
(b) Total Mononuclear Cell Count;
(c) Progenitor Cell (CD34+) enumeration;
(d) Cell Viability;
(e) ABO Group and Rh Type;
(f) Sterility as regards Bacterial and Fungal contamination status;

(g) HLA Matching (Only for allogenic Cord Blood Units).

G. STORAGE

1. The Umbilical cord blood shall be cryopreserved using a controlled rate freezing or equivalent validated procedures. The frozen storage shall be at minus (-) 196°C and shall not be warmer than minus (-) 150°C.

2. There will be no shelf life for this class of product.

H. REFERENCE SAMPLES

1. At least two reference samples shall be collected from cord blood unit product prior to cryopreservation and stored at minus 196°C and shall not be warmer than minus 150°C.

2. At least one additional reference sample shall be stored at minus 76°C or colder for the purposes other than viability analysis.

I. LABELLING

1. Initial Label placed during collection shall specify:

(a) Human Umbilical Cord Blood;

(b) Approximate Volume or weight of contents in the collection bag (UCB + Anticoagulant);

(c) Mother's name;

(d) Place of collection;

(e) Date & Time of collection;

(f) Collected by;

(g) To be Labelled in bold, "ROOM TEMPERATURE ONLY-DO NOT REFRIGERATE, DO NOT IRRADIATE";

(h) Manufacturing licence number.

2. Label at completion of processing and before issue - Cryogenic Storage Label (Statutory label) shall indicate the following:—

(a) Name of Product:—Human Progenitor Cell (HPC) - Cord Blood;

(b) Volume or weight of contents;

(c) Percentage of Cryoprotectant (DMSO);

(d) Percentage of any other additive/preservant;

(e) Date of collection (birth) .....;

(f) Date of processing.....;

(g) Name of manufacturer.....;

(h) Manufacturing licence number;

(i) Storage temperature - not less than, - 196°C and shall not be warmer than -150°C;

(j) Unique Traceability Number and/or BAR Code.

3. Issue Label at the time of release of Cord Blood Unit shall indicate the following, namely:—

(a) Name of manufacturer;

(b) Licence number;

(c) All details of the Cryogenic Storage Label;

(d) The results of Total nucleated Cells, Progenitor Cell percentage (CD34+),Viability;

(e) Results of Transfusion Transmiltable diseases testing on maternal blood;

(f) ABO Group and Rh Type;

(g) Date of processing;

(h) Result of HLA typing (allogenic);

(i) Statement "Properly identify intended Recipient and Product";

(j) A statement indicating that leukoreduction filters should not be used;

(k) Statement "Do not irradiate";

(1) Name and address of receiving hospital

J. RECORDS OR DOCUMENTATION

1. The Licensee shall maintain the following records:—

(a) Client/donor enrolment/agreement record;

(b) Collection of unit and transportation record;

(c) Master record of stored unit;

(d) HLA Matching record;

(e) Unit Release Register;

(f) Stock Register for Blood Collection Bag Cryoprotectant and Preservant, RBC Sedimentation Enhancer;

(g) Stock Register for Diagnostic Kits, Reagents and other consumables;

(h) Record on feedback after use of cord blood/Adverse reaction record.

2. The following Standard Operating Procedures shall be maintained by the licensee, namely:—

(a) Umbilical cord blood collection;

(b) Transportation of the collected Umbilical cord blood unit;

(c) Processing of Umbilical cord blood unit;

(d) Cryogenic Storage of processed Umbilical cord blood unit;

(e) Testing of maternal blood for transfusion transmittable infections;

(f) Testing of Umbilical cord blood for ABO Grouping and Rh Typing;

(g) Testing of Umbilical cord blood unit for Total Nucleated Cell Count, Mononuclear Cell Count, Progenitor Cell (CD34+) enumeration, and Viability;

(h) Testing of Umbilical cord blood stem cell Unit for Sterility;

(i) Disposal of bio medical waste;

(j) Dispensation of Umbilical cord blood unit;

(k) Preventive maintenance Protocol for all Instruments;

(1) Acceptance/Rejection procedure of consumables;

(m) Environment monitoring of classified areas;

(n) Any other standard operative procedure as requirements.

K. CORD BLOOD RELEASE

1. There shall be designated area with adequate space for procedures and records related to cord blood unit selection and release.

2. The cord blood bank shall obtain written or electronic request from the transplant physician or designee for shipment of the cord blood unit.

3. Accompanying documentation at the time of issue, from the cord blood bank shall include indications, contra-indications, caution, instruction for handling and use of the cord blood unit including short-term storage and preparation for transplantation.

4. Procedure for transportation of cryopreserved cord blood Unit within the facility shall be designed to protect the integrity of the unit arid the health and safety of the personnel.

5. Cryopreserved cord blood unit stored at-150°C or colder shall be transported in a liquid nitrogen cooled dry shipper that contains adequate absorbed liquid nitrogen and has been validated to maintain temperature below-150°C for at least 48 hours beyond the expected time of arrival at the receiving facility.]

[1084][PART XIII]
GENERAL

1. For the purposes of this Schedule, any test or method of testing described in the [1085][Indian Pharmacopoeia] shall be deemed to be a method approved by the licensing authority.

2. The licensing authority shall publish in the Official Gazette from time to time particulars of any test or method of testing approved by him.

[1086] *[SCHEDULE F(I)*

PART I
VACCINES

(A) PROVISIONS APPLICABLE TO THE PRODUCTION OF BACTERIAL VACCINES

1. Definition—(1) This part of the Schedule applies to bacterial vaccines made from any micro-organism pathogenic to man or other animal and to vaccines made from other micro-organism pathogenic to man or other animal and to vaccines made from other micro-organisms which have antigenic value.

(2) For the purposes of this part of the Schedule, a bacterial vaccine means a sterile suspension of a killed culture of the micro-organism from which the vaccine derives its name or sterile extract or derivative of a micro-organism, or a pure suspension of living micro-organisms which have been previously made aviruient.

2. Staff of Establishment—A competent expert in bacteriology with sufficient experience in the manufacture and standardisation of biological products shall be in charge of the establishment responsible for the production of bacterial vaccine and he shall be assisted by a staff adequate for carrying out the tests required during the preparation and standardisation of the vaccines.

3. Proper Name—The proper name of the vaccine shall be the name of the microorganism from which it is made followed by the word "Vaccine" unless this Schedule otherwise provides or if there is no other special provision in this Schedule, some other name as approved by the licensing authority:

Provided that in the case of the under-mentioned preparations the proper name of the vaccine may be as follows:—

1. Anthrax Spore Vaccine (Living).
2. Blackquarter Vaccine.
3. Enterotoxaemia Vaccine.
4. Fowl Cholera Vaccine.
5. Haemorrhagic Septicaemia Adjuvant Vaccine.
6. Haemorrhagic Septicaemia Vaccine (Broth).

[1087][7. Multi Component Clostridial Vaccine.

8. Haemorrhagic Septicaemia Vaccine—Alum treated.]

4. Records—Cultures used in the preparation of vaccine before being manipulated into a vaccine, should be thoroughly tested for identity by the generally accepted tests applicable to the particular micro-organisms.

The permanent records which the licensee is required to keep shall include amongst others, a record of the origin, properties and characteristics of the cultures.

5. Combined Vaccines—Vaccines may be issued either singly or combined in any proportion in the same container. In the case of combination of vaccines, a name for the combined vaccine may be submitted by the licensee to the licensing authority, and if approved, may be used as the proper name of the vaccine.

6. Preparation—Bacterial vaccines, simple or polyvalent, are prepared from selected cultures after careful examination for their identity', specificity, purity and antigenicity. They may be prepared in the following manner:—

(a) *Formal Cultures or Bacterins*.—The selected pure culture stain or strain are grown in a suitable fluid medium, at an optimum temperature, for an appropriate period. The pure growth is then exposed to the action of solution of Formaldehyde I.P. in suitable concentration and temperature. The product is finally filled in suitable sterilised containers which are subsequently sealed.

(b) *Vaccine of Bacterial Products or Bacterial Derivatives*—These vaccines are prepared by growing the organisms on suitable media and then deriving specific antigenic constituents of the bacteria by various special methods.

(c) *Living Bacterial Vaccines*—They are prepared from non-pathogenic but fully immunogenic strains of micro-organism. Strict aseptic precautions are taken throughout the preparation against the introduction of microbial contaminants.

7. General Standards—

(a) *Description*—Bacterial vaccines are colourless to yellowish brown liquids containing dead or viable bacteria in homogeneous suspension.

(b) *Identification*—All types of vaccines confer active immunity in the susceptible animals which can be demonstrated by injecting suitable experimental animals with the calculated doses of the product and subsequently determining the presence of the protective antibodies in their serum and/or by challenging the vaccinated animals by injecting virulent strain of the homologous organisms. The protected animals should survive the challenge.

(c) *Tests for Sterility*—All bacterial vaccines shall be tested for sterility in accordance with the provision of Rules 115 to 119 (both inclusive). If the vaccine contains added bactericide or bacteriostatic, a quantity of medium sufficient to render the growth inhibitor ineffective is added to the sample, or a suitable substance is added to the sample, or a suitable substance is added in a concentration sufficient to render the growth inhibitor ineffective but not itself to inhibit the growth of micro-organism.

(d) *Purity Tests for Living Bacterial Vaccine*—Petri-dishes containing suitable media are streaked with the final product and incubated at 37°C for 72 hours. The vaccine passes the test if no growth of micro-organisms other than those from which the vaccine was prepared is observed. Other tests include examination for motility of the organisms, fermentation reactions and thermoagglutination test and dye-inhibitor test in case of bruceliza vaccine.

(e) *Safety Test*—The safety of the vaccine shall be assessed by injecting it in appropriate dose in suitable susceptible animals. No animal should show any untoward, general or local reaction, within seven days after inoculation.

(f) *Potency Test*—Wherever applicable, susceptible experimental animals are inoculated with the calculated doses of the final product. The animals are challenged, after the period of immunisation, with virulent infective dose of the homologous culture along with the controls. The potency of the vaccine is assessed by the survival of the vaccinated animals and the death of the controls.

8. **Labelling—**

(a) The label on the ampoule or the bottle shall indicate:

(i) Proper name.

(ii) Contents in millilitres or doses.

(iii) Potency, if any.

(iv) Batch number,

(v) Expiry date.

(b) The label on the outside container shall indicate:

(i) Proper name.

(ii) Contents in millilitres or doses.

(iii) Batch number.

(iv) Date of manufacture.

(v) Manufacturing licence No.

(vi) Manufacturer's name and address.

(vii) "For animal treatment only".

(viii) Storage conditions.

9. Storage—Bacterial vaccines shall be stored, protected from light at temperature between 2°C to 4°C and shall not be frozen.

10. Date of Manufacture—The date of manufacture shall be, unless otherwise specified in the individual monograph in this Part, as defined in clause (b) of sub-rule (3) of Rule 109.

ANTHRAX SPORE VACCINE (LIVING)

1. Synonyms—A virulent Anthrax Spore Vaccine or Bacillus Anthracis Vaccine (Living).

2. Definition—The vaccine is a suspension of living spores of an uncapsulated avirulent strain of B. anthracis in 50 per cent glycerine saline.

3. Preparation—Avirulent B. anthracis of known antigenicity is grown on suitable medium at pH 7.4 in Roux flasks. After 72 hours incubation at 37°C, the pure sporulated culture growth which shows 70 to 80 per cent sporulation is washed with normal saline and glycerinated to the extent of 50 per cent by weight of the culture washing and the whole suspension is kept at room temperature for twenty-one days to allow for the stabilization of the spores.

4. Standards—

(a) *Description*—It is slightly opalescent or pale brown semi-viscous liquid.

(b) *Identification*—Uncapsulated B. anthracis which is avirulent can be isolated from the vaccine.

(c) *Sterility Test*—Should comply with the test for sterility described in the general monograph on "Bacterial Vaccine".

(d) *Purity Test*—Complies with the "Purity Tests for Living Bacterial Vaccine" described under the general monograph on "Bacterial Vaccine".

(e) *Safety Test*—Four healthy adult guinea-pigs each weighing 300-450 g. not previously treated with any material which will interfere with the test are inoculated subcutaneously, two with 0.2 ml. each and two with 0.5 ml. each of the unglycerinated suspension respectively. Four more guinea pigs are injected with 1:5 dilution of the glycerinated product in the same manner. Not untoward reaction should be observed and none of the animals should die of anthrax during the period of observation for seven days.

(f) *Safety and Potency Test in Sheep and Goat*—Spore count of the glycerinated suspension is made after twenty-one days from the date of glycerination. Three plates for each of the three dilutions 10^{-5}, 10^{-6}, and 10^{-7}, are made.

Eight sheeps and eight goats each weighing not less than 18 kg. are injected subcutaneously in the following manner:—

two sheep: Each subcutaneously with 10 ml. of the stock suspension (for safety).

two goats: Each subcutaneously with 5 ml. of the stock suspension (for safety).

six sheep: Each subcutaneously with one million spores suspended in 50 per cent glycerine saline solution.

six goats: Each subcutaneously with one million spores suspended in 50 per cent glycerine saline solution.

None of these animals should die of anthrax. Twenty-one days after vaccination, the animals are challenged with 100 lethal doses of virulent B. *Anthracis* spores along with two healthy sheep and two goats as controls.

All the controls should die of anthrax within 72 hours after challenge and at least 66 per cent of the vaccinated animals should survive. The animals shall be observed for a minimum of ten days from the date of challenge.

[1088][(g) *Viable Count*—The vaccine when plated on suitable media should show 10 million viable spores per cattle dose and 5 million spores per sheep dose.]

5. Labelling and Storage—Should comply with the requirements for "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccines".

[1089][**6. Expiry Date**—The date of expiry of the potency of the vaccine shall be more than two years from the date of manufacture is stored in 4°C and six months, if stored at room temperature.]

BLACKQUARTER VACCINE

1. Synonym—Blackleg Vaccine or Quarter Evil Vaccine.

2. Definition—Blackquarter Vaccine is a culture of *Clostridium chauvoei* grown in a suitable anaerobic fluid medium and rendered sterile and toxic by the addition of Solution of Formaldehyde I.P. in such a manner that it retains it immunising properties.

3. Preparation—Cultures of *Cl. chauvoei* are grown in a suitable anaerobic fluid medium and killed by the addition of a suitable concentration of solution of Formaldehyde I.P. The final product shall be adjusted to pH. 7.0

4. Standards—

(a) *Description*—It is a yellowish brown liquid containing dead bacteria in suspension.

(b) *Identification*—It protects susceptible animals against infection with *Cl. chauvoei.*

(c) *Sterility Test*—Should comply with the test for sterility described in the general monograph on "Bacterial Vaccine".

(d) Safety and Potency Test—At least six adult healthy guinea-pigs each weighing 300g. to 450 g. are injected subcutaneously each with 3 ml. of the product followed a week later by a second injection with the same dose. They should not show any systemic reaction but may show only a minimum of local reaction. Fourteen days after the second injection six of the vaccinated guinea-pigs are challenged intramuscularly with 25 viable spores of *Cl. Chauvoei* equivalent to 5. c.h.d. along with 0.2 ml. of a 5 per cent solution of calcium chloride. Two controls are used. The controls should die of the specific injection and at least 4 of the six vaccinated animals should survive before the product is passed for issue.

5. Labelling and Storage—Should comply with the requirements of "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine".

6. Expiry Date.—The date of expiry of the potency of the vaccine shall not be more than twenty-four months from the date of manufacture.

BRUCELLA ABORTUS (STRAIN 19 VACCINE) (LIVING)

1. Synonym—Contagious Abortion Vaccine (Strain 19) (Living).

2. Definition—Brucella Abortus (Strain 19) Vaccine (Living) is a suspension of a pure smooth living culture of *Br. abortus*of low virulence in normal saline solution.

3. Preparation—Forty-eight to seventy-two-hour-old growth of *Br. abortus* (Strain 19) on potato agar medium in Roux flasks washed with buffered normal saline solution pH 6.4 and the pure growth from the flasks are pooled together, 0.5 ml. of the pooled product is mixed with 4.5 ml. of normal saline solution at pH 6.4 in graduated centrifuge tube and centrifuged at 3000 r.p.m. for one hour. The percentage of cell deposit is assessed by reading the amount of cell deposit obtained.

The concentrated suspension is then diluted with buffer normal saline solution so that the final product contains 0.7 per cent bacterial cell deposit.

4. Standards—

(a) *Description*—It is an almost white turbid liquid containing live bacteria in suspension.

(b) *Identification*—It consists of Gram-negative bacilli capable of protecting susceptible animals against Brucellosis.

(c) *Sterility Test*—Should comply with the test for sterility described in the general monograph on "Bacterial Vaccine"

(d) *Purity Test*—A smear of the finished products examined microscopically after staining by Gram's method for evidence of any contamination. When grow n on suitable media, *Br. abortus* should be obtained in a pure state.

(e) *Safety Test*—Two healthy guinea-pigs each weighing 300 g. to 450 g. are inoculated subcutaneously each with 1.0 ml. of the final product. The guinea-pigs should not show excessive reaction of a toxic nature during the period of observation of ten days.

(f) *Potency Test*—Each of a group of four healthy guinea-pigs, drawn from a uniform stock and each weighing 300 g. to 450 g. is injected intramuscularly with 1 ml. of the vaccine, and is challenged nine weeks after vaccination by the intramuscular injection of 1 ml. of a suspension

containing 5,000 fully virulent *Br. abortus organisms.* Each of a group of two unvaccinated guinea-pigs is similarly injected. After a further six weeks, the guinea-pigs are killed and cultures are made from their spleens. More than half of the vaccinated guinea-pigs contain no demonstrable *Br. abortus* in the spleen; all the controls are infected.

(g) *Viable Count*—The vaccine when plated on suitable media should show between 14,000 million and 18,000 million *Br. abortus* organisms per ml. At least 80 per cent of the brucella organisms should be in the smooth phase.

5. Labelling and Storage—Should comply with the requirements of "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine". The liquid vaccine shall be issued fresh as far as possible without allowing any period of storage after manufacture.

6. Expiry Date—The date of expiry of the vaccine shall be not more than five weeks from the date of manufacture.

ENTEROTOXAEMIA VACCINE

1. Synonyms—*Clostridium Welchii*, Type D, Formal Culture : Pulpy Kidney Vaccine.

2. Definition—Enterotoxaemia Vaccine is a culture of a highly toxigenic strain of *Clostridium* type D, grown in an anaerobic medium rendered sterile and toxic by the addition of Solution of Formaldehyde I.P. in such a manner that it retains its immunising properties.

3. Preparation—Selected toxigenic strain of *Cl. Welchii* type D, is grown in a liquid medium under conditions which ensure maximum epsilon toxin production. The culture is checked for purity and toxicity as tested in mice. Solution of Formaldehyde I.P. is added in suitable concentration and the formolised culture is kept at 37°C till the production is sterile and non-toxic.

4. Standard—

(a) *Description*—It is a yellowish brown liquid containing dead bacteria in suspension.

(b) *Identification*—When injected into susceptible animals it stimulates the production of epsilon antitoxin of *Cl. Welchii*, type D.

(c) *Sterility Test*—Complies with the test for sterility described in the general monograph on 'Bacterial Vaccine'.

(d) *Safety and Potency Tests*—At least eight sheep each weighing not less than 18 kg. or twelve rabbits each weighing 1 kg. to 1.5 kg. are used for testing the safety and potency of each brew of the vaccine. Two sheep receive subcutaneously 10 ml. each and the other six sheep receive 2.5 ml. each of the product subcutaneously. The rabbits are given subcutaneously a dose of 5 ml. each. The sheep and rabbits are observed for five days. They should show only a minimum local reaction and no systemic reaction.

The sheep receiving 10 ml. are withdrawn from experiments after five days. Each of the other six sheep is inoculated with a second dose of 2.5 ml. fourteen days after the first injection. The rabbits are inoculated with 5 ml. as a second dose, after one month of the first inoculation. The day after the second inoculation the sera of sheep or rabbits are pooled separately. The pooled serum of each group of animal shall contain in each ml. not less than two international units of *Cl welchii* epsilon antitoxin which is determined by testing on mice as follows:—

One ml. of the pooled serum is mixed with one ml. of the epsilon toxin of *Cl. welchii* type D, containing 300 mouse-minimum-lethal-doses (mouse m.l.d.) and kept at room temperature for half an hour. At least two mice each weighing not less than 18 g. are each given intravenously 0.2 ml. of the mixture. As control two mice each weighing not less than 18 g. should each receive 0.2 ml. of the toxin containing 300 mouse m.l.d. per ml. diluted with equal volume of normal saline. The control mice should die within 1 to 2 hours while the mice receiving the mixture of serum and toxin should survive for at least two days. Sera containing one International Unit of epsilon antitoxin per ml. will be able to neutralise 150 mouse m.l.d epsilon toxin of *Cl. welchii* type D.

5. Labelling and Storage—Should comply with the requirements regarding "Lebelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccines".

6. Expiry Date—The expiry date of potency of the vaccine shall not more than twelve months from the date of manufacture.

FOWL CHOLERA VACCINE (POLYVALENT)

1. Synonym—Pasteurella Septica Vaccine (Avian).

2. Definition—Fowl Cholera Vaccine is a formolised pure broth culture of virulent strains of Pasteurella Septica (Avian).

3. Preparation.—The strains are grown separately in nutrient broth for 48 hours at 37°C. The pure growth is killed by the addition of a Solution of Formaldehyde I.P. in a suitable concentration. The cultures are then mixed in equal proportions and the final vaccine is bottled in suitable containers.

4. Standards—

(a) *Description*—It is a light yellow liquid containing dead bacteria in suspension.

(b) *Identification*—It protects susceptible birds against *P. aviseptica* infection.

(c) *Sterility Test*—Complies with the test for "Sterility" described under the general monograph on "Bacterial Vaccine".

(d) *Safety Test*—Two healthy young fowls each weighing not less than 400 g. or twelve healthy mice are inoculated subcutaneously each with 1 ml. of the final product. The birds should not show any untoward reaction during the period of observation for seven days.

5. Labelling and Storage—Should comply with the requirements of "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine".

6. Expiry Date—The date of expiry of potency of the vaccine shall be not more than six months from the date of manufacture.

HAEMORRHAGIC SEPTICAEMIA ADJUVANT VACCINE

1. Synonym—*Pasteurella Septica* Adjuvant Vaccine.

2. Definition—The vaccine is a homogeneous suspension of formolised agar-washed *Pasteurella septica* with liquid paraffin and lanolin.

3. Preparation—Pure growth of a highly antigenic strain of *P. Septica* in phase 1 grown on nutrient agar medium containing 0.5 per cent yeast extract is washed with 0.5 per cent formal saline. The pooled suspension is diluted with normal saline to contain approximately 2,100 million *P. Septica* organisms per ml. The safety test of this adjusted suspension is conducted on four white mice each weighing not less than 18 g. and observed for three days before it is mixed with liquid paraffin and lanolin in suitable proportion.

The mixture is blended until a homogeneous emulsion is obtained which is filled in suitable containers.

4. Standards—

(a) *Description*—It is a white thick oily liquid containing dead bacteria in suspension.

(b) *Identification*—It protects susceptible animals against infection with *P. Septica.*

(c) *Sterility Test*—It complies with the test for "Sterility" described in the general monograph on "Bacterial Vaccine".

(d) *Safety Test*—Six white mice each weighing not less than 18 g. are inoculated intraperitoneally each with 0.5 ml. of the vaccine. None of the mice should die of pasteurellosis during the observation period for seven days.

(e) *Potency Test.*—Three susceptible calves in good condition between the ages of nine months to three years are injected intramuscularly, each with 2 ml. of the vaccine, in the case of animals weighing up to 140 kg. and 3 ml. for heavier ones.

Three weeks later these animals along with two healthy animals of the same type and species are challenged subcutaneously with 18 hours old broth culture of *P. Septica* equivalent to at least 50 million mouse

minimum infective dose. Both the controls should die of pasteurellosis and at least two out of the three protected animals should survive the challenge dose for a period of seven days.

5. Labelling and Storage—Should comply with the requirements for "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine".

6. Expiry Date—The date of expiry of potency of the vaccine shall be not more than twelve months from the date of manufacture.

HAEMORRHAGIC SEPTICAEMIA VACCINE (BROTH)

1. Synonym—Pasteurella Septica Vaccine (Broth).

2. Definition—Haemorrhagic Septicaemia Vaccine is formolised culture of a virulent strain of Pasteurella septica in nutrient broth.

3. Preparation—*P. Septica* culture is grown in nutrient broth at 37°C. The pure growth is killed by the addition of a solution of Formaldehyde I.P. in a suitable concentration.

4. Standards—

(a) *Description*—It is a pale yellow liquid containing dead bacteria in suspension.

(b) *Identification*—It protects susceptible animals against infection with *P. Septica.*

(c) *Sterility Test*—Complies with the test for "Sterility" described under the general monograph on "Bacterial Vaccine".

(d) *Safety Test*—Four healthy rabbits each weighing 1 kg. to 1.5 kg. are inoculated subcutaneously each with 5 ml. of the product. There should be no untoward reaction during the period of observation for seven days'. Alternately two rabbits and six mice may be employed. The dose for mice will be 0.5 ml.

5. Labelling and Storage—Should comply with the requirements for "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine".

6. Expiry Date—The date of expiry' of potency of the vaccine shall be not more than six months from the date of manufacture.

SALMONELLA ABORTUS EQUI VACCINE

1. Synonym—Equine Abortion Vaccine.

2. Definition—Equine Abortion Vaccine is a mixture of equal parts of pure formolised cultures of smooth laboratory strains of *Salmonella abortus equi*.

3. Preparation—The strains are grown separately on plain agar in Roux flasks, for 24-28 hours at 37°C. The pure growth is washed with normal saline solution and the washings are pooled together. The suspension is standardised to contain approximately 600 million *Sal abortus equi* organisams per ml. using normal saline solution as diluent. The culture is killed by the addition of sufficient quantity of solution of Formaldehyde I.P. in a suitable concentration and the product is kept at 37°C for seven days. Potassium alum is added to give a final concentration of 1 per cent.

4. Standards—

(a) *Description*—It is an opalescent liquid containing dead bacteria in suspension.

(b) *Identification*—It protects susceptible animals against infection with *Sal. abortus equi.*

(c) *Sterility Test*—Complies with the tests for sterility described in the general monograph on "Bacterial Vaccines".

(d) *Safety Test*—Six white mice each weighing not less than 18 g. are inoculated intraperitoneally each with 0.5 ml. of the product. None of the mice should die of salmonellosis. The mice are observed for ninety-six hours.

5. Labelling and Storage—Should comply with the requirements for "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine".

6. Expiry Date—The date of expiry of potency of the vaccine shall be not more than six months from the date of manufacture.

STREPTOCOCCUS EQUI VACCINE

1. Synonym—Strangles Vaccine

2. Definition—*Streptococcus equi* Vaccine is a phenolised culture of a number of different isolates of *Streptococcus equi* in glucose serum broth.

3. Preparation—Equal proportions of forty-eight hours old pure cultures of different isolates of *Str. equi* in serum glucose broth are mixed together. The suspension is centrifuged and the deposit is washed with normal saline solution after removing the supernatant. The washed cells are suspended in normal saline and heated in a water bath at 65°C for two hours. Phenol and normal saline are added to give a final concentration of 1,200 million *Str. equi* organisms per mo. and 0.5 per cent of phenol in the vaccine.

4. Standards—

(a) *Description*—It is slightly opalescent liquid containing dead bacteria in suspension.

(b) *Identification*—It protects susceptible animals against infection with *Str. equi.*

(c) *Sterility Test*—Complies with the test for "Sterility" described in the general monograph on "Bacterial Vaccine". The nutrient broth being replaced by glucose broth.

(d) *Safety Test*—Two ponies and two rabbits each weighing not less than 1 kg. are inoculated each with 10 ml and 2 ml. respectively of the final product. The animals should not show any untoward reaction during the period of observation of seven days.

5. Labelling and Storage—Should comply with the requirements for "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine".

6. Expiry Date—The date of expiry of potency of the vaccine shall be not more than six months from the date of manufacture.

OLD ADJUVANT VACCINE AGAINST PASTEURELLOSIS IN SHEEP AND GOATS

1. Synonym—*Pasteurella Septica* Adjuvant Vaccine for Ovines and Caprines.

2. Definition—The vaccine is a homogeneous suspension of formolised agarwashed *Pasteurella septica* of ovine origin with liquid paraffin and lanolin.

3. Preparation—Pure growth of highly antigenic strains (Rl, R2, R4) in phase I grown separately on nutrient agar medium containing 0.5 per cent yeast extract is washed with 0.5 per cent Normal saline. Equal quantities of the suspension of three strains diluted with Normal saline to contain approximately 2100 million organisms per ml. is pooled together. The safety test of this adjusted pooled suspension is conducted on four white mice each weighing not less than 18 g. and observed for three days before it is mixed with liquid paraffin and lanolin in suitable proportion.

The mixture is blended until a homogeneous emulsion is obtained which is filled in suitable containers.

4. Standards—

(a) *Description*—It is a white thick oily liquid containing dead bacteria in suspension.

(b) *Identification*—It protects susceptible animals against infection with *P. Septica.*

(c) *Sterility Test*—Complies with the test for "Sterility" described in the general monograph on "Bacterial Vaccines".

(d) *Safety Test*—Six white mice each weighing not less than 18 g. are innoculated intraperitoneally each with 0.5 ml. of the vaccine. None of the mice should die of Pasteurellosis during the observation period of seven days.

The vaccine is also inoculated into six sheep and six goats in a dose of 3 ml. each intramuscularly and are observed for a period of seven days. During this period none should die of Pasteurellosis.

(e) Potency Test—Not being done at present.

5. Labelling and Storage—Should comply with the requirements regarding "Labelling" and "Storage" as laid down in the general monograph on "Bacterial Vaccine".

6. Expiry Date—The date of expiry of Potency of the Vaccine shall be not more than twelve months from the date of manufacture.

[1090][MULTICOMPONENT CLOSTRIDIAL VACCINE

1. Synonyms—Combined anaculture of *Clostridium perfringens* type C and D, *Cl. septicum* and *Cl. Oedematiens*.

2. Definition—It consists of four highly antigenic components containing the toxoids of *Cl. perfringens* type D, *Cl. perfringens* type C. *Cl. Oedematiens* and *Cl. septicum* which are prepared in double strength and then combined in such a proportion that would invoke adequate anti-toxin response in the vaccinated sheep against each antigen incorporated in the vaccine.

3. Preparation—The above strains are grown separately in suitable liquid media under conditions which ensure maximum toxin production. The cultures are checked for purity and toxicity in mice. Solution of formaldehyde I.P., of analytical grade is added to a 0.5 per cent final concentration and formalised cultures are kept at 37°C till the product is sterilised and atoxic. The formalised anacultures are pooled, precipitated by the addition of Aluminium Chloride, 20 per cent solution in distilled water to have a final concentration of the chemical to 10 per cent and pH adjusted to 6.0. The sedimer.ted toxoid is reconstituted to half the original volume in normal saline.

4. Standards—

(a) *Description*—It is a whitish liquid when shaken thoroughly to contain killed bacteria and toxoid in suspension.

(b) *Identification*—When injected into susceptible animals it stimulates the production of epsilon and beta antitoxins against C. *perfringens* type D and C and also antitoxins against *Cl. septicum* and toxin of *Cl. oedematiens.*

(c) *Sterility test*—Complies with the test of sterility described in general monograph on "Bacterial Vaccines."

(d) *Safety test*—Four sheeps each are inoculated with 10 ml. S/C of the product and these are observed for 7 days during which period the animals shall not show any local or systemic reaction.

(e) *Potency test*—Eight sheep each are inoculated with 2 doses of vaccine S/C at an interval of 21 days and bled on 10th day after 2nd inoculation for collection of serum for assessing the antitoxin titre against each antigen incorporated in the vaccine. The post inoculation serum should contain not less than 2- i.u. of epsilon and beta antitoxins of *Cl. perfringens* and 2. 5 i.u. of *Cl. Septicum* antitoxin and 4 i.u. of *Cl. oedematiens antitoxin.*

5. Labelling and Storage—Shall comply with the requirements regarding labelling and storage as laid down in the general monograph on "Bacterial Vaccines."

6. Expiry Date—The expiry date of potency of vaccine shall not be more than 6 months from the date of manufacture.

HEMORRHAGIC SEPTICAEMIA VACCINE—ALUM TREATED

1. Synonyms—*Pasteurella multocida/*(Yersinia Multocida) vaccine—Alum treated.

2. Definition—The vaccine is a formalised culture of a virulent strain of Pasteurella multocida in nutrient both treated with potash alum.

3. Preparation—A highly potent strain of *Pasteurella multocida* type I in Phase I is grown on nutrient broth at 37°C. The pure growth is killed by the

addition of a solution of Formalin I.P. in suitable concentration (0.5 per cent). This is treated with potassium alum I.P. to give a final concentration of 1 per cent.

4. Standards—

(a) Description—It is a white suspension containing dead bacteria and alum.

(b) *Identification*—It protects susceptible animals against infection with *P. Multocida.*

(c) *Sterility test*—Complies with the test for sterility described under the general monograph on "Bacterial Vaccines".

(d) *Safety test*—Four healthy rabbits each weighing 1 to 1.5 kg. are inoculated subcutaneously each with 5 ml. of the product. There shall be no untoward reaction during the period of observation for day except slight local swelling. Alternatively two rabbits and six mice may be employed. The dose for mice will be 0.5 ml.

5. Labelling and Storage—Shall comply with the requirements of labelling and storage as laid down in the general monograph on "Bacterial Vaccines".

6. Expiry Date—The date of expiry of potency of the vaccine shall be not more than six months from the date of manufacture.]

(B) PROVISIONS APPLICABLE TO THE PRODUCTION OF VIRAL VACCINES

1. Definition— (i) This part of the Schedule applies to viral vaccines live or inactivated made from any virus pathogenic to domestic animals and poultry and made from other modified viruses which have any antigenic value.

(ii) For the purpose of this part of the Schedule, a virus vaccine means a sterile suspension or a freeze dried powder containing the modified living or inactivated virus particles, which in its original unaltered stage, causes disease from which the vaccine derives its name and which has been prepared from the

blood or tissues of a suitable host in which it has been grown *in vivo* or from tissue culture.

2. Staff of Establishment—The establishment in which viral vaccines are prepared, must be under the direction and control of an expert in a bacteriology with specialised training in virology and sufficient experience in the production of viral vaccines, and he shall be assisted by a staff adequate for carrying out the tests required during the preparation and standardisation of the vaccines.

3. Proper Name—The proper name of any viral vaccine shall be the name of the disease which is caused by the particular virus from which the vaccine is produced followed by the word "Vaccine" unless the Schedule otherwise provides, if there is not special provision in the Schedule, such other name as is approved by the Licensing Authority. Provided that in the case of the undermentioned preparation the proper name of the vaccine shall be as follows:—

(i) Fowl Pox Vaccines, Chick Embryo Virus (Living)

(ii) Fowl Pox Vaccine, Pigeon Pox Virus (Living)

(iii) Horse Sickness Vaccine (Living)

(iv) Ranikhet Disease Vaccine (Living)

(v) Ranikhet Disease Vaccine F Strain (Living)

(vi) Rinderpest Goat Adapted Tissue Vaccine (Living)

(vii) Rinderpest Lapinised Vaccine (Living)

(viii) Rinderpest Lapinised Avianised Vaccine (Living)

(ix) Sheep and Goat Pox Vaccine (Living)

(x) Swine Fever Vaccine (Crystal violet)

(xi) Swine Fever Vaccine Lapinised (Living)

[1091][(xii) Foot and Mouth Disease Vaccine (Inactivated);

(xiii) Canine Hepatitis Vaccine (Living).]

[1092][**4. Records**—The seed virus used in the preparation of vaccine shall, before being used for preparing a batch, be thoroughly tested for purity, safety, sterility and antigenicity by the generally accepted tests applicable to a

particular virus. It shall not be more than five passages away from the stock seed virus, unless otherwise prescribed for a particular virus. The stock seed virus shall be maintained by seed—lot system at specified passage level and tested for bacterial, mycoplasmal and extraneous viral contamination. The permanent record which the licencee is required to keep shall include a record of the origin, properties and characteristics of the seed virus from which the vaccines are made.]

5. Tests—Viral vaccine shall be tested for sterility, safety and potency on suitable test animals and for viability in the case of live vaccines.

(a) *Sterility Test*—All Vaccines shall be tested for sterility in accordance with Rules 115 to 119. If the vaccine contains added bactericides or bacteriostatic, a quantity of a medium sufficient to render the growth inhibitor ineffective is added to the sample or a suitable substance is added in a concentration sufficient to render the growth inhibitor ineffective but not itself to inhibit the growth of micro-organisms.

(b) *Safety test*—Suitable laboratory animals or large animals or birds may be employed to test the vaccine for safety. Details of safety test are given in the individual monograph.

(c) *Potency test*—All virus vaccines for which potency test has been prescribed shall be tested for potency and only those which pass the potency test shall be issued. Details of the potency test are given in the individual monograph.

6. Storage—Live viral vaccines shall be stored, protected from light at sub-zero temperature as required. Other viral vaccines shall be stored at 2°C to 4°C but shall not be frozen.

7. Condition of housing of animals—(i) The animals used in the production of vaccine must be housed in hygienic conditions in premises satisfactory for this purpose.

(ii) Only healthy animals may be used in the production of vaccine. Each animal intended to be used as a source of vaccine must, before being passed for the production of vaccine be subjected to a period of observation in quarantine

for at least seven days. During the period of quarantine the animal must remain free from any sign of disease and must be well kept.

[1093][(iii) The poultry birds from which eggs and cell culture for production of vaccines are obtained should be housed in a manner so as to keep them free from extraneous infection and shall be screened at frequent intervals for common bacterial, mycoplasmal and viral injection. The record of the tests and their results shall be maintained by the manufacturers.]

8. Lebelling—The provisions of "Labelling" as laid down for Bacterial Vaccines shall also apply to Viral Vaccine. The following additional information shall be included on the label of the outside container.

(i) The name and percentage of bacteriostatic agent contained in the vaccine.

(ii) If the vaccine as used for sale contains any substance other than the diluent, the nature and strength of such substance.

9. Date of Manufacture—For the purpose of this part of the Schedule, the date of manufacture shall be what is given unless otherwise stated in the individual monograph, as defined in sub-clause (b) of sub-rule (3) of Rule 109.

FOWL POX VACCINE CHICK EMBRYO VIRUS (LIVING)

1. Synonym—Egg adapted Fowl Pox Vaccine (Living).

2. Definition—Fowl-pox vaccine, Chick-Embryo Virus (Living) is a suspension of a modified living virus *e.g.*,, Mukteswar Strain prepared from the chorioallantoic membrane (CAM) of the infected embryo and is either freeze dried or is issued as glycerinated liquid vaccine.

3. Preparation—Active chick-embryos obtained form *Salmonella pullorum* free flock, are used. [1094][Twelve to thirteen days old embryos are injected with a suitable dilution of the suspension of the infected members (seed virus) of chick embryo adopted fowl pox virus.] The suspension of the stock seed virus is dropped on the CAM. After an incubation at 37°C for a suitable period membranes showing discrete or confluent lesions (pocks) are harvested. These are homogenised with adequate quantity of antibiotics (penicillin and streptomycin) ampouled in 0.5 ml. quantities and freeze dried.

4. Standards—

(a) *Description*—Light mauve coloured scales.

(b) *Identification*—When reconstituted vaccine is applied to scarified area of the skin of a fowl it produced characteristic lesions of fowl pox. This product should afford protection against fowl pox.

(c) *Moisture Content*—Moisture content in the finished product should not exceed 1.0 per cent.

(d) *Safety Test*—For testing each batch of fowl pox vaccine twelve healthy cockerels, or other suitable young chicken each weighing not less than 400 g. from the same source are taken. This group of twelve birds is immunized at least twenty-one days pervious to the test, with fowl pox vaccine. The vaccine under test is reconstituted in 5 ml. of 50 per cent glycerine saline and administered to fowls as follows:—

Three of the test birds are injected subcutaneously with 0.8 ml. or 10 times the field doses of the vaccine under test. This group serves to indicate whether the product is free from other viruses and bacteria causing septicaemia or not. Three of the test birds are injected intratrecheally with 0.3 ml. or 10 times the field doses of the vaccine under test. This group serves to indicate whether the product is free from the virus of infectious laryngotracheitis and similar diseases.

Three of the test birds are injected intranasally with 0.2 ml. of the vaccine under test. This group serves to indicate whether the product is free from the virus of Coryza and similar disease.

The three remaining birds serve as controls. They are isolated and kept under observation for twenty-one days. The birds that succumb during the period of twenty-one days are subjected to a careful post-mortem examination. The product is withheld from issue until the vaccine and the test birds are shown to be free from the causative agents of any extraneous disease.

(e) *Sterility Test*—Complies with the tests for sterility as described under the general monograph on "viral vaccines."

(f) *Potency Test*—For testing of potency three unsusceptible birds each weighing not less than 400 g. are vaccinated using the field dose by the stick method and examined for "takes". Three weeks after vaccination these birds along with two unvaccinated controls are exposed to challenged virus and observed for fourteen days. The vaccinated birds should not manifest any reaction, while the controls should show active "takes".

5. Labelling—Should comply with the requirement for "Labelling" as laid down in the general monograph on "Viral Vaccines".

6. Storage and Expiry date—Freeze dried vaccine shall be expected to retain its potency for periods at temperatures as specified below:—

—15°C to —20°C — Twenty-four months

2°C to 4°C — Twelve months

Room temperature—up to one month.

The liquid vaccine shall be expected to retain its potency for periods and temperatures as specified below:

2 °C to 4 °C — six months

Room temperature— seven days

FOWL POX VACCINE PIGEON POX VIRUS (LIVING)

1. Synonym— Fowl Pox Vaccine (pigeon pox scab).

2. Definition— Fowl Pox vaccine, pigeon pox virus (living) consists of pigeon pox virus in scabs collected from artificially infected pigeons and dried.

3. Preparation—Healthy pigeons are scarified on the legs and breast, with a suitable dilution of the suspension of pigeon pox virus. The pigeons reacting satisfactorily and showing good takes are selected and the superficial skin layer scrapted by means of sharp scalpel. The material so collected is freed from feathers, homogenised and dried or freeze died. The dried pulp is powdered, sieved and ampouled in 0.3 g. quantities and sealed.

4. Standards—

(a) *Description*—Light cream coloured powder.

(b) *Identification*—When applied to feather follicles by vigorous rubbing, it produces mild reaction in fowls. The product should afford protection to fowls up to six weeks against fowl pox.

(c) *Safety Test*— For testing a batch of vaccine, twelve healthy cockerels, or other suitable young chicken from the same source are made available at the same time. This group of twelve birds is immunised at least twenty-one days previous to the test with fowl pox vaccine. The vaccine under test is reconstituted in 10 ml. of 50 per cent glycerine saline and administered to fowls as follows:—

Three of the test birds are injected subcutaneously with 0.3 ml. or 10 times the field dose of the vaccine to be tested. This group serves to indicate whether the product is free from organisms of septicaemia diseases.

Three of the test birds are injected intranasally with 0.2 of the vaccine to be tested. This group serves to indicate whether the product is free from virus of Coryza and similar diseases.

[1095][Three of the test birds are injected intrathicheally with 0.2 ml. of 10 times of the field dose of the vaccine under test. This Group serves to indicate whether the product is free from the virus of infectious laryngotracheitis and similar diseases.]

The three remaining birds serve as controls. All the birds under test are isolated and held under observation for twenty-one days. All those that succumb are subjected to careful post-mortem examination. The product is withheld from issue until the vaccine and test birds are shown to be free from the causative agents of any extraneous diseases.

(d) *Sterility Test*—Complies with the tests for sterility described under the general monograph on "Viral Vaccine".

(e) *Potency Test*—For testing of potency of a batch of vaccines three susceptible birds each weighing not less than 400 g. are vaccinated using

the field dose by the follicular method and examined for "takes". Three weeks after vaccination these birds and two healthy susceptible controls are exposed to challenge virus and are observed for fourteen days. The vaccinated birds shall manifest no reaction, while the controls must have active "takes".

5. Storage and Labelling—Should comply with the requirement of "Labelling" as laid down in the general monograph on "Viral Vaccines".

6. Expiry date—The vaccine shall be expected to retain its potency for periods at temperatures as specified below:

—15°C to —20°C — two years

2°C to 4°C — twelve months

Room temperature—up to one month.

FOWL POX VACCINE-PIGEON POX-CHICK EMBRYOS VIRUS (LIVING)

1. Synonym—Chick embryo adapted pigeon pox vaccine (Living)

2. Definition—Fowl pox vaccine (Pigeon Pox Virus) chick embryo adopted virus (Living) is a suspension of a modified living virus prepared from the chorioallantoic membranes of the infected embryos and is freeze dried.

3. Preparation—Active chick embryos obtained from *Salmonella Pullorum* free stock are used. Twelve to thirteen days old embryos are injected with a suitable dilution of the suspension of the infected membrane (stock seed viius) of chick embryo adapted pigeon pox virus. The suspension of the stock seed virus is dropped on the membrane. The inoculated eggs are incubated at 37°C for four days. One of the fourth day embryos that are living, are removed to a refrigerator for chilling for about one hour. Membranes showing discrete lesions (pocks) are harvested. These are homogenised with adequate quantities of antibiotics, ampouled in 0.5 ml. quantities and freeze dried.

4. Standards—

(a) *Description*—Light mauve coloured scales.

(b) *Identification*—When reconstituted vaccine is applied to scarified area of the skin of a fowl, it produces characteristic lesions of Fowl Pox. This product should afford protection against pox.

(c) *Moisture Content*—Moisture content in the finished product should not exceed 1.0 per cent.

(d) *Safety Test—For* testing each batch of chicks aged four to six weeks from the same source are taken. This group of twelve birds is immunised at least twenty-one days previous to the last, with fowl pox vaccine. The vaccine under test is reconstituted in 3 ml. of normal saline solution and administered as under:

Three of the test chicks are injected subcutaneously with 0.3 ml. or 10 times the field dose of the vaccine under test. The group serves to indicate whether the product is free from other viruses and bacteria causing of septicaemia or not.

Three of the test chicks are injected intra-trachally with 0.3 ml. or ten times the field dose. This group serves to indicate whether the product is free from the viruses of infections laryngeotracheiti and similar diseases.

Three of the test chicks are injected with 0.2 ml. 1/N of the vaccine under test. This group serves to indicate whether the product is free from the virus of coryza and similar diseases.

The remaining three chicks serve as controls. They are isolated and kept under observation for twenty-one days. The birds that succumb during the period of observation are subjected to careful post-mortem examination. The product is withheld from until the vaccine and the test birds are shown to be free from the causative agents of any extraneous disease.

In addition to the above, similar groups of pigeons aged six to nine months old are also injected in a similar way to eliminate psittacosis.

(e) *Sterility Test*—Should comply with the tests for sterility described under the general monograph on 'Viral Vaccine'

(f) *Potency Test*—For testing potency of a batch of vaccine three susceptible chicks of three to four weeks of age are vaccinated by feather

forthicle method (a few forthicles on one leg are injected) and these are examined for 'takes'.

Three weeks after vaccination these chicks along with two unvaccinated chicks are exposed to challenge virus (virulent fowl pox virus) and observed for fourteen days. The vaccinated chicks should not manifest any reaction while controls should show active 'takes'.

5. Labelling—Should comply with the requirement for "Labelling" as laid down in the general monograph on "Viral Vaccines".

6. Storage—The freeze dried product is expected to retain its potency for periods at temperatures as specified below:—

—15°C to —20°C — two years

2°C to 4°C — twelve months

Room temperature—up to one month.

SHEEP POX VACCINE (LIVING)

1. Synonym—Sheep Pox Vaccine; Goat pox vaccine.

2. Definition—Sheep pox vaccine consists of sheep pox virus collected from sheep artificially infected with sheep pox virus and freeze dried.

3. Preparation—Healthy yearling sheep are infected artificially by subcutaneous injection on the undersurface of the previously shaved abdomen with 200—300 cc. of the freeze dried sheep pox virus (seed material) diluted in 1:1 Normal saline solution. On the sixth or seventh day after injection oedematous swelling develops in the injected area with thermal reaction. The sheep which develop good swelling are slaughtered and the gelatinous material present under the skin in the infected area is collected under sterile conditions. This material is mixed with 2 parts by volume of sterile peptone broth of pH 7.2 and homogenised. The homogenised suspension is filtered ampouled in 0.5 ml. quantities and freeze dried.

4. Standards—

(a) *Description*—White Scales.

(b) *Identification*—Reconstituted vaccine when applied over the scarified area of the skin of the abdominal region of sheep will produce characteristic local lesion of pox.

(c) *Moisture content*—The moisture content should not exceed 1.0 per cent.

(d) *Safety Test*—Two rabbits each weighing not less than 1 kg. are injected subcutaneously each with 1 ml. of 1:100 dilution of the vaccine in normal saline solution. These animals are observed for fourteen days. The animals should remain normal.

(e) *Sterility Test*—Complies with the tests for sterility described under the general monograph on 'Viral Vaccine'.

(f) *Potency Test*—Four yearling sheep are vaccinated on the inner surface of the ear by scarification method. The contents of one ampoule of F.D. Sheep Pox vaccine are constituted in 10 cc of 50 per cent glycerine saline solution, characteristic takes develop in the scarified area with ulceration and scab formation. Three weeks later these and two more susceptible sheep (Controls) are challenged by scarifying with a suspension of the previous brow of the vaccine of the undersurface of the abdomen. The controls should develop typical lesions of pox and the vaccinated should remain normal.

5. Labelling—Should comply with the requirements of 'labelling' as laid down in the general monograph on 'Viral Vaccine'.

6. Storage and expiry date—The vaccine shall be expected to retain its potency for periods at temperatures as specified below:

—15°C to —20°C — two years

2°C to 4°C — twelve months

Room temperature—fifiteen days.

HORSE SICKNESS VACCINE (LIVING)

1. Synonym—African Horse Sickness Vaccine; Mouse adapted Polyvalent Horse Sickness Vaccine (Living).

2. Definition—Horse sickness vaccine is a suspension of live mouse adapted strains of Horse Sickness Virus (onderstepoort) prepared from the brains of infected mice and is freeze dried.

3. Preparation—Thirty to thirty-five-day-old white mice are infected intracerebrally with 0.05 ml. of a suitable dilution of the seed virus (6 or 7 types, as the case may be). Groups of large numbers of mice are injected separately with each type of the virus and are housed at 27°C to 32°C. A majority of these become paralytic on the third and fourth day when they are scarified and their brains collected and stored at —15°C to —20°C till the day of processing. For preparing the polyvalent vaccine, equal number of brains collected from mice infected with different types of the virus are homogenised with 5-10 times its volume of sterile lactose buffer medium (pH 7.2) containing antibiotics. The suspension is centrifuged at 1500 r.p.m. for five minutes. The supernatant liquid is distributed in ampoules in suitable quantities and freeze dried.

4. Standards—

(a) *Description*—White scaly material.'

(b) *Identification*—This product affords protection to horse against horse sickness.

(c) *Safety Test*—Four healthy mice thirty to thirty-five days old are injected intraperitoneally with 0.2 ml. of 10:1 dilution of the vaccine and kept under observation for ten days. All the mice should remain normal throughout the period of observation.

(d) *Sterility Test*—Should comply with the test for sterility described under the general monograph on 'Viral Vaccine'.

(e) *Viability Test*—Each batch of vaccine is titrated in tenfold dilutions using four mice of thirty to thirty-five days old for each dilution. Each mouse is injected intracerebrally with 0.05 ml. and kept under observation for ten days. Mortality and survival ratios are noted and Ld

50 is determined. The minimum acceptable titre is 10-4- Ld 50 per 0.05 ml.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Viral Vaccines'.

6. Storage —The vaccine may be expected to retain its potency for twelve months if stored —15°C to —20°C and about six months if stored in refrigerator at 2°C to 4°C.

RABBIES VACCINE (INACTIVATED)

1. Synonym—Antirabic Vaccine (Inactivated).

2. Definition—Rabies vaccine is a suspension of the brain tissue of animals, that have been infected with a suitable strain of rabies fixed virus, inactivated with phenol or some other suitable agent.

3. The following particulars relating to this vaccine are the same as those relating to Antirabic vaccine described in Part D of Schedule F to these rules, namely:—

(i) Strain of fixed Rabies Virus to be used;

(ii) Staff of Establishment;

(iii) Condition and housing of animals;

(iv) Precaution to be observed in preparation;

(v) Records;

(vi) Issue.

4. Preparation—Healthy sheep or any other suitable species of animal are inoculated subdurally or intracerebrally with an appropriate dose of suspension of a suitable strain of rabbit brain passaged rabies fixed virus. The sheep or animals which get paralysed from the sixth day onwards after the inoculation are scarified and their brains collected aseptically. Brain tissue is weighed individually and a suspension of suitable concentration of brain tissue prepared in buffered saline is strained through gauze. The suspension treated

with phenol or some other suitable inactivating agent is incubated for an appropriate period.

5. Standards—

(a) *Description*—A grey to pale yellow opalescent suspension.

(b) *Identification*—Appropriate doses protect mice against subsequent intracerebral inoculation with suitable strain of fixed rabies virus.

(c) *Safety Test*—Not less than five mice, each weighing at least 18 gm, are inoculated intracerebrally with not less than 0.03 ml. of the suitably diluted vaccine. None of the animals should show symptoms of rabies or die of the disease during period of observation of three weeks.

(d) *Sterility Test*—Should comply with the test for sterility described under the general monograph on 'Viral Vaccine'.

6. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Viral Vaccine'. In addition the label on the container shall indicate the percentage of brain-tissue present in the vaccine.

7. Storage—The vaccine may be expected to retain its potency for about six months if stored in refrigerator at 2°C to 4°C.

RABIES VACCINE (LIVING)

1. Definition—Rabies vaccine (living) is a freeze dried suspension of chick-embryo tissue infected with a suitable attenuated strain of rabies virus.

2. Preparation—It may be prepared by the following method. Seed virus consisting of a suspension of the Flury or other suitable strain of chick adapted virus that has been maintained by passage in chick embroys is injected into the yolksacs of fertile eggs incubated for a suitable period. After incubation for a further ten days, the embroys, are harvested and grind in water for injection to give 33 per cent suspension. The suspension is centrifuged to remove coarse particles and the supernatant fluid is distributed into ampoules in 3 millilitre quantities, and freeze-dried. The vaccine is reconstituted immediately before use by adding 3 millilitres of water for injection to the contents of an ampoule.

3. Standard—It complies with the requirements of general standard of viral vaccines for abnormal toxicity, sterility, and labelling with the following additions:—

(a) *Description*—Dry honey-coloured flakes or powder, readily dispersible in water.

(b) *Identification*—It protects guinea-pig against a subsequent inoculation of rabies street virus. It is distinguished from the inactivated rabies vaccine by its ability to produce rabies encephalitic on intracerebral injection into mice.

(c) *Safety Test*—The guinea-pigs used in the test for potency should not show any marked local or systemic reaction during the three weeks following injection with the vaccine.

(d) *Sterility Test*—Complies with the tests for sterility described under the general monograph on 'Viral vaccine'.

(e) *Potency Test*—The contents of an ampoule are dispersed in water for injection to give a 5 per cent suspension and not fewer than twenty guinea-pigs, drawn from a uniform stock and each weighing 350g to 500g, are each injected intramuscularly with 0.25 ml. of this suspension. Three weeks later, these guinea-pigs and an equal number of similar unvaccinated control guinea-pigs are each inoculated with 0.1 ml. of a suitable dilution of canine salivary gland suspension of street virus which is maintained as a 20 per cent suspension at 70°C or lower. The guinea-pigs are observed for thirty days; not less than 80 per cent of the control guinea-pigs die of rabies and not less than 70 per cent of the vaccinated guinea-pigs are protected.

4. Storage—Freeze-dried vaccine should be stored at refrigeration temperatures 2°C to 4°C.

5. Labelling—The life of the vaccine at room temperature and at refrigeration temperature should be stated on the label.

6. (a) Action and uses—Rabies vaccine (living) is used for the prophylactic inoculation of dogs against rabies; one injection should provoke a

serviceable immunity lasting for at least a year. The vaccine has been used to a limited extent on cattle.

(b) Dose—By intramuscular injection : Dogs, the contents of one ampoule reconstituted in 3 ml. of water for injection; cattle five times the dog dose.

RANIKHET DISEASE VACCINE (LIVING)

1. Synonym—New castle disease Vaccine (Living); pheumoenteritis Vaccine (Living).

2. Definition—Ranikhet Disease vaccine is a suspension of a modified living virus *e.g.* its, (Mukteswar strain) prepared from infected embroys and fluids and is freeze dried.

3. Preparation—Good fertile eggs obtained from Salmonella pullorum free flock are incubated in an egg incubator. Ten days old vigorous embroys are infected with 0.1 ml. of a suitable dilution of a suspension of the virus. Inoculation is done in the allantoic cavity. Embroys are incubated at suitable temperature. Eggs showing dated embryos twenty-four hours after incubation are discarded. After forty-eight hours incubation the eggs are candled and those showing dead embryos are chilled for a suitable period of time, while embryos alive beyond forty-eight hours are discarded. The fluids and embryos are then collected and spot haemogglutination carried out. The material is homogenised in a blender and ampouled in a aliquots of 0.5 ml. quantities and freeze dried.

4. Standards—

(a) *Description*—Light brown scales.

(b) *Identification*—This product affords protection to fowls against Ranikhet Disease.

(c) *Safety Test*—For testing each batch of freeze dried Ranikhet Disease Vaccine, twelve healthy young chickens, all from the same source each weighing not less than lOOg. are taken and immunised against Ranikhet Disease. Fourteen days later, these birds are tested as follows with the contents of one ampoule suspended in 100 ml. of normal saline.

Three of the test birds are injected subcutaneously with 0.1 ml. equivalent to ten times the field dose of the vaccine to be tested. This group serves to indicate whether the product is free from viruses or organisms of septicaemica disease. Three of the test birds are injected intratracheally with 0.1 ml. equivalent to ten times the field does of the vaccine to be tested. This group serves to indicate whether the product is free from the virus of infectious laryngotracheitis, [1096][***] and similar diseases.

The three remaining birds serve as controls.

[1097][Three of the test birds are injected intranasally with 0.2 ml. of the vaccine to be tested. This group serves to indicate whether the product is free from virus of Coryza and similar diseases.]

All the treated birds and controls are observed daily for fourteen days. All the test birds that succumb are subjected to careful post-mortem examination. The product is not issued until the birds under test are shown to be free from the causative agents of any extraneous diseases.

(d) *Sterility Test*—Should comply with the test for sterility described in the general monograph on 'Viral Vaccine'.

(e) *Potency Test*—Four susceptible birds eight to twelve weeks old and each weighing not less than 400 g. are vaccinated by injecting subcutaneously 1 ml. of a 10^{-5} dilution of the product. Two weeks after vaccination these birds and four non-protected birds are challenged by injecting subcutaneously each with 1.0 ml. of a 1:100 dilution of virulent virus (liver and spleen suspension) or 1.0 ml. of a 1:100 dilution of fluid from the embryo infected with virulent Ranikhet Disease virus. The non-protected birds should show symptoms of Ranikhet Disease and die and all the protected birds should remain normal during an observation period of fourteen days.

5. Labelling—Should comply with the requirements of "Labelling" as laid down in the general monograph on 'Viral Vaccines'.

6. Storage—The vaccine when stored at -15°C to -20°C may be expected to retain the potency for about one year and about three months if stored in a

refrigerator at 2°C to 4°C. The product should not be used if stored for more than ten days outside the refrigerator.

RANIKHET DISEASE VACCINE F. STRAIN (LIVING)

1. Synonyms—New castle disease vaccine F. Strain (Living).

2. Definition—Ranikhet disease vaccine F. Strain is a suspension of a naturally modified living virus (F. strain) prepared from the infected embryos, devoid of beaks and eyes and fluids in a frozen state.

3. Preparation—Good fertile eggs obtained from *Salmonella pullorum* free flock are incubated in an egg incubator. Eight days old vigorous embryos are infected with 0.1 ml. of 1:100 suspension of Ranikhet Disease vaccine F strain virus. Inoculation is done via the allantoic cavity. Embryos are incubated at 37°C. Eggs are candled every day up to four days and the dead ones are discarded. Final candling of the embryos is carried out on the fourth day and only the living ones are chilled in a refrigerator for one hour. The fluids embryos are collected separately. The fluids are tested for spot haemogglutination and sterility test is carried out. The beaks and eye balls of the embryos are removed. The materials are homogenised with adequate quantities of antibiotics in a cool warning blender and ampouled in aliquots of 0.5 ml. quantity and freeze dried.

4. Standards—

(a) *Description*—Light brown scales.

(b) *Identification*—This product affords protection to baby chicks against Ranikhet disease.

(c) *Moisture content*—The moisture content should not exceed [1098][1.0] per cent.

(d) *Potency Test*—For testing each batch of the vaccine twelve one-day-old chicks are given two drops 1/N of the field dose of the vaccine (5 ampoules selected at random may be reconstituted in 50 ml.) of cold normal saline solution. These are observed for fourteen days and the vaccinated chicks should remain normal throughout the period of observation. This serves the safety test also.

On the fourteenth day the vaccinated chicks are challenged with two drops 1 : 50 virulent Ranikhet Disease virus along with 8 control chicks. Four of the controls receive two drops 1/N of the virulent virus while the rest of the four receive 0.5 ml. of the virulent vims. The control chicks should succumb to the challenge virus showing symptoms of Ranikhet Disease while the protected chicks should remain normal throughout the observation period of fourteen days.

(e) *Sterility Test*—Should comply with the tests for sterility described in the general monograph on 'Viral Vaccines'.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Viral Vaccines'.

6. Storage—The vaccine when stored at -15°C to -20°C may be expected to retain the potency for about one year and about three months if stored in a refrigerator at 2°C to 4°C. When removed from the refrigerator, the product should not be used later than ten days.

RINDERPEST GOAT ADAPTED TISSUE VACCINE (LIVING)

1. Synonym—Goat-adapted Cattle Plague Vaccine; Goat Tissue Vaccine (Living).

2. Definition—Rinderpest Goat-adapted Tissue Vaccine is the homogenised freeze dried preparation of spleen pulp of goats artificially infected with the suitable strain of rinderpest virus.

3. Preparation—Healthy susceptible goats are quarantined for a period of ten days. After this period a batch of selected goats are injected subcutaneously with 2 ml. of a suitable dilution of the suspension of the seed virus. The donor goats are scarified after a suitable period when the litre of the virus in the animal body is expected to be maximum, usually four days, and the spleen from animals free from any pathological change or signs are collected under sterile conditions. Smear from each spleen is examined microscopically to exclude spleen which are contaminated from the production batch.

The spleen is freed from fat and fascia and is blended into a smooth pulp in a grinder. The pulp is spread on a shallow dish of glass or stainless steel and is freeze dried.

The freeze dried pulp is then ground in a fine powder and sieved. The powder is ampouled in 0.25 g. or 0.125 g. quantities and freeze dried.

4. Standard—

(a) *Description*—Dark brown or chocolate coloured scales or powder.

(b) *Identification*—The product affords protection to susceptible animals against rinderpest.

(c) *Moisture content*—Not more than 1.0 per cent.

(d) *Safety Test*—Each batch of vaccine shall be tested for safety in laboratory animals and cattle or buffalo calves as follows:—

(i) *Small animals*—At least two guinea-pigs each weighing 300 g. to 450 g. and two adult rabbits each weighing 1 kg. to 1.5 kg. should be injected each with 1 ml. of 1:100 suspension of the vaccine subcutaneously and kept under observation for seven days. None of the animals should die. Alternatively, a batch of six white mice each weighing not less than 18 g. may be used, each mouse receiving 0.5 ml. of a dilution 1:100 suspension subcutaneously. None of the animals should die.

(ii) *Large animals*—Either cattle of good grade of susceptibility (hill cattle) or buffalo calves may be employed. For each batch of vaccine, three animals should be injected subcutaneously with 1 ml. of 1:8000 dilution of the vaccine. These animals should be kept under observation for twelve to fourteen days. None of the animals should show any untoward reactions.

(e) *Sterility Test*—Complies with the tests for sterility described under the general monograph on 'Viral Vaccines'.

(f) *Potency test*—The animals receiving 1 ml. 1:8000 dilution of vaccine used under safety test mentioned above and kept under

observation for fourteen days should be challenged with 1 ml. of 1 per cent suspension of stock Rinderpest Virulent virus. None of the animals should die of rinderpest within a period of ten days. This test serves as a short potency test for each of the batches.

For conducting a detailed potency test the following procedure may be followed:— Dilution 1:8000, 1:12000 and 1:16000 shall be tested and for each dilution three susceptible cattle or buffalo calves should be used. Each animal is inoculated subcutaneously with 1 ml. of a dilution of the vaccine, followed twelve of fourteen days later with a standard challenge dose of virulent rinderpest bull virus containing in 1 ml. of a 1:100 suspension of spleen tissue. Two unvaccinated bovines, each receiving the same quantity of the challenge dose act as controls. These are kept under observation for fourteen days. The end point of protection titre is assessed on the death or survival rate and the dose contained in one gramme of vaccine calculated on the basis of 20 to 40 minimum protective doses being equivalent to one vaccinating dose.

(g) *Virulence and viability Test*—Two to four goats each weighing not less than 18 kg. are injected with 2 ml. of 1:100 suspension of the vaccine and kept under observation for ten days. These animals should show reaction characterised by pyrexia (rise of about 2°C) anorexia and dullness.

5. Labelling—Should comply with the requirement of 'Labelling' as laid down in the general monograph on 'Viral Vaccines'.

6. Storage—The vaccine may be expected to retain its potency for twelve months if stored at -15°C to -20°C or about three months if stored at 2°C to 4°C.

RINDERPEST LAPINISED VACCINE (LIVING)

1. Synonym—Rabbit Adapted Cattle Plague Vaccine (Living) Lapinised Vaccine (Living).

2. Definition—Rinderpest Lapinised Vaccine is a suspension of a modified living virus *(e.g.,* Nakamura III Strain) prepared with the blood spleen and mesenteric lymph glands of infected rabbits and is freeze dried.

3. Preparation—Adult rabbits possibly from a known stock, each weighing not less than 1 kg. free from cocidiosis and snuffles, are injected intravenously with 1 ml. of a suitable dilution of a suspension of the stock seed virus. Donor rabbits are scarified after a suitable period when the titre of the virus in the animals is expected to be the maximum usually the third day.

Ten millilitres of blood is collected from each rabbit in a defibrinating flask under aseptic condition. Later the animals are sacrificed and the spleen and mesenteric lymph glands collected. Each rabbit is subjected to a thorough post-mortem examination to observe lesions of rinderpest infection.

After harvesting, the blood and the organs (spleen and glands) are homogenised in suitable proportion if necessary. Adequate quantities of penicillin and streptomycin may be added. The homogenised material is ampouled in suitable quantities and freeze dried.

4. Standards—

(a) *Description*—Dark chocolate coloured mass.

(b) *Identification*—This product affords protection to susceptible animals against rinderpest.

(c) *Moisture content*—Not more than 1.0 per cent.

(d) *Safety Test*—For testing a batch 2 guinea-pigs each weighing not less than 300 g. are injected subcutaneously with 1 ml. of a 1:100 suspension of the vaccine. Alternatively, a group of six white mice each weighing not less than 18 g. is used. Each animal receives subcutaneously 0.5 ml. of 1:100 suspension of the vaccine. None of the test animals should die within a period of seven days.

(e) *Sterility Test*—Should comply with the tests for sterility described in the general monograph on 'Viral Vaccines'. If antibiotics have been added the inoculum should be neutralised before doing the test.

(f) *Potency Test*—Dilutions 1:100,1:200,1:400 and 1:800 shall be tested and for Qach dilution 2 susceptible cattle (hill bulls) or buffalo calves should be used. Each animal is inoculated subcutaneously with 1 ml. of a dilution of the vaccine, followed twenty-one days later with a standard

challenge dose of a virulent rinderpest bulls virus contained in 1 ml. of a 1:100 suspension of spleen tissue. Two unvaccinated bovines each receiving the same quantity of the challenge virus serve as controls. These animals are kept under observation for fourteen days. The end point of the protecting titre is assessed on the death or survival rate and the dose contained in one gramme of vaccine calculated on the basis of twenty minimum protective doses being equivalent to one vaccinating dose.

(g) *Virulence and Viability Test*—Four rabbits each weighing 1 to 1.5 kg. are injected subcutaneously with 1 ml of 1:100 suspension of the vaccine. The animals should react typically showing all the symptoms of rinderpest in rabbit.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Viral Vaccine'.

6. Storage—The vaccine may be expected to retain its potency for six months if stored at —15°C to —20°C or about a month if stored at 2°C to 4°C.

RINDERPEST LAPINISED AVIANISED VACCINE (LIVING)

1. Synonym—Lapinised Avianised Vaccine (Living).

2. Definition—Rinderpest Lapinised Avianised Vaccine is a suspension of a modified live rinderpest virus of low virulence prepared either with the whole chick embryo or the viscera of the infected chick embryo.

3. Preparation—Twelve or thirteen days old active chick embryos from a flock free from Salmonella pullorum infection are injected intravenously with a suitable dilution of the suspension of the stock seed virus in six per cent glucose solution. The embryos are incubated at 38.5°C for five days. At the end of this incubation period, eggs which show living embryos are selected for the preparation of the vaccine. The viscera of the chicks are harvested, care being taken to reject of gizzard and gall bladders. The material is homogenised in a blender with adequate quantities of antibiotics (penicillin and streptomycin added if necessary), and primary freeze dried done. This freeze dried material is ground into a fine powder, ampouled in suitable quantities and finally subjected to secondary freeze drying and sealed under vacuum.

4. Standards—

(a) *Description*—Pale cream or yellow coloured sterile powder.

(b) *Identification*—This product affords good grade of immunity to susceptible animals against rinderpest.

(c) *Moisture content*—Not more than 1.0 per cent.

(d) *Safety test*—For testing each batch, a group of six mice each weighing not less than 18 g. is used. Each mouse is injected subcutaneously with 0.5 ml. of a 1:100 suspension. Alternatively, two guinea pigs each weighing not less than 300g. and two rabbits each weighing not less than 1 kg. are injected with 1 ml. of 1:100 suspension subcutaneously. These animals should not show any untoward reaction during the period of observation for seven days.

(e) *Sterility test*—Should comply with the test for sterility as laid down in the general monograph on 'Viral Vaccines'.

(f) *Potency test*—Healthy highly susceptible cattle (hill bulls) or buffalo calves should not be used for testing the potency of each batch of vaccine in suitable dilution. For each dilution two highly susceptible animals should be used. Each animal is inoculated subcutaneously with 1 ml. of a dilution of the vaccine, followed twenty-one to twenty-eight days after with a standard challenge dose of a virulent rinderpest bull virus contained in I ml. of a 1:100 suspension of spleen tissue. Two unvaccinated bovines, each receiving the same quantity of the challenge virus serve as controls. All these animals are kept under observation for fourteen days. The end point of protective titre is assessed on the death or survival rate and the dose contained in one gramme of vaccine calculated on the basis of forty minimum protective doses being equivalent to one vaccinating dose.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Viral Vaccine'.

6. Storage and Expiry Date—The vaccine shall be expected to retain its potency for the period at temperatures as specified below:

—15°C to —20°C — Six months.

2°C to 4°C. — One months.

SHEEP AND GOAT POX VACCINE (LIVING)

1. Synonym—Sheep Pox vaccine. Goat Pox vaccine.

2. Definition—Sheep and Goat Pox Vaccine consists of the virus contained in the scabs collected from sheep artificially infected with the virus.

3. Preparation—Healthy yearling sheep are infected artificially on the shaved portion of the abdomen with a suitable dilution of the suspension of the stock seed virus 50 per cent glycerine saline solution. The material from the semi-dried areas where the pock lesions are evident is collected and dried over calcium chloride or phosphorous pentoxide under vacuum. Dry scabs are powdered, sieved, ampouled in suitable quantities and sealed.

4. Standards—

(a) *Description*—Light cream coloured powder.

(b) *Identification*—This product when applied to scarified area of the skin of the sheep or goats produces characteristic local lesions of pox and should afford protection to sheep and goat against Sheep and Goat Pox.

(c) *Safety Test*—Two rabbits each weighing not less than 1 kg are injected subcutaneously each with 1 ml. of a 1:100 dilution of the vaccine in normal saline solution. These animals are observed for fourteen days. The animals should remain normal.

(d) *Sterility Test*—Complies with the tests for sterility described under the general monograph on 'Viral Vaccines'.

(e) *Potency Test*—Four yearling sheep are inoculated with 1:100 suspension of the vaccine in 50 per cent glycerine saline on a scarified area on the abdomen. Fourteen days later, these and two more susceptible sheep are inoculated by the same method with stock virus and observed for a period of fourteen days. The control animals should develop typical lesions of pox and the vaccinated animals should remain normal.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Viral Vaccine'.

6. Storage and Expiry Date—The vaccine shall be expected to retain its potency for the period at temperatures as specified below:

—15°C to —20°C — Twenty months.

2°C to 4°C. — Three months.

Room temperature — Fifteen days.

FOWL SPIROCHAETOSIS VACCINE (CHICK EMBRYO ORIGIN)

1. Synonym—Tick Fever Vaccine.

2. Definition—The vaccine consists of a merthiolated suspension of chorioallantoic membrane, internal viscera and blood of chick embryos infected with a vaccine strain of spirochaetes and freeze dried.

3. Preparation—Eleven days old developing chick embryos are infected with 0.2 ml. of sterile fresh blood containing spirochaetes *via* the chorioallantoic membrane. The inoculated embryos are incubated at 37°C and candled daily and the dead ones are discarded. On the seventh day the living embryos are chilled in the refrigerator for two hours. The chilled embryos are harvested separately and necrotic lesions in liver noted. Representative samples of blood should be examined for teaming spirochaetes. The internal vicera, chorio allanotic membranes and the blood are collected. The material is pooled, weighed and held in deep freeze at —15°C to —20°C for period of one week. Thereafter the material is blended with equal quantity of Merthiolate (final concentration of merthiolate in the suspension should be 1:10,000) thoroughly for three times, each time the motor running at full speed and the vaccine is ampouled in 2 ml. quantities and freeze dried.

4. Standards—

(a) *Description*—Light brownish scales.

(b) *Identification*—The vaccine affords protection when inoculated into the fowls against spirochaetosis.

(c) *Moisture content*—The moisture content should not exceed 1.0 per cent.

(d) *Safety and Potency Test*—Six healthy cockerels ten to twelve weeks old are used for this purpose. Each ampoule of vaccine is reconstituted in 10 ml. of cold distilled water and the six cockerels are injected intramuscularly each with 1 ml. of the reconstituted vaccine and the birds are observed for a period of ten days and the vaccinated birds should remain normal throughout the period of observation. The vaccinated birds are challenged with 0.2 ml. intramuscularly with virulent spirochaete blood along with two susceptible controls. Temperature and blood smear examination of the challenged birds and controls should be carried out daily for a period of ten days. The blood smears of vaccinated birds should remain negative for spirochaetes during the entire period of observation. The controls should react and show spirochaetes in the blood.

(e) *Sterility Test*—Complies with the tests for sterility described in the general monograph on 'Bacterial Vaccine'.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Bacterial Vaccine'.

6. Storage— The vaccine when stored at —15°C to —20°C may be expected to retain the potency for about one year and about two months if stored in refrigerator at 2°C to 4°C.

SWINE FEVER VACCINE CRYSTAL VIOLET

1. Synonym—Crystal Violet Swine Fever vaccine, Hog Cholera Vaccine.

2. Definition—Swine fever vaccine, crystal violet is a suspension of blood of swine that have been infected with a suitable virulent anti-genic strain of swine fever virus, inactivated with 0.25 per cent crystal violet ethylene glycol at 37°C for fourteen days.

3. Preparation—Susceptible healthy pigs of six to seven months of age belonging to a well established strain or breed are used. Body weight of these animals of this age may vary according to the breed but optimum weight is

considered as between 75 to 100 kg. Animals used for production may be procured from well established farms and kept under quarantine for fourteen days. These are injected intramuscularly with a suitable dilution of the suspension of the virulent blood viruses. Bleeding of the clinically injected animals is carried out on the sixth day. The defibrinated blood from each animal is strained and stored separately in sterile glass containers. To the four parts of defibrinated bloods, one part of 0.25 per cent crystal violet—ethylene glycol is added and the suspension after thorough mixing, is stored at 37°C (- 0.5) for two weeks. The product is filled in 20 ml. volumes in sterile vials and labelled on the completion of tests.

4. Standards—

(a) *Description*—Very dark violet suspension.

(b) *Identification*—This product affords protection against swine fever but not against African Swine Fever.

(c) *Safety Test*—Two young pigs weighing about 15 to 30 kg. are injected subcutaneously each with 40 ml. of the vaccine batch to be tested. In addition, one unvaccinated susceptible pig is placed in contact.

(d) *Sterility Test*—Should comply with the test for sterility described under the general monograph in 'Viral Vaccines'.

(e) *Abnormal toxicity test*—Two guinea-pigs are given 1 ml. of vaccine intramuscularly.

Two guinea-pigs are given 2 ml. of the vaccine intraperitoneally.

Two mice are given 0.5 ml. of the vaccine subcutaneously.

(f) *Potency Test*—Four susceptible pigs weighing between 20-30 kg. are injected with 5 ml. of the vaccine subcutaneously. After twenty-one days these are challenged with 1ml. of suitable dilution of the challenge virus subcutaneously. The dose must contain at least 1000 minimum infective doses. At least two control pigs should be used.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph on 'Bacterial Vaccine'.

6. Storage. -The vaccine may be expected to retain the potency for twelve months if stored in refrigerator at 2°C to 4°C.

SWINE FEVER VACCINE LAPINISED (LIVING)

1. Synonym—Lapinised swine fever vaccine, freeze dried lapinised swine fever vaccine.

2. Definition.—Swine fever lapinised vaccine consists of the suspension of a modified live swine fever virus prepared from spleens of infected rabbits and is freeze dried.

3. Preparation—Healthy adult rabbits weighing approximately 1000 gms. or over, free from coccidiosis snuffles etc. are injected intravenously with a suitable dose of a dilution of the modified rabbit adapted virus. Rabbits are sacrified at the height of reaction and spleens are collected with sterile precautions. The collection is later homogenised in a blender using ten per cent yolk phosphate buffer as a diluent. The suspension is ampouled in 0.5 ml. quantities and freeze dried.

4. Standards—

(a) *Description*— Light Scales.

(b) *Identification*— This product affords protection against swine fever.

(c) *Moisture content*—The moisture content should not exceed 1.0 per cent.

(d) *Safety Test*—Six mice are injected each with 0.5 ml. of a 1:100 suspension of the vaccine. These are kept under observation for seven days. None should die.

(e) *Viability Test*—Two healthy rabbits are injected intramuscularly with 1 ml. of 1:100 suspension of the vaccine. These animals show thermal reaction.

(f) *Sterility Test*—Should comply with the test for sterility described under general monograph on 'Viral Vaccine'.

(g) *Potency Test*—The vaccine batch under test should be tested on susceptible healthy pigs weighing between 20-30 kg. Two animals for each dilution may be used. The dilutions tested are 1:10,1:15,1:50 and 1:100. One millilitre of each of these dilutions is injected subcutaneously. One healthy, susceptible, unvaccinated in contact animal should be kept along with the vaccinated animals.

Fourteen to twenty-one days later these animals along with two controls are injected subcutaneously with 1ml. of the challenge virus containing at least 1000 minimum infective doses.

5. Labelling—Should comply with the requirements of 'Labelling' as laid down in the general monograph or 'Viral Vaccines'.

6. Storage—The vaccine may be expected to retain its potency for six months if stored at temperature ranging between —10°C to —15°C and for seven days at 2°C to 4°C in the refrigerator.

[1099] *[FOOT AND MOUTH DISEASE VACCINE (INACTIVATED)*

1. Synonym—Inactivated Tissue culture mono or polyvalent Food and Mouth Disease Vaccine.

2. Definition—Foot and Mouth Disease Vaccine is a liquid product or preparation containing one or more types of foot and mouth disease virus which have been inactivated in such a way that its immunogenic property is maintained. It may also contain an adjuvant. The vaccine is described as monovalent, bivalent, trivalent or polyvalent depending on the number of types of virus used.

3. Preparation—The virus is propagated in suitable cell culture. The cell culture is infected with an appropriate inoculum of virus and incubated at a suitable temperature for multiplication of virus. The virus is harvested and cellular debris removed by Alteration. Inactivation is carried out by a suitable agent such as formaldehyde solution or an aziridine compound. The adjuvant may be aluminium hydroxide and/or saponin. In case of inactivated gel vaccine the antigen is concentrated by sedimentation at plus 4 degree C. For preparing a polyvalent vaccine, monovalent antigens are mixed in appropriate quantities to give the final mixture which is the formulated vaccine.

4. Standards—

(a) *Description*— Aluminium hydroxide gel vaccines settle down to variable degree on storage leaving the supernatant clear.

(b) *Identification*—It protects cattle against Food and Mouth Disease due to homologous type/sub-type of virus.

(c) *Sterility test*—It shall comply with the tests for sterility as prescribed under the general monograph of "viral vaccines".

(d) *Safety test*—The test is carried out on fully susceptible cattle not less than 12 months of age and which have not been sensitized either by vaccination or previous infection. Inoculate 3 susceptible cattles each with 2 ml. of finished product at multiple sites on tongue by intradermal route and observe for 4 days. The same animals are inoculated on 4th day with 3 cattle doses subcutaneously and are observed for a further period of 6 days. The animals should not develop any signs of FMD and remain normal.

(e) *Potency test*—Each batch of the vaccine is to be tested in susceptible cattle of not less than 15 months of age. The potency test in cattle can be done either by:

(i) PD_{50} method—The vaccine shall be tested by the determination of PD_{50} in susceptible cattle by challenging animals vaccinated with appropriate dilution of the vaccine made in adjuvanted or non-adjuvanted diluent as appropriate.

A minimum of 5 animals should be used per dilution and 2 unvaccinated animals to be included as controls to the challenge. All animals are needle challenged with 10,000 ID_{50} of the homologous strain of virus by inoculation on the tongue on the 21st day of post-vaccination.

The control animals are to be similarly challenged. Animals are observed for 10 days for the development of lesions. Unprotected animals shows generalised lesions due to FMD. Control animals must show generalised lesions, from the number of animals

protected in each group the PD_{S0} content of the vaccine is calculated. The vaccine passes the test if an observed PD_{50} value of 3 or greater is obtained in the test.

(ii) Percentage protection method in which groups of ten healthy susceptible cattle are each injected subcutaneously with the vaccinating dose and 14— 21 days later the cattle are challenged by intradermal injection into three separate sites on the tongue with 10,000 ID_{50} of the strain of virus used in the preparation of the vaccine. The vaccine can be passed if at least seven out of the ten in the group are protected against the development of generalised infection whereas all the controls should react by developing primary and secondary lesions observable in the mouth and feet.

For other reasons and if cattle testing is not possible then the potency of the vaccine may be assessed in guinea pigs either by Lucam 'C' index or PD_{50} method by challenging those which have been previously vaccinated, provided that a correlation has been established between guinea pig challenge test and cattle challenge results.

The estimation of serum neutralizing antibody titre in cattle may be considered as a supportive test to evaluate potency of vaccine.

However, potency testing of vaccines in cattle, of batches whenever by other accepted methods of testing is in doubt, at least one out of every five batches, be undertaken.

5. Labelling—It is labelled as described under the requirements of 'Labelling' as laid down in the general monograph, with the additional requirements that the label on the container states the virus types used in the preparation.

6. Storage—It should be protected from light and stored between 4°C to 8°C. Under these conditions it may be expected to retain its potency for not less than 12 months. Freezing of aluminium hydroxide vaccine must be avoided. The frozen product will not be fit for use.]

CANINE HEPATITIS VACCINE (LIVING)

1. Synonym—Infectious Canine Hepatitis Vaccine (Living), Canine Hepatitis Cell Culture Vaccine.

2. Definition—Canine Hepatitis Vaccine (Living) as a freeze dried preparation of tissue culture fluid containing the cell culture adopted canine hepatitis virus.

3. Preparation—Canine hepatitis vaccine shall be prepared from virus bearing cell culture fluid.

Only stock seed virus which has been established as pure, safe and immunogenic shall be used in the preparation of the vaccine.

Immunogenicity test—Each lot of stock seed virus shall be tested for immunogenicity as follows:—

Thirteen Canine Hepatitis susceptible dogs, 8-14 weeks old shall be used for the test (10 vaccinates and 3 controls). Blood samples may be drawn from these animals and individual serum samples tested for the presence of antibodies against canine hepatitis virus. Ten dogs shall be injected subcutaneously with predetermined quantity of the virus and remaining 3 dogs are kept as unvaccinated controls. The dose calculation will be based on virus titration in suitable cell culture system. Not less than 14 days post vaccination, the vaccinated and controls shall each be challenged intravenously with virulent infectious canine hepatitis virus and observed daily for 14 days. At least 2 out of 3 controls should die and the survivors shall show the clinical signs of canine hepatitis. Nine out of ten vaccinated dogs shall survive and shall not show any signs of infectious canine hepatitis during the observation period.

The stock seed virus shall be tested once in 5 years and maintained under standard conditions as prescribed.

The stock seed virus may be inoculated on a suitable tissue culture system and may be incubated for five to seven days.

The tissue culture fluid is then harvested and titrated in cell culture system for virus content. After appropriate dilution and pooling, the

material is stored at minus 20°C until freeze dried. Each vaccine dose shall contain not less than $10^{3.5}$ $TCID_{50}$ dose.

4. Standards—

(a) *Description*—The dried product is a pinkish cream material readily dispersible in water. The reconstituted vaccine is a pinkish liquid.

(b) *Identification*—It causes characteristic cytopathic effect in dog, pig and ferret kidney monolayers. This can be neutralised by specific antiserum. When inoculated into dogs, the development of specific neutralizing antibodies can be demonstrated by suitable serological tests.

(c) *Moisture content*—In the finished product moisture content shall not exceed 1.0 per cent.

(d) *Sterility test*—Shall comply with the tests for sterility as described under the general monograph on "Viral Vaccines".

(e) *Safety test*—

Mouse safety test—Vaccine prepared for use as recommended on the label shall be tested. Eight mice shall be inoculated intracerebrally with 0.3 ml. and 8 mice shall be inoculated intiaperitoneally with 0.5 ml. Both the groups shall be observed for seven days. If unfavourable reaction attributable to the product occurs in two or more mice in either group during their observation period, the batch is unsatisfactory.

Dog Safety test—Each of the two susceptible pups aged 8-14 weeks shall be injected with vaccine equivalent of 10 vaccinating doses from the batch reconstituted with sterile diluent and administered in the manner recommended on the label and observed for 21 days. None of the pups shall show any unfavourable reaction during the period of observation.

(f) *Potency test, Virus Titration*—Samples of finished product shall be tested for virus titre in suitable cell culture system. The batch shall have a virus titre of not less than $10^{3.5}$ $TCID_{50}$ dose.

Potency test in dogs—Two healthy susceptible dogs of 8-14 weeks of age shall be injected subcutaneously with one Vaccine dose. 14 days after vaccination, specific neutralizing antibodies from both the dogs shall be demonstrable by serological tests.

5. Labelling-—Shall comply with the requirements for labelling as laid down in the general monograph on "Viral vaccines."

6. Storage—The dry product shall be stored at temperature of minus 20°C or below. The vaccine is expected to retain its potency for about 6 months in freezing chamber of the refrigerator (temperature) approximately minus 8°C.

DUCK PLAGUE VACCINE

1. Definition—Duck plague vaccine is a suspension of modified living virus prepared from infected chick embryos.

2. Preparation—Fresh fertile hen's eggs obtained from Salmonella free flocks are incubated in an Incubator. Nine days old embryos are injected with 0.2 ml. of the suitable dilution (1 in 100) of the suspension of the virus on the CAM and incubated at 37°C for 5 days post-inoculation. Dead embryos of the 3rd, 4th and 5th days post-inoculation are harvested. The embryos (devoid of head and legs), clear fluid and the membranes are collected and homogenised in a Blender, ampouled in 0.5 ml. quantities and freeze dried.

3. Standards—

(a) *Description*—Light brown scales.

(b) *Identification*—This product affords protection to the ducks against duck plague.

(c) *Safety test*—Four healthy, 8 to 12 weeks old ducks weighing not less than 600 gms. are inoculated subcutaneously with 1ml. of 10^{-1} dilution of the vaccine and observed for a period of 14 days. During the period of observation, the ducks shall not show any untoward reaction.

(d) *Sterility test*—Shall comply with the test for sterility described in the general monograph on "Viral Vaccines".

(e) *Potency test*—Six susceptible ducks 8 to 12 weeks old each weighing not less than 600 gms. are inoculated subcutaneously with 1 ml. of 10^{-3} dilution of the vaccine. The minimum virus contents in 1 ml. dose of the vaccine shall be $10^{3.5}$ EID_{50}. 14 days later these ducks are challenged subcutaneously each with 1 ml. of 10^{-2} dilution of the virulent duck plague virus (1000 $DEID_{50}$) alongwith 2 unprotected young ducks of about 8-12 weeks age. The unprotected ducks shall show symptoms of duck plague and die within 10 days. While the protected ducks shall remain normal during the observation period of 14 days.

4. Labelling—Should comply with the requirements of labelling as laid down in general monograph on "Viral Vaccines".

5. Storage—Vaccine when stored at minus 15°C to minus 20°C may be expected to retain its potency for one year and about three months if stored in the freezing chamber of Refrigerator, i.e. its, minus 5°C.

AVIAN ENCEPHALOMYELITIS VACCINE (LIVING)

1. Synonyms—Avian Encephalomyelitis Vaccine Freeze dried.

2. Definition—A virus bearing tissue and fluid suspension from embryonated hen's eggs-

3. Preparation—The stock seed virus which has been established as pure, safe and immunogenic shall be used for preparing the vaccine.

(i) Each lot of stock seed virus shall be tested for pathogenicity by chicken embryo inoculation test:

(a) One dose of the seed lot shall be mixed with 9 volumes of sterile heat inactivated specific, antiserum to neutralise vaccine virus in the product.

(b) After neutralization, 0.2 ml. of serum vaccine mixture shall be inoculated into each of at least 20 fully susceptible chicken embryos (0.1 ml. of the inculum shall be inoculated on CAM of 9-11 days old embryos and 0.1 ml. in the allantoic sac.)

(c) Eggs shall be candled for 7 days. Deaths occurring during first 24 hours shall be discarded but at least 18 viable embryos shall survive 24 hours post inoculation for a valid test. All embryos and CAMs from embryos which die after the first day shall be examined.

(d) If the death or abnormality attributable to the inoculum occur, the seed lot is unsatisfactory.

(ii) *Immunogenicity test*—Avian encephalomyelitis susceptible chicks, all of same age (8 weeks old) shall be used. Twenty chickens shall be inoculated with the field dose of the virus by prescribed route. Ten additional chickens of same age and flock shall be held as unvaccinated controls.

At least 21 days post vaccination, the controls and vaccinates shall be challenged intracerebrally with Virulent avian encephalomyelitis virus, and observed each for 21 days. At least 80 per cent of controls shall show signs of avian encephalomyelitis or die. At least 19 to 20 vaccinates shall remain free from clinical avian encephalomyelitis during the observation period for the stock seed virus to be satisfactory.

4. Standards—

(a) *Description*—Greyish white flakes easily dispersible in the diluent.

(b) *Identification*—At least 5-6 days old embryonated eggs (from hens with no history of infection with avian encephalomyelitis) shall be inoculated with 0.1 ml of undiluted vaccine into the yolk sac and kept in incubator and then transferred to the brooder where they are allowed to hatch. The hatched chicks shall be raised for 7 days. More than 5 per cent of hatched chicks shall manifest the typical symptoms (weak-leg, leg paralysis tremor etc.) at the end of this period.

(c) *Moisture content*—Shall not exceed 1.0 per cent.

(d) *Sterility test*—Shall comply with the test for sterility described under general monograph on "Viral Vaccines".

(e) *Safety test*—At least 25 avian encephalomyelitis susceptible birds (6-10 weeks of age) shall be vaccinated with 10 field doses by the recommended route and observed each day for 21 days. If unfavourable

reactions attributable to the vaccine occur during the observation period, the batch of vaccine is unsatisfactory.

(f) *Potency Test*—

(i) The vaccine shall be titrated for virus content. To be eligible for release, the batch shall have a virus titre of at least $10^{2.5}$ EID_{50} per dose.

(ii) At least 10 susceptible chickens shall be vaccinated with the field dose of the vaccine by prescribed route and 10 chickens from same batch and source shall be kept as unvaccinated controls.

At least 21 days post-vaccination, both the groups shall be challenged intracerebrally with Virulent avian encephalomyelitis virus and observed for 21 days. At least 8 out of 10 controls shall develop recognisable signs or lesions of avian encephalomyelitis and at least 8 out of 10 vaccinates should remain normal.

5. Labelling—Shall comply with the requirement of labelling as laid down in general monograph of "Viral Vaccines".

MAREK'S DISEASE VACCINE (LIVING)

1. Synonyms— Herpes virus of Turkey vaccine HVT vaccine (Living).

2. Definition—Marek's disease vaccine is a suspension of cell free fluid containing live virus.

3. Preparation—The stock seed virus which has been established as pure, safe and immunogenic in avian species shall be used for preparing the seed virus for vaccine production.

(i) *Safety Test*—The stock seed virus shall be non-pathogenic for chickens as determined by the following procedure:

The groups of at least 25 chickens each at one day of age shall be used. These chickens shall be of the same source and batch, be susceptible to Marek' disease and be kept in isolated group.

Group I: Each Chicken shall be injected with 0.2 ml. of 10 times as much viable virus as will be contained in one dose of vaccine by intramuscular route.

Group II : Shall serve as controls. At least 20 chickens in each group shall survive for four days post injection. All chicken that die shall be necropsied and examined for lesions of Marek's disease and cause of death . The test shall be judged according to the following:—

At 120 days of age, the remaining chicken in both the groups shall be weighed, killed and necropsied. If at least 15 chickens in each of these two groups have not survived the 120 days period or if any of the chickens of Group-I have gross lesions of Marek's disease at necropsy or if the average body weight of the chickens in Group I is significantly (Statistically) different from the average of Group-II at the end of 120 days, the lot of stock seed virus is unsatisfactory.

(ii) *Purity test*—Shall be conducted in chickens and no lesions other than those typical of Turkey Herpes virus shall be evidenced.

(iii) *Immunogenicity test*—Sixty susceptible day old chicks are used. Thirty of them inoculated with the seed virus in a dose corresponding to the field dose of the final vaccine and 14-21 days later challenged by intrabdominal route with virulent Marek's disease virus, with the other 30 non-vaccinated control chicks. At the end of the observation period when the chicks are 20 weeks old, the surviving chickens are examined for the presence of antibody against Marek's disease by serological tests and post-mortem inspection for lesions of Marek's disease.

Any bird dead is thoroughly examined and the cause of death ascertained by necropsy/histopathological examination. All the surviving birds are killed and necropsied. The protection index (PI) is determined by following procedure:

1. Per cent. MD = $\frac{\text{No. with MD lesions}}{\text{}}$

No. with MD lesions + No. of -ve Survivours (effective No.)

2. P.I. = Per cent. MD in controls- Per cent. MD in vaccinated x100

Per cent. MD in controls

Master seed virus should have P.I. of the least 80 per cent.

Eighty per cent of the chicks in the control group must fall ill specifically. If more than 80 per cent of the vaccinated chickens do not show symptoms or signs of Marek's disease, the seed virus is regarded as sufficiently effective and can be used for production of vaccine.

The seed virus is propagated in duck embryo fibro-blast cell culture, chick embryo fibroblast or any other suitable cell culture (specific pathogen free SPF flock) and when the peak passage level is attained the cell monolayer is suspended in cold diluent of the following composition.

SPGA Stabilizer
0.218 % sucrose
0.0038 % monosodium phosphate
0.0072 % dipotassium phosphate
L Monosodium glutanate 0.0049 M
1 per cent bovine albumin Fraction (V)

0.25 per cent EDTA (Sterilised by Sitz filteration and stored at minus 10°C). The virus is freed from cells by ultrasonication for 3 minutes interrupted after every 30 seconds) at 100 MA and freeze dried at minus 60°C preferably in shelf freeze dried in convenient volumes. The doses per ampoule vial is calculated after titrating the freeze dried product in terms of plaque forming units (PFU) in the corresponding cell monolayers.

4. Standards—

(a) *Description*—The cell free freeze dried HVT vaccine looks uniformly greyish in colour and easily dispersible in the specified diluent.

(b) *Identification*—The vaccine on inoculation in suitable cell culture system shall cause cytopathic effect typical of Herpes virus of Turkey.

Specific antiserum of Herpes virus of Turkey shall neutralize the cytopathic effect.

(c) *Moisture content*—Moisture content shall not exceed one per cent.

(d) *Sterility test*—Shall comply with the test prescribed in general monograph on "Viral Vaccines".

(e) *Safety test*—At least 25 one day old chickens shall be injected with ten times of the field dose of vaccine by intramuscular route. The chickens shall be observed each day for 21 days. Chickens dying during the period shall be examined, cause of death determined and the results recorded as follows:—

(i) If at least 20 chickens do not survive the observation period, the test is inconclusive.

(ii) If lesions of any disease or cause of death are directly attributable to the vaccine the vaccine is unsatisfactory.

(f) Potency *test*—The sample shall be titrated in the cell culture system. A satisfactory batch shall contain at least 1500 plaque forming units (PFU) per dose at the time of release and maintain at least 1000 PFU till the end of expiry period.

5. Labelling—Shall comply with the requirement of labelling as laid down in general monograph of "Viral Vaccines".

6. Storage and expiry date—The freeze dried call free HVT vaccine may be stored at 4°C for 6 months.

GOAT POX VACCINE (LIVING CELL CULTURE)

1. Synonym— Goat Pox Vaccine (living), attenuated goat pox vaccine.

2. Definition—Goat Pox vaccine is freeze dried preparation, prepared by growing attenuated goat pox virus in kid kidney/testicular cell culture.

3. Preparation.—Primary kidney/testicular cell cultures of disease free kid are used. The monolayers infected with the seed virus are incubated at 37°C.

The cultures are harvested by three cycles of freezing the thawings 6 to 7 days post infection when more than 80 per cent cells show CPE. The suspension is centrifuged at 1000 rpm for 10 minutes to remove cellular debris being stored at minus 20°C. The suspension is freeze dried after addition of 5 per cent Lactalbumin hydrolysate and 10 per cent sucrose.

4. Standards—

(a) *Description*—Light yellow colour.

(b) *Identification*—The product affords protection to goat against goat pox.

(c) *Moisture content*—The moisture content shall not exceed 1.0 per cent.

(d) *Safety tests*—

(i) *Laboratory animals*—Six mice, 3 guinea pigs and 3 rabbits are inoculated with 0.2 ml. intraperitoneally, 0.5 ml. and 1.0 ml. subcutaneously, respectively with 10 field doses of the vaccine. The inoculated animals during the observation period of 80 days shall remain normal.

(ii) *Goat*—Two susceptible goats of 6 to 8 months of age are inoculated in postauxiliary region by subcutaneous route with one hundred field dose of the vaccine. The inoculated animals shall not develop more than a local reaction 2 to 3 cms. These animals shall be observed for 10 days.

(e) *Sterility test*—Shall comply with the test for sterility described under the general monograph on "Viral Vaccine".

(f) *Titration in cell culture*—Four randomly selected samples are inoculated in kid kidney cell cultures using 5 tubes for each dilution. The titration shall be repeated thrice. One thousand $TC1D_{50}$ is used as a field dose.

(g) *Potency Test*—The three susceptible goats (8-10 months) are inoculated with 1/ 10th field dose and 3 susceptible goats (8-10 months) with one field dose, subcutaneously. Three in

contact controls are also kept with the inoculated goats. Three animals are observed for a period of 14 days and their body temperature recorded daily. The vaccinated animals shall not show any thermal, local or generalised reaction. Twenty one days post-infection, the vaccinated and controls are challenged with 10,000 $TCID_{50}$ of virulent goat pox virus by intradermal route. The temperature of these goats are recorded for a period of 14 days. The vaccinated goats shall not develop localised or generalised reaction while control goats shall develop high fever, localised reaction or even generalised reaction in some cases.

5. Labelling—Shall comply with the requirement of labelling as laid down in general monograph of "Viral Vaccines".

6. Storage and expiry date—The vaccine is expected to retain its potency for 12 months if stored at minus 15°C to minus 20°C and for three months at 2°C to 4°C.

SHEEP POX VACCINE (INACTIVATED)

1. Synonym— Formal gel sheep pox vaccine.

2. Definition—Sheep pox vaccine is a formaline inactivated gel treated tissue vaccine.

3. Preparation.—Healthy susceptible sheep of 8-12 months of age are inoculated subcutaneously with 500 ml. of the 1:100 dilution of the Russian Virulent Sheep Pox Virus. Seven to eight day post inoculation skin of the abdomen alongwith the oedema is collected. The infected tissues are homogenised in 10 per cent concentration in phosphate buffer (ph 7.4-7.6) which after the extraction of the virus in mixed with sterile gel and buffer in following proportion:—

6 per cent aluminium hydroxide gel—50 per cent.

Phosphate Buffer (pH 7.6)—35 per cent.

10 per cent suspension—15 per cent.

This is later formalised and kept at 20-25°C/10°C for varying periods.

4. Standards—

(a) *Description*—It is a greyish white suspension. During storage the gel settles at the bottom, upper layer of the suspension is clear.

(b) *Identification*—The product affords protection to sheep against sheep pox.

(c) *Safety test*—This is carried out by inoculating 2 white mice with 0.2 ml., one guinea pig with 1.0 ml and one rabbit with 3.0 ml. of vaccine. The animals should remain clinically healthy for 10 days.

(d) *Sterility test*—This is done by seeding the vaccine on usual bacterial media. The plates and tubes are incubated for 10 days at 37°C. If the pathogenic bacteria are found, the vaccine is rejected while with non-pathogenic bacteria the vaccine is passed for field use.

(e) *Potency test*—This is done by inoculating 4 non-immune susceptible sheep preferably exotic breed of 1-2 years with 3 ml. of vaccine in the thigh, subcutaneously.

The vaccinated sheep are challenged 15 days after inoculation alongwith 3 controls each with 0.1 ml. of virulent virus containing 200 infective doses intradermally under the tail. The sheep are observed for 10 days and their skin reaction recorded. The vaccine is considered potent if all the vaccinated, sheep do not show thermal or local skin reaction. Vaccine is also potent if 3 vaccinated animals do not develop any reaction and one shows abortive skin reaction, while at least 2 of the 3 controls develop typical sheep pox reaction at the site of inoculation.

5. labelling—Shall comply with the requirement of labelling as laid down in general moncgraph of "Viral Vaccines".

6. Storage —The vaccine shall be stored at 4°C to 5°C. It keeps well at above temperature upto 12 months.

SHEEP POX VACCINE (LIVING CELL CULTURE)

1. Synonym— Sheep Pox vaccine (Living), attenuated sheep pox vaccine.

2. Definition—Sheep pox vaccine is freeze dried preparation prepared by growing attenuated sheep pox virus is lamb kidney/testicular cell cultures.

3. Preparation—Primary cell cultures prepared from kidney/testicles of disease free lambs are used. The mono layers infected with the seed virus are incubated at 37°C. The cultures are harvested by 3 cycles of freezing and thawing 6 to 7 days post infection when more than 80 per cent cells show C.P.E. The suspension is centrifuged at 1000 r.p.m. for 10 minutes to remove cellular debris before being stored at minus 20°C. The suspension is freeze dried after addition of 5 per cent Lactalbumin hydrolysate and 10 per cent sucrose.

4. Standards—

(a) *Description*—Light yellow colour.

(b) *Identification*—The product affords protection to sheep against sheep pox.

(c) *Moisture contents*—The moisture contents should not exceed 1.00 per cent.

(d) *Safety test:*—

(i) Six mice, 3 guinea pigs and 3 rabbits are inoculated with 0.2 ml. intraperitoneally 0.5 ml. and 1.0 ml. subcutaneously, respectively containing 10 field doses of the vaccine. The inoculated animals during the observation period of 10 days should remain normal.

(ii) One hundred field doses of the vaccine are inoculated subcutaneously into each of 2 susceptible sheep in postaxillary region. Inoculated animals shall not develop more than a local reaction of 2 to 3 cms.

(e) *Sterility test*—Shall comply with the test for sterility as described under the general monograph on 'Viral Vaccines".

(f) *Titration in cell culture.*—Four randomly selected samples reconstituted in a maintenance medium are inoculated in lamb kidney cell cultures using 5 tubes for each dilution. The titrations shall be repeated

thrice. The $TCID_{50}$ to be calculated by Reed and Muench Method. One thousand $TCID_{50}$ is calculated as one field dose.

(g) *Potency test*—Three susceptible sheep 8-10 months old are inoculated with 1/10th, field dose and 3 susceptible sheep with one field dose, subcutaneously. Three in contact controls are also kept with the inoculated sheep. These animals are observed for a period of 14 days and their temperature is recorded daily. The vaccinated animals should not show any thermal; local or generalized reactions. Twenty one days post-infection the vaccinated and controls are challenged with 10,000 ID_{50} of virulent sheep pox virus by intradermal route. The temperature of these sheep are recorded for a period of 14 days. The vaccinated sheep should not develop localised or generalised reaction while control sheep should develop high fever, localised reaction or even generalised reaction in some cases.

5. Labelling—Shall comply with the requirement of labelling as laid down in general monograph of "Viral Vaccines".

6. Storage and expiry date—The vaccine is expected to retain its potency for 12 months if stored at minus 15°C to minus 20°C and for three months at 2°C to 4°C.

TISSUE CULTURE RINDERPEST VACCINE

1. Synonym— Cell Culture Rinderpest Vaccine.

2. Definition—Tissue Culture Rinderpest Vaccine is a freeze dried preparation of live modified rinderpest virus adapted to and propagated in cell culture.

3. Preparations—Primary or secondary monolayer cultures of the kidney cells (Bovine or any other suitable animals) taken from kidney from healthy animals free from any pathological changes shall be used. When secondary cultures are used they shall have retained their original morphology and Karyotype. Kabete 'O' strain of Rinderpest virus developed by East African Veterinary Research Organisation (Plowrights strain between the passage levels of 99th and 100th passages) shall be used. The virus harvested from cell monolayer culture prepared from the kidneys of a single calf or serially

cultivated bovine kidney cells (Not more than 10 passages away from the Primary) inoculated with the same seed and harvested together, will be freeze dried with stabilisers in suitable quantities.

4. Standards—It complies with the requirements of general standards of viral vaccine:

(a) *Description*—Dry light yellow coloured flakes readily soluble in chilled saline or buffered saline.

(b) *Identifications*—(i) Protects cattle against a subsequent challenge with virulent or caprinised rinderpest virus.

(ii) It is titrable in tissue culture systems capable of supporting the multiplication of this virus. The test shall be made on at least three separate occasions using a cell culture derived from different animals.

(iii) Specificity test shall be performed using an appropriate serum neutralisation test.

(c)Sterility *test*—Each batch shall be tested for bacterial and mycotic sterility as given in the general monograph on "Viral Vaccines".

(d) Innocuity *test*—Shall be made on each batch in at least two guinea pigs and six mice. These animals shall be observed for atleast two weeks for any untoward reaction.

(e)*Safety and efficacy test*—The test for safety and efficacy shall be performed using the pooled reconstituted contents of not less than 4 ampoules taken at random. The vaccine shall be injected subcutaneously into each of at least two susceptible cattle free from specific antibodies using the quantity containing not less than 100 field doses and two further cattle and using l/10th of a field dose (calculated on the basis of 1000 $TCID_{50}$ as one field dose). The animals shall be housed with at least two unvaccinated animals and observed for a period of three weeks. The vaccine passes the safety test if the cattle show no signs of unusual clinical reactions.

At the end of three weeks all the four animals will be challenged alongwith two incontact cattle with a challenge dose of not less than 10^4 $ACID_{50}$ of virulent Rinderpest virus. The vaccine passes the potency/efficacy test if the in contact animals develop rinderpest and all the vaccinated animals remains normal.

5. Labelling—Shall comply with general monograph on "Viral Vaccines". Each ampoule or at least 50 per cent ampoules in a lot shall contain at least following print:

(i) TCRP Vaccine.
(ii) Batch No. with year
(iii) General instructions for use.

6. Storage—The vaccine when stored at minus 20°C and plus 4°C will maintain its titre for 2 years and 6 months respectively.

CANINE DISTEMPER VACCINE

1. Synonym—Canine Distemper Vaccine (Living)—Freeze dried.

2. Definition—It is freeze dried preparation of either tissues from chick embryo containing egg adapted strain of canine distemper virus or the cell culture in which modified virus has been cultivated.

3. Preparation—Canine distemper vaccine shall be prepared from virus bearing cell culture, fluid or infected chorioallantoic membrane. Only stock seed virus which has been established as pure, safe and immunogenic shall be used for the preparation of vaccine Stock seed virus propagated in chicken embryo shall be tested for pathogen by chicken embryo test. One volume of the virus shall be mixed with 9 volumes of specific sterile heat inactivated serum to neutralise the virus. Mixture shall be inoculated into twenty (9 to 11 days old) chicken embryo (with 0.1 ml. on CAM and 0.1 ml in alantoic sac). Embryonated eggs shall be candled for 7 days daily. Deaths occurring in the first 24 hours shall be discarded. CAMS of embryos which die after 24 hours shall be examined. When necessary embryo sub-culture shall be made to determine the cause of death. The test should be concluded on the 7th day cost inoculation.

The surviving embryos and their CAMS are examined. If deaths or abnormality due to the inoculum occur, the seed virus is unsatisfactory.

Immunogenicity test—Thirteen susceptible dogs 8-14 weeks old, shall be used for the test (ten vaccinates and 3 controls). Blood samples are drawn from these animals and individual sample is tested for antibodies against canine distemper. The dogs shall be injected with a predetermined quantity of the virus and remaining 3 dogs are used as unvaccinated controls. The dose shall be based on the virus titration. At least 21 days post infection the vaccinated and controls shall be challenged intramuscularly with the same dose of virulent canine distemper virus and the animals observed each day for 21 days. At least 2 out of 3 controls should die and survivor should show the symptoms typical of canine distemper. At least 9 out of 10 vaccinated animals should survive and should not show any clinical signs of canine distemper during the observation period. The stock seed virus should be tested for immunogenicity at least once in 5 years, if maintained under suitable conditions of storage. Eight days old chicken embryos from a healthy flock are inoculated on their chorioallantoic membrane with bacteriologically sterile virus suspension of egg adapted strain. After incubation for a period of five days, infected membrane and embryos are harvested. The individual embryo is tested for bacterial sterility. Those free from bacterial contamination are made into a 20 per cent suspension in a suitable medium. The suspension is distributed in a single dose quantity into the ampoules or vials and freeze dried.

The ampoules are sealed under vacuum or with pure dry sterile nitrogen before sealing. Alternatively, the virus may be grown on the suitable cell culture. Cells along with the suspending fluid is harvested, distributed in single dose quantity in ampoules and freeze dried.

4. Standards—

(a) *Description*—It is a dry product, pinkish cream material, readily dispersible in water or a suitable solvent.

(b) *Identification*—It infects CAM of fertile eggs. This is neutralised by canine distemper antiserum. It does not cause distemper after injection into susceptible ferrets or dogs but immunizes them against the disease.

(c) *Moisture content*—Moisture content in the finished product shall not exceed more than 1.0 per cent.

(d) *Sterility test*—Shall comply with the test for sterility as described in the general monograph on "Viral Vaccines".

(e) *Safety test*—(i) Mice safety test : Reconstituted vaccine as recommended on the label shall be tested.

Eight mice, 4 weeks old shall be inoculated intracerebrally with 0.03 ml. and 8 mice shall be inoculated intraperitoneally with 0.5 ml. Both groups shall be observed for 7 days, if unfavourable reaction attributable to the product in either 2 or more mice in either group is observed during observation period, the batch is unsatisfactory.

(ii) *Dog Safety test*—Inject two healthy dogs, eight to fourteen weeks old that have previously been shown to be free from distemper virus-neutralising antibodies by the recommended route with twice the dose stated on the label and observe for 21 days. No significant local or general reaction develops.

(i) *Potency test*— (i) Titration : Final samples of finished product shall be tested for virus titre, and when tested at any time within the expiry period, it should contain not less than 10^3 ID_{50} per dose.

(ii) It shall be carried out in dogs. Two healthy susceptible dogs each of 8-14 weeks of age free from distemper neutralising antibodies are injected subcutaneously each with one vaccinating dose. Serum samples shall be collected from each dog 14 days after vaccination and these shall have specific neutralizing antibodies at a dilution of 1:100.

5. Labelling—Shall comply with the requirements of labelling as laid down in the general monograph on "Viral Vaccines".

6. Storage and expiry date—For the freeze dried product the expiry date is one year when stored at minus 20°C.

AVIAN INFECTIOUS BRONCHITIS VACCINE (LIVING)

1. Synonym—Avian Infectious Bronchitis Vaccine (Living) freeze dried.

2. Definition—It is freeze dried product of low viruent Avian Infectious Bronchitis Virus grown in embryonated hen's eggs of cultivated in cell culture.

3. Preparation—Only stock seed virus which has been established as pure, safe and immunogenic shall be used. Each lot of stock seed virus shall be tested for other pathogens by chicken embryo inoculation tests as follows:—

A lot of seed virus shall be mixed with 9 volumes of sterile, heat-inactivated specific antiserum to neutralise and the vaccine virus serum mixture shall be inoculated into each of at least 20 fully susceptible chicken embryos of 9-11 days old (0.1 ml. on CAM and 0.1 ml. in the allantoic sac). Eggs are candled daily for 7 days. Death occurring during first 24 hours shall be discarded but at least 18 viable embryos shall survive 24 hours post inoculation for a valid test. All embryo and CAMS from embryos shall be examined which die after 24 hours. If necessary embryo subcultures shall be made to determine the cause of death. The test shall be concluded on the 7th day post inoculation and surviving embryos including the CAM shall be examined. If death or abnormality to the stock seed virus occur, the seed lot is unsatisfactory.

Each lot of stock seed virus shall be tested for immunogenicity as below:—

Bronchitis susceptible chickens of the same age and source shall be used. For each method of administration recommended on the label and for each serotype against which protection is claimed, 20 chicks shall be used as vaccinates. Ten additional chickens for each serotype against which protection is claimed shall be held as unvaccinated controls. 21 to 28 days post vaccination all vaccinates and controls shall be challenged by eye drops with virulent Bronchitis virus. A separate set of vaccinates and controls shall be used for each serotype against which protection is claimed. The challenge virus shall have a titre of at least $10^{4.6}$ EID_{50} per ml. Trachea swabs shall be taken once 5 days post challenge from each vaccinates and controls. Each swab shall be placed in test tube containing 3 ml. of tryptose phosphate broth and antibiotics. The tubes and swabs shall be swirled thoroughly and stored at minus 40°C pending egg inoculation. For each chicken swabs at least 5 chicken embryos, 9-11 days old shall be inoculated in the allantoic cavity with 0.2 ml. of broth from each tube. All the embroys surviving 3rd day post inoculation shall be used in evaluation. A tracheal swab shall be positive for virus recovery when any of the embryos

show typical infectious bronchitis virus lesions such as stunting, curling, kidney urates, clubbed down or death during 4-7 days post inoculation period.

Ninety per cent of the controls should prove positive for virus recovery. If less than 90 per cent of the controls are negative for virus recovery, the stock seed is unsatisfactory. The stock seed virus should be tested for immunogenicity once in 5 years provided it is maintained under standard conditions of the bronchitis virus storage.

4. Standards—

(a) *Description*— It is greyish-white product easily dispersible in the diluent.

(b) *Identification*—

(i) The contents of the ampoule are suspended as per the instructions for the field use. The 0.2 ml. of the suspension shall be inoculated in the allantoic cavity of 9-11 days old chicken embryo and are incubated for 7 days. The leisons typical of infectious bronchitis shall be observed in the embryos at the end of incubation period. The allantoic fluid shall not agglutinate the chicken RBC's.

(ii) Specific antisera against avian infectious bronchitis virus should neutralise the vaccine virus.

(c) *Moisture content*—Moisture content in the finished product should not exceed 1.0 per cent.

(d) *Sterility test*—Complies with the test for sterility as described under the general monograph on "Viral Vaccines".

(e) *Safety test*—Ten healthy susceptible chickens 5-10 days old from the same source, batch shall be vaccinated with ten field doses of the vaccine and alongwith five chicks from same batch as unvaccinated controls by the prescribed route and observed 7 or 21 days post vaccination. Neither severe respiratory symptoms nor death shall occur to more than one experimental chicks. None of the unvaccinated control shall show any clinical symptoms.

(f) *Potency test*—The minimum virus content of the freeze dried product shall be not less than 103.5 EID 50 per bird. The virus content of the vaccine shall be titrated as below:—

Serial ten fold dilution of the freeze dried material will be made in typetose phosphate broth. Three to five embryonated eggs (9-11 days old) shall be inoculated with 0.1 ml. of each dilution into the allantoic cavity and observed daily for 7 days.

Deaths occurring during the first 24 hours shall be discarded. The surviving embryos are examined for the evidence of infection and EID50 shall be calculated by the Reed and Muench Method/Spearman and Karber method.

5. Labelling—Shall comply with the requirements of labelling as laid down in the general monograph on "Viral Vaccines".

6. Storage and expiry date—Can be stored at 4°C for six months.]

PART II

ANTISERA

PROVISIONS APPLICABLE TO THE PRODUCTION OF ALL SERA FROM LIVING ANIMALS

1. Definitions—(i) This part of the Schedule applies to anti-bacterial sera, antiviral sera and anti-toxic sera which are prepared by injecting bacteria or viruses or their products into buffalo-bulls or other suitable animals so as to produce active immunity which is manifested by the formation of anti-body.

(ii) For the purpose of this part of the Schedule an antiserum means sterile liquid antiserum concentrated and unconcentrated, solutions of globulins or their derivatives or solid forms which can be reconstituted when necessary.

2. Staff of Establishment—The establishment shall be under the direction and control of a competent expert in bacteriology and serology with adequate training in immunology and standardisation of biological products and knowledge of animal management. He shall be assisted by a staff adequate for

carrying out the tests required during the course of preparation of the sera and standardisation of the finished products.

3. Proper Name—The proper name of the antiserum shall be the recognised scientific name of the disease or its causative organism or some generally recognised abbreviations thereof preceded by the prefix 'anti', and followed by the word 'serum' as for example, 'Anti-anthrax serum'. The proper name of any antitoxin may be formed from the word 'Anti-toxin' preceded by the name of the organism from which the toxin was prepared, and followed, if desired, by a term indicating the source of the strain of that organism provided where there is no special provision in the Schedule, the name as approved by the licensing authority may be adopted.

4. Records—(1) The permanent records which the licensee is required to keep shall include the following particulars:—

(a) As to the cultures—Evidence of the identity and specificity of the cultures.

(b) As to the procedure used in immunising the animals:

(i) The method of preparing the cultures or antigen used for immunisation.

(ii) The dosage and methods employed in administering the culture or antigen.

(iii) The period in the course of immunisation at which blood is withdrawn for the preparation of the serum.

(c) Any test which may have been applied to the serum to determine its content of specific antibodies or its specific therapeutic potency and purity.

(2) If the licensee desired to treat the performance of any tests recorded under sub-paragraph (i)(c) of this paragraph as determining the date of completion of manufacture for the purpose of Rule 109 he shall submit full particulars of the proposed test to the licensing authority and obtain his approval.

5. Cultures—The cultures used in immunising the animals shall be at all times open to inspection, and specimens shall be furnished for examination at the request of the licensing authority.

6. Quantity—(a) Any antiserum shall be issued for veterinary use in the form of either—

(i) Actual serum, *i.e.*, the liquid product of decantation of the coagulated blood or plasma without any addition, other than antiseptic or subtraction, or

(ii) A solution of the purified serum proteins containing the specific antibodies.

(b) At the time of issue, the liquid shall be clear or show at the most a slight opalescence or precipitate. Preparations of the natural serum shall not contain more than 10 per cent of solid matter. A solution of serum protein shall not contain more than 20 per cent of solid matter.

7. Precautions to be observed in preparation.—(i) Laboratories where sera are exposed to the air in the course of the process of preparation must be separated by a sufficient distance from stables and animal houses to avoid the risk of aerial contamination with bacteria from animal excreta, and must be rendered fly-proof to prevent such contamination by insects. Such laboratories must have impervious walls and floors and must capable of being readily disinfected when necessary.

(ii) A special room with impervious walls must be provided for the collection of blood from the living animals.

(iii) An efficient system of manure removal must be used which will prevent its accumulation in the vicinity of any room where blood or serum is collected or handled.

(iv) An adequate number of sterilizers must be provided for the sterilization of all glassware or other apparatus with which the serum may come into contact in the course of its preparation.

(v) All processes to which the serum is subjected during and after the collection from the animals, must be designed to preserve its sterility, but in the case of an artificially concentrated sera it shall suffice that the process of concentration is conducted with scrupulous cleanliness and in such a manner as to avoid unnecessary dangerous contamination.

(vi) The laboratories in which the testing of sera for potency, sterility and freedom from abnormal toxicity are carried out must be adequate for the purpose. An adequate supply of animals for use in such tests and suitable housing for such animals must be provided.

(vii) Provision must be made for complying with any special conditions which may be laid down in the Schedule relating to the production and issue of the particular serum, in respect of which the licence is granted.

8. Unhealthy or Infected Animals—If an animal used in the production of sera is found to be suffering from an infection except one produced by living organisms against which it is being immunized, or shows sign of serious or persistent ill health not reasonably attributable to the process of immunisation, the licensee shall immediately report the matter to the licensing authority and shall, if the authority orders an inspection and the Inspector so directs, cause such animal to be killed and a post mortem examination of it to be made, and take steps to prevent any serum obtained from the animal being sold or offered for sale until permission is given by the licensing authority. If the result of the post-mortem is such as to bring under suspicion, the health of any of the other animals used for the production of sera, the licensing authority may prohibit the use of those animals for the production of sera or may take such other steps as may be necessary to prevent the issue of sera which may be dangerous to animal health:

Provided in the case of emergency, the person is charge of the establishment may order the destruction of an animal used in the production of sera and suspected of infection, and shall in that case give notice forthwith to the licensing authority and shall permit an Inspector to be present at the post mortem examination.

9. Conditions and Housing of Animals—(i) The animals used in the production of sera should be adequately housed under hygienic environments.

(ii) Only healthy animals free from disease should be used in the preparation of sera.

(iii) Every animal intended to be used as the source of serum must be subjected to a period of observation in quarantine for at least seven days before being admitted to the animal sheds in which the serum-yielding animals are housed.

(iv) In case of horses and other equidae, every animal used as source of serum shall either be actively immunized against tetanus or shall be passively immunized against the disease by injection of tetanus antitoxin in such doses as to ensure the constant presence of that antitoxin in the blood during the whole period of the use of the animal as a source of serum.

ANTI-SERA AND THEIR GENERAL STANDARD

Anti-sera contain the immune substances that have a specific prophylactic or therapeutic action when injected into animals exposed to or suffering from a disease due to specific micro-organism or its toxin. Anti-sera are classified into three groups:

(i) Antitoxic sera (Antitoxin)
(ii) Antibacterial sera.
(iii) Antiviral sera.

Anti-sera are usually issued in an unconcentrated form for animal use but may be concentrated and also freeze dried. However, for the purpose of the Schedule the word 'anti-sera is also used for the unconcentrated liquid sera only. A suitable bacteriostatic agent in a concentration sufficient to prevent the growth of micro-organisms is added to the liquid serum.

GENERAL STANDARD

1. Description—Liquid native or unconcentrated anti-sera are yellow or yellowish brown in colour. They are initially transparent but may become ttirbid

with age. They are almost odourless except for the odour of any bacteriostatic agent that may have been added.

2. Identification—The test for identity is described in the individual monograph.

3. Acidity or Alkalinity—All native anti-sera have a pH of 7.0 to 8.5.

4. Abnormal Toxicity—All anti-sera shall comply with the following test for freedom from abnormal toxicity:—

(a) Two healthy mice each weighing not less than 18 g. are injected subcutaneously each with 0.5 ml. of the sample and observed for five days. None of the mice should show any abnormal reaction or die.

(b) Two healthy guinea pigs each weighing 300 g. to 450 g. are injected subcutaneously each with 5 ml. of the sample and observed for seven days. None of the guinea pigs should show any abnormal reaction or die.

5. Sterility—All anti-sera shall comply with the tests for sterility described in Rules 115 to 119.

6. Potency—The potency of each preparation, when the available methods permit, is determined by the appropriate biological assay, and it is described under the individual monograph.

7. Total Solids—Native anti-sera should not contain more than 10 per cent solid matter.

8. Labelling—Should comply with the provisions for 'Labelling' as laid down for 'Bacterial Vaccines'.

9. Storage—Liquid preparations of anti-sera shall be stored, protected from light at temperature between 2°C to 4°C and shall not be frozen.

10. Date of Manufacture—The date of manufacture shall be unless otherwise specified in the individual monograph in this part as defined in clause (b) of sub-rule (3) of Rule 109.

11. Containers—All anti-sera are distributed in sterilised containers of a material which is inert towards the substance and which are sealed to exclude micro-organisms.

12. Expiry Date—The expiry date of potency of all sera shall not be more than twenty-four months after the date of manufacture.

ANTI-ANTHRAX SERUM

1. Synonym—Bacillus Anthracis Anti-serum.

2. Definition—Anti-axthrax serum is the serum of animals that confers a specific protection against Bacillus anthracis.

3. Preparation—The anti-serum may be prepared in buffalo bulls after repeated injections of cultures of *B. Anthracis* of a virulent strain.

4. Standard—It complies with the requirements in the general provisions for anti-sera under Description, Acidity or Alkalinity, Abnormal Toxicity, Sterility Solids, Labelling, Storage and Expiry date.

Identification—It protects animals against infection with *B. Anthracis.*

ANTI-BLACKQUARTER SERUM

1. Synonym—Blackleg Anti-serum, Clostridium Chauvoei-Anti-serum.

2. Definition—Anti-Blackquarter serum is the serum of suitable animals containing the substances that have a specific neutralising effect on *Clostridium Chauvoei.*

3. Preparation—It is prepared by injecting subcutaneously or intramuscularly increasing dose of formolised cultures of *Cl. Chauvoei* into buffalo-bulls.

4. Standard—It complies with the requirements described in the general provisions for anti-sera under Description, Acidity or Alkalinity, Abnormal toxicity, Sterility, Solids, Labelling, Storage and Expiry date.

Identification—It protects susceptible animals against infection with virulent strains of *Cl. Chauvoei.*

ANTI-FOWL-CHOLERA SERUM

1. Synonym—Pasteurella Septica Anti-serum (Avian).

2. Definition—Fowl Cholera Anti-serum is the serum of animals containing the substances that confer a specific protection to fowls against virulent strain of Pasteurella Septica (Avian).

3. Preparation—Anti-serum is prepared from buffalo-bulls after they have been subjected to an injection of killed cultures of virulent strain of Pasteurella Septica (Avian) followed by injections of living cultures of the same organism.

4. Standard—It complies with the requirements described in the general provision for anti-sera under Description, Acidity or Alkalinity, Abnormal toxicity, Sterility, Solids, Labelling, Storage and Expiry Date.

Identification—It protects susceptible fowls against infection with *Pasteurella Septica* (Avian) and its homologous strains.

ANTI-HAEMORRHAGIC SEPTICAEMIA SERUM

1. Synonym—Pasteurella Septica Antiserum.

2. Definition—Anti-Haemorrhagic Septicaemia Serum is the serum of animals containing the substances that confer a specific protection to susceptible animals against virulent strains of *Pasteurella Septica.*

3. Preparation—The anti-serum is prepared from buffalo-bulls after they have been subjected to repeated injections of formolised cultures of standard strain *Pasteurella Septica* with adjuvants, followed by suitable doses of virulent culture of the organism.

4. Standard—It complies with the requirements described in the general provisions for anti-serum under Description, Acidity or Alkalinity, Abnormal toxicity, Sterility, Solids, Labelling, Storage and Expiry date.

Identification—It protects susceptible animals against infection with homologous strains of *Pasteurella Septica*.

ANTI-RINDERPEST SERUM

1. Synonym—Cattle Plague Anti-serum.

2. Definition—Anti-rinderpest serum is the serum of buffalo-bulls containing the substances that confer a specific immunity to susceptible animals against virulent strains of the virus of rinderpest.

3. Preparation—The anti-serum is prepared from buffaloes who have reacted to a dose of virulent rinderpest virus, which is injected simultaneously with a predetermined quantify of anti-rinderpest serum so as to control the severity of the reaction (serum-simultaneous-method).

4. Standard—It complies with the requirements described in the general provisions for anti-sera under Description, Acidity or Alkalinity, Abnormal toxicity, Solids, Labelling, Storage and Expiry date.

(i) *Identification*—It protects susceptible animals against rinderpest.

(ii) *Potency*—Five buffalo-calves of about one year of age in good condition are used for the test. Three are injected subcutaneously with the anti-rinderpest serum under test at the rate of 10 ml. per 46 kg. body weight, subject to a minimum of 20 ml. per animal. These together with the two remaining, are simultaneously injected subcutaneously at a different site with 1 ml. of a 1 : 100 dilution of spleen suspension of virulent bull-virus.

The animals should be observed for fourteen days during which time the serum treated animals should exhibit no symptoms of rinderpest other than rise in temperature and slight intestinal disturbances, while the controls develop more severe symptoms or die.

SALMONELLA PULLORUM ANTI-SERUM

1. Synonym—Salmonella Pullorum Anti-serum.

2. Definition—Salmonella Pullorum anti-serum is the sera from fowls and contains antibodies against Salmonella Pullorum. It is used for standardizing batches of Salmonella Pullorum antigens and also used as a control along with the sera suspected for pullorum disease.

3. Preparation—The serum is prepared after intravenous inoculation with smooth culture suspension of *Salmonella Pullorum* in healthy birds.

4. Standard—It complies with the requirements in the general provisions for antisera under Description, Acidity, Alkalinity, Sterility, Solids, Labelling, Storage and Expiry Date.

Identification—It should give positive agglutination with Salmonella pullorum antigen.

STANDARD ANTI-BRUCELLA ABORTUS SERUM

1. Synonym—National counterpart of standard anti-Brucella abortus serum.

2. Definition—Standard anti-Brucella abortus serum is the serum which contains 1000 International Units (I.U.) per ml. and is used for standardizing batches of brucella antigens and is also used as a control along with the sera suspected for burcellosis.

3. Preparation—The serum is prepared after intravenous inoculation of suspension of smooth culture of B. abortus (strain 99) in rabbits or cattle and subsequently diluting it suitably with brucella-free healthy serum such that when tested with standardized Brucella abortus tube test antigen, it gives 50% agglutination at 1/500 final serum dilution.

4. Standard—It complies with the requirements in the general provision for anti-sera under Description, Acidity, Alkalinity, Sterility, Solids, Labelling, Storage and Expiry date.

Identification—It should give agglutination with Brucella antigen.

PART III

DIAGNOSTIC ANTIGENS

PROVISIONS APPLICABLE TO THE MANUFACTURE AND STANDARDISATION OF DIAGNOSTIC AGENTS (BACTERIAL ORIGIN)

1. Definition—This part of the Schedule applies to reagents of bacterial origin employed for various tests.

2. Staff of Establishment—A competent expert in bacteriology with sufficient experience in the manufacture and standardisation of veterinary biological products shall be in charge of the establishment responsible for the production of various diagnostic agents of bacterial origin and he may be assisted by a staff adequate for carrying out the tests required during the preparation and standardisation of various diagnostic agents.

3. Proper Name—The proper name of any diagnostic agent is the name of microorganism from which it is made, followed by the word 'antigen' unless the Schedule otherwise provides, or, it may be derived from the name of the organism responsible for the causation of the disease or if there is no special provision in the Schedule, the name approved by the Licensing Authority. In the case of the undermentioned preparations the proper name of the diagnostic agent may be as follows:—

1. Abortus Bang Ring (A.B.R.) Antigen.
2. Brucella Abortus Coloured Antigen.
3. Brucella Abortus Plain Antigen.
4. Johnin.
5. Mallein.
6. Salmonella Abortus Equi "H" Antigen.
7. Salmonella Pullorum Coloured Antigen.
8. Salmonella Pullorum Plain Antigen.
9. Tuberculin.

4. Records—Culture used in the preparation of diagnostic agents of bacterial origin must, before being manipulated into an agent be thoroughly tested for identity by the generally accepted tests applicable to the particular micro-organism. The permanent-record which the licensee is required to keep shall amongst other include a record of the origin, properties and characteristics of the cultures.

5. Preparation—Diagnostic agents of bacterial origin are prepared from selected cultures after their careful examination for the identity, specificity, purity and antigenicity'. They may be prepared in the following manner:—

(a) *Formolised antigens*—The selected pure culture strain grown in a suitable medium at an optimum temperature for an appropriate period. The pure growth is then exposed to the action of a solution of Formaldehyde I.P. in a suitable concentration and at an appropriate temperature for a suitable period.

(b) In some cases, the diagnostic agents are prepared by growing the organisms on suitable media and then deriving specific protein constituents for the bacteria by various methods.

6. General Standards—

(a) *Description*—Diagnostic agents may be clear opalescent or coloured liquids.

(b) *Identification*—Some exhibit specific agglutination when mixed with the serum of the animals infected with homologous organisms and other when injected into the animal body in appropriate doses cause specific reactions like hypersensitiveness, local and general reaction, if the animal is infected with homologous organism.

(c) *Sterility Test*—All antigens shall be tested for sterility in accordance with Rules 114 to 119.

(d) *Standardisation*—It is carried out either by determining the definite cell concentration in the product or by observing the general and local reactions in healthy and artificially infected animals with various standard dilution of the product.

7. Labelling—As under general provisions for the bacterial vaccines with the addition that it is meant for diagnostic purposes only.

8. Storage—All antigens are stored, protected from light at a temperature between 2°C to 4°C.

9. Date of Manufacture—The date of manufacture shall be unless otherwise specified in the individual monograph in this part as defined in clause (b) of sub-rule(3) of rule 109.

ABORTUS BANG RING (ABR.) ANTIGEN

1. Synonym—Milk Ring Test Antigen.

2. Definition—The antigen is a suspension of pure growth culture of standard strain of *Brucella abortus* strain 99 strained supravitally with 2, 3, 5, triphenyl tetrazolium chloride suspended in 0.85 per cent saline containing 1 per cent glycerol and 1 per cent phenol.

3. Preparation—Smooth strain of *Brucella abortus* strain 99 is grown on potato infusion agar for 48 to 72 hours in Roux flasks, at 37°C. Condensation fluid if any is pipetted off before washing. Each flask is washed with about 20 ml. of normal saline. The pooled washing is filtered through a gauze and the filtrate is collected in a measuring cylinder. To every 500 ml. of the filtrate lg. of 2, 3, 5, triphenyl tetrazolium chloride is added immediately. The container is shaken for thirty minutes till the tetrazolium salt is dissolved. The product is taken out and kept in at 37°C for two hours. After incubation the product is heated at 65°C in a water bath for thirty minutes. It is cooled and centrifuged at 3000 r.p.m for one hour. The supernatant is pipetted off and sediment is suspended in normal saline containing 1 per cent glycerol and 1 per cent phenol and filtered through sterile cotton wool. This forms concentrated antigen.

STANDARDIZATION OF THE STRAINED ANTIGEN

An aliquot portion of the microbial suspension stained with phenyltetrazolium is taken, representing the initial undiluted suspension. 1 ml. per tube of this initial undiluted stained suspension is added to six test tubes, followed by increasing quantities of the glycerolphenol diluent as follows:—

Tube	Undiluted Stained Suspension	Diluent
1	1	0.6
2	1	0.8
3	1	1.0
4	1	1.2
5	1	1.4

6	1	1.6

The contents of each tube are then diluted tenfold with the same diluent and serve as antigen for a tube agglutination test with the Standard Serum (or its national counterpart). In this way, six seroreactions will be carried out. During this procedure, the concentrated strained microbial suspension should be kept in the refrigerator at 4°C.

The agglutination reactions are read after forty-eight hours at the agglutination titre of the Standard Serum, previously determined with the usual unstained antigen in the test tube, corresponds to the correct dilution of the standard antigen.

The next step, therefore, is to dilute the concentrated stained suspension to the same extent as the tube whose tenfold dilution has given the correct agglutination titre *i.e.*, the concentration of antigen in the tube before the tenfold dilution had been made.

4. Standards—

(a) *Description*—It is red colour liquid containing dead bacteria in suspension.

(b) *Identification*—It shows formation of a specific cherry red coloured ring in the cream layer when mixed with pooled samples of milk taken from animals suffering from brucellosis.

(c) *Sterility Test*—Should comply with the tests for sterility described in the general monograph of 'Diagnostic Antigen'. The tests shall, however, be done before colouring.

5. Labelling and Storage—Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph of 'Diagnostic Antigen'.

6. Expiry Date—The date of expiry of potency shall be not more than nine months from the date of manufacture when stored at 2°C to 4°C.

BRUCELLA ABORTUS COLOURED ANTIGEN

1. Synonym—Brucella Abortus Cotten Strain 99 coloured Antigen.

2. Definition—Brucella Abortus coloured Antigen is a suspension of pure smooth cultures of Brucella abortus strain 99 in phenolised glycerine saline, the bacteria being coloured by the addition of crystal violet and brilliant green. This antigen is used for plate test for serological diagnosis of brucella infection.

3. Preparation—Seventy-two hours old growth of Brucella Abortus strain ninety-nine in smooth form on potato infusion agar medium in Roux flasks is washed with phenolised glycerine saline (containing 12 per cent sodium chloride, 20 per cent glycerine and 0.5 per cent phenol.). The washed growth is filtered through a pad of absorbent cotton wool and the suspension is coloured by the addition of 1 ml. each of 1 per cent aqueous solution of crystal violet and brilliant green for every 250 ml. of the suspension. The product is heated for sixty minutes in a water bath at 60°C before it is standardised.

4. Standards—

(a) *Description*—It is a greenish violet liquid containing dead bacteria in suspension.

(b) *Identification*—It gives specific agglutination when mixed with the serum of the animal infected with brucella organism.

(c) *Sterility Test*—Should comply with the tests for sterility described in the general monograph on 'Diagnostic Antigen'.

(d) *Standardisation*—0.5 ml. of the antigen is mixed with 4.5 ml. of normal saline solution in Hopkins graduate tube. The mixture is centrifuged at 3000 r.p.m. for sixty minutes and the percentage of bacterial cells present in the original antigen is assessed by noting the height of the cell deposit. The antigen is then standardised so as to contain 10 per cent cell deposit.

5. Labelling and Storage—Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph of 'Diagnostic Antigen'.

Expiry Date—The date of expiry of potency shall be not more than nine months from the date of manufacture when stored at 2°C to 4°C.

BRUCELLA ABORTUS PLAIN ANTIGEN

1. Synonym—Brucella Abortus Strain 99 Plain Antigen.

2. Definition—Brucella Abortus Plain Antigen is a suspension of pure smooth cultures of Brucella Abortus Strain 99 in phenol-saline.

3. Preparation—Seventy-two hours old growth of Brucella Abortus Strain 99 in smooth form on potato infusion agar medium in Roux flasks is washed with normal saline solution. The washed growth is filtered through a pad of absorbent cotton wool and the suspension is kept at 60°C for sixty minutes on water bath to kill the organisms. It is then preserved by the addition of phenol in a final concentration 0.5 per cent.

4. Standards—

(a) *Description*—An opalescent liquid containing dead bacteria in suspension.

(b) *Identification*—It gives specific agglutination when mixed with the serum of animals infected with brucella organism.

(c) *Sterility Test*—Would comply with the tests for sterility described in the general monograph on 'Diagnostic Antigen'.

(d) *Standardisation*—Mix the concentrated antigen well and dilute 1 ml. with 0.5 per cent phenol saline until it corresponds to about tube four of Brown's opacity tubes. Further dilutions of the antigen adjusted to opacity Tube No. 4 are made. The particular dilution that gives 50 per cent agglutination with antibrucella abortus serum (containing 1000 International Units) at 1 : 500 final serum dilution, is assessed as the diluting factor for the concentrated antigen. The bulk of the contracted antigens is accordingly diluted for issue as standard antigen.

5. Labelling and Storage— Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph on 'Diagnostic Antigen'.

6. Expiry Date—The date of expiry of potency shall be not more than nine months from the date of manufacture when stored at 2°C to 4°C.

JOHNIN

1. Definition—The Johnin is a preparation of a fluid n.edium in which *Mycobacterium para tuberculosis* has been grown in artificial culture and which has been freed by filtration from the bacilli.

2. Preparation—Young culture of selected strain of *Mycoparatuberculosis* of bovine origin is grown on synthetic medium and incubated at 37°C for ten to twelve weeks. Flasks showing lucurient and pure growth are steamed for three hours thereafter kept at room temperature overnight. The contents are filtered through fine meshed sieve. The filtrate is concentrated over a steam bath to one-tenth of its original volume and kept in cold storage for fourteen days before being filtered through Seitz filter. The product is dispensed in ampoules and hermetically sealed.

3. Standards—

(a) *Description*—A yellowish brown to brownish liquid.

(b) *Identification*—It produces hot, painful and oedematous swelling at the site of inoculation in animals infected with Mycoparatuberculosis organism.

(c) *Sterility Test*.—Should comply with the test for sterility described in the general monograph on 'Diagnostic Antigens'.

(d) *Potency Test*—Two animals, previously infected with Mycoparatuberculosis and two healthy animals are each injected intradermaliy in the neck region with 0.1 ml. of the product. Forty eight hours later, the injection is repeated at the site. The product should produce a typical reaction in the infected animals in the form of a hot painful and oedematous swelling at the site of inoculation persisting for at least forty eight hours after the second injection. Control animals should not show such reaction.

4. Labelling and Storage— Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph on 'Diagnostic Antigen'.

5. Expiry Date—The date of expiry of potency shall be not more than two years from the date of manufacture when stored at 2°C to 4°C.

MALLEINS

1. Definition—(i) Malleins are preparations of fluid media in which the *Actinobacillus mellei* has been grown in artificial culture and which have been freed by filtration from the bacilli.

(ii) For the purposes of this Schedule malleins are classified into (a) Mallein-subcutaneous and (b) Mallein intradermopalpebral (I.D.P.).

2. Preparation—

(a) *Mallein subcutaneous*—Three to four weeks old pure growth of standard strain of A. mallei grown on synthetic medium is steamed for one hour in Koch's steam sterilizer. One part of 5 per cent phenol solution is added to every nine part of the dead culture which is then filtered through Seitz filter.

(b) *Mallein Concentrated*—The procedure is the same as for Mallein subcutaneous except, that the filtrate is evaporated in porcelain dish over steam to half the original volume before addition of phenol. Five per cent phenol solution is added in sufficient quantity to the concentrated product, to give a final concentration of 0.5 per cent.

3. Standards—

(a) *Description*—A yellowish to brown viscous liquid.

(b) *Identification*—It produces hot tense, painful swelling when injected into the animals infected with *A. mallei* organisms.

(c) *Sterility Test*—Should comply with the test for sterility described in the general monograph on 'Diagnostic Antigens'.

(d) *Potency Test*—

(i) *Mallein-subcutanecus*—Two ponies, previously sensitised with A. Mallei and controls, are injected each with 1 ml. of the

product subcutaneously in the neck region. The animals are observed for local reaction and rise in temperature. Local reaction is manifested by a hot tense, painful swelling becoming prominent within twenty-four hours. The rise in temperature is observed by recording the body temperature at the time of inoculation and subsequently at short intervals. A rise in temperature of 1°C or more above normal is indicative of infection.

(ii) *Mallein Intra-dermo-Palpebral—(I.D.P.)*—Two ponies previously sensitized with A. Mallei and two healthy ponies are injected intradermaliy with 0.2 ml. of the product near the rim of the lower eye lid of one eye. Typical reactions such as painful swelling of the palpebral tissue with mucopurulent discharge from the eye is indicative of infection. The healthy ponies should not show such reactions.

Similar test in other eye is performed with a previously determined patient mallein using as a standard. When the local reactions produced by intradermo palpebral infections of the two preparations are comparable the batch is passed for issue.

4. Labelling and Storage— Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph on 'Diagnostic Antigen'.

5. Expiry Date—The date of expiry of potency shall be not more than two years from the date of manufacture when stored at 2°C to 4°C.

SALMONELLA ABORTUS EQUI 'H' ANTIGEN

1. Synonym—Equine Abortion Diagnostic Antigen.

2. Definition—Salmonella Abortus Equi Antigen is suspension of a pure smooth culture of actively *motile Salmonella Abortus equi* in formal saline.

3. Preparation—Standard stain of S. Abortus Equi is grown on nutrient agar in Roux flasks at 37°C for twenty-four hours. The pure growth in Roux flasks is washed with normal saline and diluted to contain approximately 800 million organisms per ml. Solution of Formaldehyde I.P. is added to give a final

concentration 0.5 per cent and the formolised product is incubated at 37°C for twenty-four hours. The final product is dispensed in suitable containers.

4. Standards—

(a) *Description*—A slightly opalescent liquid containing dead bacteria in suspension.

(b) *Identification*—It gives specific agglutination when mixed with the serum of the animals infected with S. Abortus Equi organisms.

(c) *Sterility Test*—Should comply with the test for sterility described in the general monograph on 'Diagnostic Antigens'.

5. Labelling and Storage— Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph on 'Diagnostic Antigens'.

6. Expiry Date—The date of expiry of potency shall be not more than nine months from the date of manufacture when stored at 2°C to 4°C.

SALMONELLA POLLORUM COLOURED ANTIGEN

1. Synonym—Bacillary White Diarrhoes (B.W.D.) Antigen.

2. Definition—The antigen is a suspension in a solution containing 1 per cent Formaline, 1 per cent KH_2P0_2 and 0.85 per cent Sodium Chloride of pure smooth culture of a standard strain of *Salmonella Pullorum.*

3. Preparation—Standard strain of *S. Pullorum* is grown on sulphur agar medium in Roux flasks for five days at 37°C. The pure growth is washed with 1.0 per cent Formol Saline.

Standardisation

The antigenic cells suspension is then centrifuged (preferably in cold centrifuge) for half an hour at 4000 rotations per minute and the packed cell volume determined. The packed cell is then resuspended in a solution containing 1 per cent formalin, 1 per cent. KH_2P0_4 and 0.85 per cent sodium chloride, 1 ml. of packed cell is suspended in 10 ml. of the resuspendiary

solution, mixed thoroughly and is passed through a cotton wool pad. The turbidity of the antigenic suspension is usually between 100 to 125 times Mac Farland scale standard and optimum 3 cc. of a 1 per cent aqueous solution of crystal violet are added to 100 ml. of the antigenic suspension. After making the dye the antigen is allowed to stand forty-eight hours before use. The average yield per Roux flask of culture medium is about 50 ml. The antigen should be bottled in 10 ml. or 20 ml. quantity in amber-coloured bottles and corked with rubber caps and paraffin sealed and preserved until required for use within the expiry period. This antigen reacts instantly with the blood of all carrier birds and remains permanently negative with that of non-infected birds.

This antigen gives good reactions with positive sera whose titre is even as low as 1:20.

4. Standards—

(a) *Description*—Violet coloured liquid containing dead bacteria in suspension.

(b) *Identification*—It gives specific agglutination when mixed with the serum of birds infected with S. Pullorum infection. It is used for carrying out plate agglutination test for serological diagnosis for *S. Pullorum* infection in birds.

(c) *Sterility Test*—Should comply with the test for sterility described in the general monograph of 'Diagnostic Antigens.' The test shall be done before addition of 'Crystal violet'.

5. Labelling and Storage—Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph on 'Diagnostic Antigens'.

6. Expiry Date—A six-month expiration date for this antigen is recommended. However, it is advisable to use fresh ones as far as possible. This antigen should be preserved at 4° to 6° in dark place in the refrigerator and should not be exposed to hot weather condition for longer than necessary before use in the field.

SALMONELLA PULLORUM PLAIN ANTIGEN

1. Synonym—Bacillary White Diarrhoes (B.W.D.) Plain Antigen.

2. Definition—The antigen is a suspension of pure smooth culture of Salmonella Pullorum in phenol saline.

3. Preparation—Forty eight hours old pure culture of smooth strain of S. Pollorum is washed with 0.5 per cent phenol saline and the pooled suspension is adjusted to contain approximately 800 million organisms per ml. by the addition of more carbon saline. The suspension is kept at room temperature for twenty-four hours, and dispensed in suitable containers.

4. Standards—

(a) *Description*—An opalescent liquid containing dead bacteria in suspension.

(b) *Identification*—It gives specific agglutination when mixed with the serum of birds infected with *S. Pullorum.*

(c) *Sterility Test*—Should comply with the tests for sterility described in the general monograph on 'Diagnostic Antigen.'

5. Labelling and Storage—Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph on 'Diagnostic Antigens'.

6. Expiry Date—The date of expiry of potency shall be not more than nine months from the date of manufacture when stored at 2°C to 4°C.

TUBERCULINE

(i) Tuberculines are preparations of fluid media on which Mycobacterium tuberculosis has been grown in artificial culture and which has been freed by filtration from the bacilli.

(ii) For the purposes of the Schedule tuberculines are classified in (a) Tuberculine-Subcutaneous (b) Heat concentrated synthetic Medium (H.C.S.M.) Tuberculine (c) Avian tuberculine.

2. Preparation—(a) *Tuberculine subcutaneous*—Flasks containing Henley and Dorset synthetic medium are inoculated with standard human strains of Myco. Tuberculosis previously grown on glycerol-beef broth medium for ten days. After ten to twelve weeks of incubation at 37°C flasks containing pure growth are steamed for three hours. The contents are filtered through fine meshed sieve and the volume is made up to its original with phenolised distilled water such that the final concentration of phenol is 0.5 per cent. It is then filtered through Seitz filter.

(b) *Heat Concentrated Synthetic Medium (H.C.S.M.) Tuberculine*—To the strained liquid obtained after sieving as in the method of preparation of tuberculine subcutaneous, glycerol is added in the proportion of 122 ml. per litre of the original volume of medium used. The mixture is evaporated to one-fifth of the original volume on a steam bath. An equal volume of 1 per cent phenol in distilled water is added after the mixture is cooled. The product is stored at 47°C for fourteen days before it is filtered through Seitz filter. It is then dispensed in ampoules.

(c) *Avian Tuberculine Concentrated*—The procedure is the same as for Tuberculine Concentrated (H.C.S.M.) except that standard strain of Mycotuberculosis (Avian) is used in its preparation.

3. Standards—

(a) *Description*—A yellowish brown viscous liquid.

(b) *Identification*—When injected intradermaliy into the animal infected with tuberculosis diffused swelling occurs depending upon the allergic status of the animal, the magnitude of dose and specificity of the product. In non-infected animals this reaction is not observed.

(c) *Sterility Test*—Should comply with the test for sterility described in the general monograph on 'Diagnostic Antigens'.

(d) *Potency Test*—(i) *Tuberculine subcutaneous*—Six large white guinea-pigs each weighing not less than 300-450 g. are individually inoculated intramuscularly with 0.5 mg. (moist growth from solid plants) of Mycobacterium tuberculosis three weeks prior to test of each batch of tuberculine : the following dilutions of (a) test tuberculine and (b) standard tuberculine are used:—

1 in 200, 1 in 400, 1 in 800, 1 in 1000.

The six sensitized guinea pigs are depilated on one flank and after about twenty-four hours each animal inoculated intradermaliy with 0.2 ml. of each dilution of the two tuberculines in two rows. The reactions are read after twenty-four and forty eight hours. When the local reactions produced by the graded inter-dermal injections of the two preparations are comparable the brew is passed for issue.

(ii) *Heat Concentrated Synthetic Medium (H.C.S.M.) Tuberculine*—Six adult white guinea pigs each weighing not less than 300-450 g. and sensitized three weeks previously with 0.5 mg. (moist growth from solid plants) of *Myco-Tuberculosis* bovine type, injected intramuscularly are used for test of each batch. The following dilutions of (a) test tuberculine and (b) standard tuberculine are used:—

1 in 500, 1 in 1000, 1 in 2000 and 1 in 4000.

The six sensitized guinea pigs are depilated on one flank and after twenty-four hours each animal is inoculated intradermaliy with 0.2 ml. of each dilution of the two tuberculines in two rows. The reactions are read after twenty four and forty eight hours. When the local reaction produced by the graded intradermic injections of the two preparations are comparable, the test tuberculine is passed for issue. The tuberculine is dispensed in ampoules.

(iii) *Avian Tuberculine*—Six adult fowls, with well developed wattles, sensitized at least three weeks previously by intramuscular injection with 10 mg. moist weight (from solid plants) of twenty one days old culture of Mycobacterium tuberculosis (Avian Type) are used for potency test of each batch. In each fowl, one wattle is inoculated with 0.2 ml. of undiluted test tuberculine and the other wattle with similar quantity of

undiluted standard tuberculine. The reactions in each fowl are read after twenty four hours and forty eight hours and if comparable the product is passed for issue.

5. Labelling and Storage— Should comply with the requirements of 'Labelling' and 'Storage' as laid down in the general monograph on 'Diagnostic Antigens'.

6. Expiry Date—The date of expiry of potency shall be not more than two years from the date of manufacture when stored at 2°C to 4°C.

PART IV

GENERAL

1. For the purposes of this Schedule any test or method of testing described in the [1100][British Pharmacopoeia (Veterinary)] shall be deemed to be a method approved by the licensing authority.

2. The licensing authority shall publish in the Official Gazette from time to time particulars of any test or method of testing approved by him.]

[1101]***[SCHEDULE F(II)***

(See rule 124C)

STANDARDS FOR SURGICAL DRESSINGS

Synonyms—Bandage Cloth, Bleached Bandage Cloth, Rolled Bandage, Open Wove Bandage, Cotton Bandage Cloth.

Bandage Cloth consists of cotton cloth of plain weave made from machine spun yarn of suitable count to comply with a bleached count between 20 tex and 25 tex for warp and between 25 tex and 30 tex for weft. The fabric contains no filling, sizing or dressing material. It may be supplied uncut and folded or cut to suitable sizes and rolled.

Description for uncut bandages—Uncut bandages are cotton cloth of plain weave, in one continuous length showing no joints or seams, with well-formed

selvedges. The cloth is bleached to a good white, is clean and odourless and reasonably free from weaving defects and from seed and leaf debris.

Description for cut bandages—Same as for uncut bandages, except for selvedges which shall not be included in cut bandages. In addition, both the extremes and edges of cut bandages shall be straight and evenly cut, with reasonable freedom from loose threads.

Threads per dm — Wrap not less than 150 and weft not less than 85.

Weight in glm^2 — 57 + 5.

Length and Width—The length and width shall not be less than 99 per cent each of the length and width stated on the label. For cut bandages, each of the bandages in a packing complies with this requirement.

Foreign matter —Not more than 2 per cent.

Fluorescence—When viewed under screened ultra-violet light, not more than occasional points of fluorescence are observed.

Packing, Labelling and Storage—Bandage Cloth shall be packed securely so as to allow normal handling and transport without tearing and exposing the contents. In packages of cut and rolled bandages, each bandage shall also individually be wrapped in a suitable paper. The net content is stated on the label in terms of length and width. Bandage Cloth must be stored in packed condition, protected from dust. The packings of Bandage Cloth shall be labelled prominently with the words "Non-sterile".

Absorbent Gauze—*Synonyms*—Gauze; Unmedicated Gauze; Absorbent Cotton Gauze.

Absorbent Gauze is cotton fabric of plain weave, supplied in various widths and lengths. The Gauze is bleached and free from any sizing, dressing or filling material. The yard used is machine spun cotton yarn, of suitable count to comply with a bleached count between 17 and 25 tex in the finished fabric.

Description—Cotton cloth, plain weave, with a simple selvedge present on both sides to prevent unravelling of yam. The cloth is bleached to a good white,

is clean, odourless, reasonably free from fabric defects and adhering sand debris from cotton seeds and leaves, or any other foreign matter.

Threads per dm — Wrap not less than 75 and weft not less than 55.

Weight in glm^2 — 30 + 5.

Length and Width—Not less than 98 per cent each of the length and width stated on the label.

Absorbency—Average sinking time not more than 10 seconds.

Fluorescence—When viewed under screened ultra-violet light not more than occasional points of fluorescence are observed.

Foreign matter—Not more than 1 per cent.

Sterility—If sterile, the contents comply with the test for sterility.

Packing, Labelling and Storage—Absorbent Gauze is folded and packed with such material and so securely as to protect its absorbency and allow normal handling and transport without tearing and exposing the contents. The net content is stated on the label in terms of length and width. The packages shall be labelled prominently with the words "Non-Sterile". If sterile, it shall be so stated on the label, and the packing method and material shall be such as to maintain the sterility. The absorbent Gauze must also comply with the Sterility Test. Absorbent Gauze must be stored in packed conditions protected from moisture and dust.

METHODS OF TEST

Defect in fabric—The sample is unfolded, opened and held against diffused daylight or spread on black topped table to locate and identify prominently visible defect in yam and fabric construction. The fabric shall be reasonably free from holes, slubs, snarls and naps as well as the following:—

Odour—Misty odour, or any objectionable smell like that of chemicals or materials used in sizing and bleaching.

Skewness—(For Bandage Cloth only). A condition where warp and weft do not keep at right angles to each other.

Defective selvedge—The selvedge tearing and allowing yam to unravel, and loop formation at selvedge.

Crack—Prominent streaks of space or gaps between warp or weft yarns.

Double ends—More warp threads woven as one, due to wrong draw.

Sloughing—Entanglement in the fabric of a bulk of yarn that has slipped off the weft yam due to loose widing.

Measurement to length and width—Length is the distance from end to end, along one edge of the fabric, and width is the perpendicular distance from one edge to the opposite edge.

Length—Fix a metre scale to a table or mark off the division of one metre on a table edge. Starting from one end, spread the fabric flat on that table in a single layer keeping one selvedge parallel to the scale; smoothcn the fabric without stretching it, to avoid creases, and mark off with a coloured pencil, on the selvedge exactly one metre. Shift the fabric and measure in the same way the second mete and so on for the entire length of the fabric making a mark at each metre. Note down the total length in metres. Repeat this at the opposite selvedge, as well as on the fabric folded approximately about middle. The average of the three readings is the length. For cut bandages, one measurement at the middle of the bandage by folding it length-wise will suffice.

Width—Lay the portion of the fabric to be measured flat and smooth on table, but do not stretch fabric except sufficiently to render it creaseless. At the place where mark had been made on the selvedge in measuring the length measure the perpendicular distance to the opposite selvedge with a metre scale. Note the width, repeat this at every mark made in measuring the length. The average of all the readings is the width of the fabric. For cut bandages, width shall be measured at every 50 cm., and average reported as width.

Threads per dm—(For samples not less than 15 m. in Length.)

Weft—At the third metre from one extreme locate three places one at about 5 cm. below the top selvedge, a second in the middle and third at about 5 cm.

above the bottom selvedge, all three in a vertical row. Take a rectangular plate (made of suitable material such as plastic or aluminium) with the rectangular opening of 5 cm. x 10 cm. cut in it. Keep the plate on the fabric horizontally so that the left 5 cm. side and bottom (10 cm. side) edges of the opening coincides with a weft and warp yarn respectively; count the number of weft yams within the opening for the length of 10 cm. Repeat this at the other two selected places, and note down the average of three readings. Repeat this at every third metre in the sample and calculate the average weft per dm.

Warp—Keep the rectangular plate, this time vertically with left (10 cm. side) and bottom (5 cm. side) edge of opening coinciding with a weft and warp yam respectively. Count the number of warp yams within the opening for 10 cm. and note down. Repeat this for about 10 selected places in the samples taking care that the same set of warp yarns is not counted more than twice and calculate the average warp per dm. Magnifying glass mounted on stand may be used for counting.

For samples less than 15 m. in length, locate as many different places as the dimension of the fabric permits, the total being not less than 10 for each sample, and calculate the warp and weft per dm. as above.

For cut bandages, all the warp threads in the samples are counted, taking care to leave 5 mm. at the cut edge, and weft is counted at every 50 cm. at any place about the middle of the bandage.

Weight per unit area—For samples not less than 15 m. in length, cut out pieces of fabric from the entire length of the sample, representative places being taken from areas at every third or fourth metre so that the total area of all the pieces so collected is not less than 3 sq. metre. Weight the pieces accurately, measure the dimension of each of the pieces and calculate the area and weight of all the pieces. From the average area and average of weight thus obtained, calculate the area per sq. metre.

For samples less than 15 m. in length, take pieces in such manner that the total area of the selected pieces is not less than 20 per cent of the total area of the sample

For cut bandages, pieces of 50 cm. in length, cut from 5 different cut bandages in a packing should be taken and weight calculated as an average of 5 readings.

Absorbency—Take a glass trough of approximate size length 30 cm. x width 30 cm x depth 25 cm. with straight thick walls and flat bottom. Fill it almost full with distilled water leaving only about 5 cm. from the top rim of trough. Maintain the water at 27[l]'C ± 1°C.

Cut out from any five places located equidistant down the length of the entire sample, square pieces, each weighing one gm. (+ 10 per cent). For each piece in such a manner that a square of approximately 5 cm. x 5 cm. is obtained. Keep one of the folded test specimen between two glass plates and place 1 kg. weight on the top for 10 minutes. Remove the weight. Lift the specimen with forceps and gently place it on the surface of water (the specimen should be lightly pinched in the middle with the blunt forceps having no serrations). As soon as the specimen touches the water surface start a stop watch which is stopped when the entire sample disappears below the surface of the water. Record the time taken. Repeat the test with the other four-test specimens. Calculate the average time in seconds.

Foreign Matter—Dry about 5 g. of the sample to constant weight at 105°C and weight the dried sample accurately. Extract the dried sample with chloroform for one hour in an apparatus for the continuous extraction of drugs. Remove the extracted sample to a beaker and allow the evaporation of residual chloroform. Wash the material 12 times with hot water, using about 1000 ml. for each washing and wringing the material by hand after each washing; pass all water through a fine sieve (100 mesh.). Place the washed material and any loose threads or fibres from the sieve in a beaker, cover with a 0.5 per cent aqueous solution of diastase and maintain at 50°C until free from starch. Allow to cool, filter the solution through a sieve; return sample and loose fibres to a beaker. Repeat the washing process as before with hot water. Dry the material to constant weight at 105°C, and determine the loss in weight. Calculate the percentage of foreign matter, which is equal to the loss in weight, with reference to the sample dried to constant weight, at 105°C.

If the sample is tested with iodine and is known to be free from starch, the treatment with solution of diastase and the second series of washing with hot water may be *omitted.*

Cloth for manufacture of Plaster of Paris Bandages, cut and uncut Synonyms: Bleached Bandage Cloth for Plaster of Paris, Rolled Bandage for Plaster of Paris.

Cloth for Plaster of Paris Bandages shall consist of cotton cloth of leno weave made from yarn of suitable count. It may be supplied cut or uncut of various widths and lengths.

Description—(a) *For uncut bandages*—Cotton cloth of leno weave, in one continuous length showing no joints or seams, and with selvedges. The cloth is bleached to a good white, is clean and odourless and reasonably free from weaving defect as well as from seed and leaf debris; the cloth may be dressed if necessary and if so, shall not dust off when unrolled.

(b) *For cut bandages*—Same as for uncut bandages except for selvedges which shall not be included and the bandages shall be cut evenly with straight edges and be reasonably free from loose threads.

Threads per dm.—

Warp—Average not less than 150/dm.; and *Weft*—average not less than 75/dm.

Weight in gm.lm.^{2}—35 ± 5.

Length and Width—The length and width for uncut bandages shall not be less than 98 per cent each of the length and width stated. For cut bandages a tolerance of ± 5 cm. in length and ± 0.5 cm. in width may be allowed, and each of the bandages in packing complies these requirements.

Fluorescence—When viewed under screened ultra violet light not more than occasional points of fluorescence are observed.

Packing, Labelling and Storage—Bandage Cloth for Plaster of Paris shall be packed securely so as to allow normal handling and transport without tearing and exposing the contents. In packages of cut and rolled bandages, each

bandags shall also individually be wrapped in suitable paper. The package shall be labelled as "Cloth for Plaster of Paris Bandage". The net content is stated on the label in terms of number of rolls and length and width. Bandage Cloth for Plaster of Paris must be stored in packed condition protected from dust.]

[1102][*SCHEDULE F(III)*

***(See* rule 124D)**

STANDARD FOR UMBILICAL TAPES

(A) STANDARDS FOR STERILISED UMBILICAL POLYESTER TAPE—

Description—A uniform strand of Polyester yam prepared by braiding and may be finished with a suitable silicone finishing material, white to yellowish-white in colour. Tape shall be sterilised by Gamma Radiation or by any other suitable method approved by the Licensing Authority.

Other requirements—The Umbilical Polyester Tape shall conform to the claims made on the label in respect of length and width.

Tensile strength—The Umbilical Polyester Tape shall have Tensile strength of not less than 4 kgs. on straight pull.

Packing and labelling—The Umbilical Polyester Tape shall be packed in sealed Polythene bags or sealed plastic containers which ensure that when packed, the tape is sterile. The packing shall protect the tape from contamination and damage. Every packing offered for sale shall bear a clear and permanent marking with the following particulars:—

(i) The proper name of the drug i.e. Umbilical Polyester Tape 'Sterile'.

(ii) Manufacturer's name and address.

(iii) Batch Number.

(iv) Licence number under which the tape is manufactured.

(v) Date of manufacture and the date of expiry.

(vi) Length and width of the Tape.

Storage condition— It should be stored in a cool place protected from light

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(B) STANDARDS FOR STERILISED UMBILICAL COTTON TAPE—

Description—A uniform stand of cotton yam prepared by braiding and may be finished with a suitable silicone finishing material, white to yellowish-white in colour. The tape shall be sterilised by Gamma Radiation or by any other suitable method approved by the Licensing Authority.

Other Requirement—The Umbilical Cotton Tape shall conform to the claims made on the label in respect of length and width.

Tensile Strength—The Umbilical Cotton Tape shall have a Tensile strength of not less than 4 kg. on straight pull.

Packing and Labelling—The Umbilical Cotton Tape shall be packed in sealed Polythene bags or sealed plastic containers which ensure that when packed the tape is sterile. The packing shall protect the tape from contamination and damage. Every packing offered for sale shall bear a clear and permanent marking with the following particulars:—

(i) The proper name of the drug, *i.e.*, Umbilical Cotton Tape 'Sterile'.

(ii) Manufacturer's name and address

(iii) Batch Number.

(iv) Licence number under which the tape is manufactured.

(v) Date of manufacture and the date of expiry.

(vi) Length and width of the Tape.

Storage condition—It should be stored in a cool place protected from light.]

[1103][SCHEDULE FF

(See rule 126A)

STANDARD FOR OPHTHALMIC PREPARATIONS

Part A. Ophthalmic Solutions and Suspensions

Ophthalmic Solutions and Suspensions shall—

(a) be sterile when dispensed or when sold in the unopened container of the manufacturer, except in case of those ophthalmic solutions and suspensions which are not specifically required to comply with the test for 'Sterility' in the Pharmacopoeia.;

(b) contain one or more of the following suitable substances to prevent the growth of micro-organisms :

(i) Benzalkonium Chloride, 0.01 per cent (This should not be used in solutions of nitrates or salicylates).

(ii) Phenyl mercuric nitrate, 0.001 per cent.

(iii) Chlorobutanol 0.5 per cent.

(iv) Phenyl ethyl alcohol 0.5 per cent:

Provided that solutions used in surgery shall not have any preservative and be packed in single dose container:

Provided further that the licensing authority may in his discretion authorise the use of any other preservative or vary the concentration prescribed on being satisfied that its use affords equal guarantee for preventing the growth of micro-organisms;

(c) be free from foreign matter;

(d) be contained in bottles made of either neutral glass or soda glass specially treated to reduce the amount of alkali released when in contact of aqueous liquids, or in suitable plastic containers which would not in any way be incompatible with the solutions.

The droppers to be supplied with the containers of ophthalmic solutions and suspensions shall be made of neutral glass or of suitable plastic material and when supplied separately shall be packed in sterile cellophane, or other suitable packings;

(e) In addition to complying with the provisions of labelling laid down in the rules the following particulars shall also be shown on the label—

(1) *of the containers*

(i) The statement 'Use the solution within one month after opening the container'

(ii) Name and concentration of the preservative, if used.

(iii) The words 'NOT FOR INJECTION'.

(2) *of container or carton or package leaflet*

(i) Special instructions regarding storage, wherever applicable.

(ii) A cautionary legend reading as

"WARNING : (i) if irritation persists or increases, discontinue the use and consult physician.

(ii) Do not touch the dropper tip or other dispensing tip to any surface since this may contaminate solutions."

Part B. Ophthalmic Ointments Ophthalmic Ointments shall—

(a) be sterile when dispensed or when sold in the unopened container of the manufacturer;

(b) be free from foreign matter;

(c) in addition to complying with the provisions for labelling laid down in the rules the following particulars shall be shown on the container or carton or package leaflet—

(i) Special instructions regarding storage wherever applicable.

(ii) A cautionary legend reading

"WARNING : If irritation persists or increases, discontinue the use and consult physician.."]

[1104]*[SCHEDULE G*

(See rule 97)

Aminopterin
L-Asparaginase
Bleomycin
Busulphan; its salts
Carbutamide
Chlorambucil;its salts
Chlorothiazide and other derivatives of 1, 2, 4 benzothiadiazine
Chlorpropamide; its salts
Chlorthalidone and other derivatives of Chlorobenzene compound.
[1105][Cis-Platin]
Cyclophosphamide; its salts
[1105][Cytarabine]
Daunorubicin
Di-Isopropyl Eluorophosphate
Disodium Stilboestrol Diphosphate
Doxorubicin Hydrochloride
Ethacrynic Acid, its salts

Ethosuximide
Glibenclamide
Hydantoin; its salts; its derivatives, their salts
Hydroxyurea
Insulin, all types
[1105][(Lomustine Hydrochloride)]
Mannomustine; its salts
Mercaptopurine; its salts
Metformin; its salts
Methsuximide
Mustine, its salts
Paramethadione
Phenacemide
Phenformin; its salts
5-Phenylhydantoin; its alkyl and aryl derivatives; its salts
Primadone
[1106][Procarpazine Hydrochloride]
Quinthazone
Sarcolysine
[1107][(Sodium-2-Mercaptoethanesulfonate]
Tamoxiten Citrate
Testolactone
Thiotepa
Tolbutamide
Tretamine; its salts
Troxidone

Antihistaminic substances the following, their salts, their derivatives, salts of their derivatives

Antazoline
Bromodiphenhydramine
Buclizine
Chlorcyclizine
Chlorpheniramine
Clemizole
Cyproheptadine
Diphenhydramine
Diphenylpyraline
Doxylamine Succinate
Isothipendyl
Mebhydrolin Napadisylate
Meclozine
Phenindamine
Pheniramine
Promethazine
Thenalidine
Triprolidine

Substances being tetra-N-Subs. derivatives of Ethylene Diamine or Prophylenediamine.

Note.—Preparations containing the above substances excluding those intended for topical or external use are also covered by this Schedule.]

[1108][*SCHEDULE H]*

(See rules 65 and 97)

PRESCRIPTION DRUGS

1. Abacavir
2. Abciximab
3. Acamprosate Calcium
4. Acebutol Hydrochloride
5. Aclarubicin
6. Albendazole
7. Alclometasone Dipropionate
8. Actilyse

9. Acyclovir
10. Adenosine
11. Adrenocorticotrophic Hormone (Acth)
12. Alendronate Sodium
13. Aliopurinol
14. Alphachymotrypsin
15. [1109][***]
16. Alprostadil
17. Amantadine Hydrochloride
18. Amifostine
19. Amikacin Sulphate
20. Amiloride Hydrochloride
21. Aminepline
22. Aminoglu tethimide
23. Aminosalicylic Acid
24. Amiodarone Hydrochloride
25. Amitriptyline
26. Amlodipine Besylate
27. Amoscanate
28. Amoxopine
29. Amrinone Lactate
30. Analgin
31. Androgenic Anabolic, Oestrogenic & Progestational Substances
32. Antibiotics
33. Apraclonidine
34. Aprotinin
35. Organic Compound of Arsenic
36. Arteether
37. Artemether
38. Artesunate
39. Articaine Hydrochloride
40. Atenolol
41. Atracurium Besylate Injection
42. Atorvastatin
43. Auranofin
44. Azathioprine
45. Aztreonam
46. Bacampicillin
47. Baclofen
48. Balsalazide
49. Bambuterol
50. Barbituric Acid
51. Basiliximab
52. Benazepril Hydrochloride
53. Benidipine Hydrochloride
54. Benserazide Hydrochloride
55. Betahistine Dihydrochloride
56. Bethanidine Sulphate
57. Bezafibrate
58. Bicalutamide
59. Biclotymol
60. Bifonazole
61. Bimatoprost
62. Biperiden Hydrochloride
63. Biphenyl Acetic Acid
64. Bitoscanate
65. Bleomycin
66. Primonidine Tartrate
67. Bromhexine Hydrochloride
68. Bromocriptine Mesylate
69. Budesomde
70. Bulaquine
71. Bupivacaine Hydrochloride
72. Bupropion
73. Buspirone
74. Butenafine Hydrochloride
75. Butorphanol Tartrate
76. Cabergoline
77. Calciumdobesilate
78. Candesartan
79. Capecitabine
80. Captopril
81. Carbidopa
82. Carbocisteine
83. Carboplatin
84. Carboquone
85. Carisoprodol
86. L-Camitine
87. Carteolol Hydrochloride
88. Carvedilol
89. Cefadroxyl
90. Cefatoxime Sodium
91. Cefazolin Sodium
92. [1110][****
93. ****
94. ****

95. ****
96. ****
97. ****
98. ****]
99. Cefuroxime
100. Celecoxib
101. Centchroman
102. Centbutindole
103. Centpropazine
104. Cetirizine Hydrochloride
105. [1111][***]
106. Chlormezanone
107. [1112][***]
108. Chlorpromazine
109. Chlorzoxazone
no. Ciclopirox Olamine
111. Cimetidine
112. Cinnarizine
113. Ciprofloxacin Hydrochloride Monohydrate / Lactate
114. Cisplatin
115. Citalopram Hydrobromide
116. Clarithromycin
117. Clavulanic Acid
118. Clidinium Bromide
119. Clindamycin
120. Clobazam
121. Clobetasol Propenate
122. Clobetasone 17-Butyrate
123. [1113][***]
124. Clofibrate
125. Clonazepam
126. Clonidine Hydrochloride
127. Clopamide
128. Clopidogre! Bisulphate
129. Clostebol Acetate
130. Clotrimazole
131. Clozapine
132. [1113][***]
133. Colchicine
134. Corticosteroids
135. Cotrimoxazole
136. Cyclandelate
137. Cyclosporins
138. Daclizumab
139. Danazole
140. Dapsone
141. Desloratadine
142. Desogestrol
143. Dexrazoxane
144. Dextranomer
145. [1111][***]
146. Dextropropoxyphene
147. [1111][***]
148. Diazoxide
149. Diclofenac Sodium/Potassium/Acid
150. Dicyclomin Hydrochloride
151. Didanosine
152. Digoxine
153. Dilazep Hydrochloride
154. Diltiazem
155. Dinoprostone
156. [1114][***]
157. Dipivefrin Hydrochloride
158. Di-sodium Pamidronate
159. Disopyramide
160. Docetaxel
161. Domperidone
162. Donepezil Hydrochloride
163. Dopamine Hydrochloride
164. Dothiepin Hydrochloride
165. Doxapram Hydrochloride
166. Doxazosin Mesylate
167. Doxepin Hydrochloride
168. Doxorubicin Hydrochloride
169. Drotrecogin-Alpha
170. Ebastine
171. Econozole
172. Efavirenz
173. Enalapril Meleate
174. Enfenamic Acid
175. Epinephrine
176. Epirubicine
177. Eptifibatide
178. Ergot, Alkaloids of whether Hydrogenated or not, their Homologoues, Salts

179. Esomeprazole
180. Estradiol Succinate
181. Estramustine Phosphate
182. Etanercept
183. Ethacridine Lactate
184. [1115][***]
185. Ethamsylate
186. Ethinyloestradiol
187. [1115][***]
188. Etidronate Disodium
189. Etodolac
190. Etomidate
191. Etoposide
192. Exemestane
193. Famciclovir
194. Famotidine
195. Fenbendazole
196. Fenofibrate
197. Fexofenadine
198. Finasteride
199. Flavoxate Hydrochloride
200. 5-Fluorouracil
201. Fludarabine
202. Flufenamic Acids
203. Flunarizine Hydrochloride
204. Fluoxetine Hydrochloride
205. Flupenthixol
206. Fluphenazine Enanthate and Decanoate
207. Flurazepam
208. Flurbiprofen
209. Flutamide
210. Fluticasone Propionate
211. Fluvoxamine Maleate
212. Formestane
213. Fosfestril Sodium
214. Fosinopril Sodium
215. Fossphenytoin Sodium
216. Fotemustine
217. Gabapentin
218. Galanthamine Hydrobromide
219. Gallamine, its Salts, its Quaternary Compound
220. Gancyclovir
221. Ganirelix
222. Gatifloxacin
223. Gemcitabine
224. Gemfibrozil
225. Gemtuzumab
226. Genodeoxycholic Acid
227. Gliclazide
228. Glimepiride
229. Glucagon
230. Glycopyrrolate
231. Glydiazinamide
232. Goserelin Acetate
233. Granisetron
234. Guanethidine
235. Gugulipid
236. Halogenated Hydroxyquinolines
237. Haloperidol
238. Heparin
239. Hepatitis B. Vaccine
240. Hyaluronidase
241. Hydrocorisone 17-Butyrate
242. Hydrotalcite
243. Hydroxizine
244. Ibuprofen
245. Idebenone
246. Iindapamide
247. Imipramine
248. Indinavir Sulphate
249. Indomethacin
250. Insulin Human
251. Interferon
252. Intravenous Fat Emulsion
253. Iobitridol
254. Iohexol
255. Iopamidol
256. Iomeprol
257. Iopromide
258. Irbesartan
259. Irinotecan Hydrochloride
260. Iron Preparation for Parenteral use
261. Isepamicine
262. Isocarboxside
263. Isoflurane

264. Isonicotnic Acid Hydrazine and other Hydragine Derivatives of Isonicotinic Acid
265. Isosorbide Dinitrate/Mononitrate
266. Isotretinoin
267. Isoxsuprine
268. Itopride
269. [1116][***]
270. Ketoconazole
271. Ketoprofen
272. Ketorolac Tromethamine
273. Labetalol Hydrochloride
274. Lacidipine
275. Lamivudine
276. Lamotrigine
277. Latanoprost
278. Lefunomide
279. Lercanidipine Hydrochloride
280. Letrozole
281. Leuprolide Acetate
282. Levamesole
283. Levarterenol
284. Levobunolol
285. Levocetirizine
286. Levodopa
287. [1115][***]
288. Levovist
289. Lidoflazine
290. Linezplid
291. Lithium Carbonate
292. Lofepramine Decanoate
293. Loperamide
294. Lorazepam
295. Losartan Potassium
296. Loteprednol
297. Lovastatin
298. Loxapine
299. Mebendazole
300. Mebeverine Hydrochloride
301. Medroxy Progesterone Acetate
302. Mefenamic Acid
303. Mefloquine Hydrochloride
304. Megestrol Acetate
305. Meglumine Iocarmate
306. Melagenina
307. Melitracen Hydrochloride
308. Meloxicam
309. Mephenesin, its Esters
310. Mephentermine
311. [1117][***]
312. Mesterolone
313. Metaxalone
314. Methicillin Sodium
315. Methocarbamol
316. Methotraxate
317. Metoclopramide
318. Metoprolol Tartrate
319. Metrizamide
320. Metronidazole
321. Mexiletine Hydrochloride
322. Mianserin Hydrochloride
323. Miconazole
324. [1117][***]
325. Mifepristone
326. Milrinone Lactate
327. Miltefosine
328. Minocycline
329. Minoxidil
330. Mirtazapine
331. Misoprostol
332. Mitoxantrone Hydrochloride
333. Mizolastine
334. Moclobemide
335. Mometasone Furoate
336. Monteiukast Sodium
337. Morphazinamide Hydrochloride
338. Mosapride
339. [1117][***]
340. Mycophenolate Mofetil
341. Nadifloxacin
342. Nadolol
343. Nafarelin Acetate
344. Nalidixic Acid
345. Naproxen
346. Narcotic Drugs listed in Narcotic Drugs & Psychotropic Substances Act, 1985
347. Natamycin

348. Nateglinide
349. N-butyI-2-cyanoacrylate
350. Nebivolol
351. Nebumetone
352. Nelfinavir Mesilate
353. Netilmicin Sulphate
354. Nevirapine
355. Nicergoline
356. Nicorandil
357. Nifedipine
358. Nimesulide
359. Nimustine Hydrochloride
360. [1117][***]
361. Nitroglycerin
362. Noreth Isterone Enanthate
363. Norfloxacin
364. Octylonium Biomiae
365. Ofloxacin
366. Olanzapine
367. Omeprazole
368. Omidazole
369. Orphenadrine
370. Orthoclone Sterile
371. Oxazepam
372. Oxazolidine
373. Oxcarbazepine
374. Oxethazaine Hydrochlorid
375. Oxiconazole
376. Oxolinic Acid
377. Oxprenolol Hydrochloride
378. Oxybutynin Chloride
379. Oxyfedrine
380. Oxymetazoline
381. Oxyphenbutazone
382. [1118][***]
383. Ozothine
384. Paclitaxel
385. Pancuronium Bromide
386. Pantopiazole
387. Para-Amino Benzene Sulphonamide, its Salts & Derivatives
388. Parp-Amino Salicylic Acid, its Salts, its Derivatives
389. Parecoxib
390. Paroxetine Hydrochloride
391. D-Penicillamine
392. [1117][***]
393. Pentoxifylline
394. Pepleomycin
395. Phenelzineh Sulphate
396. Phenobarbital
397. Phenothiazine, Derivatives of and Salts of its Derivatives
398. Phenylbutazine
399. Pimozide
400. Pindolol
401. Pioglitazone Hydrochloride
402. Piracetam
403. Piroxicam
404. Pituitary Gland, Active Principles of, not otherwise specified in this Schedule and their Salts
405. Polidocanol
406. Polyestradiol Phosphate
407. Poractant Alfa
408. Praziquantel
409. Pred nimustine
410. Prednisolone Stearoylglycoiate
411. Prenoxdiazin Hydrochloride
412. Promazine Hydrochloride
413. Promegestone
414. Propafenon Hydrochloride
415. Propanolol Hydrochloride
416. Propofol
417. Protristyline Hydrochloride
418. [1117][***]
419. Pyrvinium
420. Quetiapine Fumerate
421. Quinapril
422. Quiniaine Sulphate
423. Rabeprazole
424. Racecadotril
425. Raloxifene Hydrochloride
426. Ramipril Hydrochloride
427. Ranitidine

428. Rauwolfia, Alkaloids of, their Salts, Derivatives of the Alkaloids or Rauwolfia
429. Reboxetine
430. Repaglinide
431. Reproterol Hydrochloride
432. Rilmenidine
433. Riluzone
434. Risperidone
435. Ritonavir
436. Ritodrine hydrochloride
437. Rituximab
438. Rivastigmine
439. Rocuronium bromide
440. Ropinirole
441. Rosoxacin.
442. Rosiglitazone meleate
443. Salbutamol sulphate
444. Salicyl-azo-sulphapyridine
445. Salmon calcitonin
446. Saquinavir
447. Satranidazole
448. Secnidazole
449. Septopal beads & chains
450. Serratiopeptidase
451. Sertraline hydrochloride
452. Sibutramine hydrochloride
453. Sildenafil citrate
454. Simvastatin
455. Sirolimus
456. Sisomicin sulphate
457. S-neominophagen
458. Sodiumpico sulphate
459. Sodium cromoglycate
460. Sodium hyaluronate
461. Sodium valproate
462. Sodium and maglumine iothalamates
463. Somatostatin
464. Somatotropin
465. Sotalol
466. [1119][***]
467. Spectinomycin hydrochloride
468. Spironolactone
469. Stavudine
470. Sucralfate
471. Sulphadoxine
472. Sulphamethoxine
473. Sulphamethoxypyridazine
474. Sulphaphenazole
475. Sulpiride
476. Sulprostone hydrochloride
477. Sumatriptan
478. Tacrine hydrochloride
479. Tamsulosin hydrochloride
480. Trapidil
481. Tegaserod maleate
482. Teicoplanin
483. Telmisartan
484. Temozolamide
485. Terazosin
486. Terbutaline sulphate
487. Terfenadine
488. Terizidone
489. Terlipressin
490. Testosteroneun decoanoate
491. Teratolol hydrochloride
492. Thalidomide
493. [1119][***]
494. Thiocolchicoside
495. Thiopropazate, its salts
496. Thymogene
497. Thymosin-alpha1
498. Tiaprofenic acid
499. Tibolone
500. Timolol maleate
501. Tinidazole
502. Tizanidine
503. Tabramycin
504. Tolfenamic acid
505. Topiramate
506. Topotecan hydrochloride
507. [1119][***]
508. Tranexamic acid
509. Tranylcypromine, its salts
510. Trazodone
511. Tretinoin
512. Trifluperazine

513. Trifluperidol hydrochloride
514. Triflusal
515. Trimetazidine dihydrochloride
516. Trimipramine
517. Tripotassium dicitrate bismuthate
518. Tromantadine hydrochloride
519. Urokinase
520. Valsartan
521. Vasopressin
522. Vecuronium bromide
523. Venlafaxine hydrochloride
524. Verapamil hydrochloride
525. Verteporfin
526. Vincristine sulphate
527. Vinblastine sulphate
528. Vindesine sulphate
529. Vinorelbine tatrate
530. Xipamide
531. Zidovudine hydrochloride
532. Ziprasidone hydrochloride
533. Zoledronic acid
534. [1119][***]
535. Zopiclone
536. Zuclopenthixol
[1120][537.Etizolam]
[1121][538.Alclometasone
539.Beclomethasone
540.Betamethasone
541.Desonide
542.Desoximetasone
543.Dexamethasone
544.Diflorasone diacetate
545.Fluocinonide
546.Huocinolone acetonide
547.Halobetasol propionate
548.Halometasone
549.Methylprednisone
550.Prednicarbate
551.Triamcinolone acetonide]
[1336][552. Acitretin]

Note: —1. Preparations exempted under proviso to para 2 of Note to Schedule X shall also be covered by this Schedule.

2. The salts, esters, derivatives and preparations containing the above substances excluding those intended for topical or external use (except ophthalmic and ear/nose preparations containing antibiotics and/or steroids) are also covered by this Schedule.

3. The inclusion of a substance in this Schedule does not imply or convey that the substance is exempted from the provisions of Rule 122A/122B.]

[1122][4. The salts, esters, derivatives and preparations containing [1123][steroids or Hydroquinone] for topical or external use shall also be covered under this Schedule.

[1124][5. Notwithstanding anything contained in these rules, the provisions of rule 65 and rule 97 in respect or drugs specified from serial number 538 to serial number 551 inserted *vide* Notification number G.S.R. 277(E), dated 23rd March, 2018 published in the Gazette of India, Extraordinary, Part II, Section

(3), Sub-section (i) shall be on voluntary basis for a period commencing on the day on which this notification shall come into force and ending on the 31st March, 2019 and thereafter shall be mandatory.]

[1125][*SCHEDULE H1*

(*See* rules 65 and 97)

1. Alprazolam
2. Balofloxacin
3. Buprenorphine
4. Capreomycin
5. Cerdinir
6. Cefditoren
7. Cefepime
8. Cefetamet
9. Cefixime
10. Cefoperazone
11. Cefotaxime
12. Cefpirome
13. Cefpodoxime
14. Ceftazidime
15. Ceftibuten
16. Ceftizoxime
17. Ceftriaxone
18. Chlordiazepoxide
19. Clofazimine
20. Codeine
21. Cycloserine
22. Diazepam
23. Diphenoxylate
24. Doripenem
25. Ertapenem
26. Ethambutol Hydrochloride
27. Ethionamide
28. Feropenem
29. Gemifloxacin
30. Imipenem
31. Isoniazid
32. Levofloxacin
33. Meropenem
34. Midazolam
35. Moxifloxacin
36. Nitrazepam
37. Pentazocine
38. Prulifloxacin
39. Pyrazinamide
40. Rifabutin
41. Rifampicin
42. SodiumPara-aminosalicylate
43. Sparfloxacin
44. Tniacetazone
45. Tramadol
46. Zolpidem

[1126][47. Oxytocin]

[1127][48. Tapentadol]

[1341]["49. Oseltamivir
50. Zanamivir"]

[1339][SCHEDULE H2

[See sub-rules (6) and (7) of rule 96]

S No.	*Brand name of the formulation*
1.	ACILOC 150 MG TABLET 30
2.	ACILOC 300 MG TABLET 20
3.	ACTEMRA 400 MG INJECTION 1
4.	ACTRAPID HUMAN 40 IU INJECTION 10 ML
5.	AEROCORT WITH DOSE COUNTER 50/50 MCG INHALER 200 MDI
6.	AJADUO 25/5 MG TABLET 10
7.	ALLEGRA 120 MG TABLET 10
8.	ALLEGRA 180 MG TABLET 10
9.	AMBISOME 50 MG INJECTION 20 ML
10.	AMICIN 500 MG INJECTION 2 ML

S No.	Brand name of the formulation
11.	AMLOKIND-AT 50/5 MG TABLET 10
12.	ASCORIL D PLUS NEW 5/2/10 MG SYRUP 100 ML
13.	ASCORIL LS 1/30/50 MG SYRUP 100 ML
14.	ASCORIL PLUS 50/1.25/2 MG EXPECTORANT 120 ML
15.	ASTHAKIND DX 5/2/15 MG SYRUP 100 ML
16.	ASTHALIN 100 MCG INHALER 200 MDI
17.	AUGMENTIN DUO 500/125 MG TABLET 10
18.	AVOMINE 25 MG TABLET 10
19.	AXCER 90 MG TABLET 14
20.	AZEE 500 MG TABLET 5
21.	AZITHRAL 500 MG TABLET 5
22.	BECOSULES CAPSULE 20
23.	BECOSULES Z CAPSULE 20
24.	BETADINE 10 % OINTMENT 20 GM
25.	BETADINE 10 % SOLUTION 100 ML
26.	BETADINE MINT 2 % GARGLE 100 ML
27.	BETNESOL 0.5 MG TABLET 20
28.	BETNOVATE C 0.1/3 % CREAM 30 GM
29.	BETNOVATE N 0.1/0.5 % CREAM 20 GM
30.	BETNOVATE N 0.1/0.5 % CREAM 25 GM
31.	BETT 0.5 ML INJECTION 0.5 ML
32.	BEVON SYRUP 200 ML
33.	BIO D3 MAX 500 MG/0.25MCG/400MCG/120MG CAPSULE 15
34.	BRILINTA 90 MG TABLET 14
35.	BRO ZEDEX 50/1.25/4 MG SYRUP 100 ML
36.	BUDECORT 0.5 MG RESPULES 2 ML
37.	CALCIROL 60000 IU GRANULES 1 GM
38.	CALDIKIND PLUS 500 MG/0.25MCG/400MCG/60MG CAPSULE 10
39.	CALPOL 500 MG TABLET 15
40.	CALPOL 650 MG TABLET 15
41.	CALPOL PEAD 250 MG SUSPENSION 60 ML
42.	CANDIFORCE 200 MG CAPSULE 7
43.	CCM 250 MG TABLET 40
44.	CEFAKIND 500 MG TABLET 10
45.	CEFTUM 500 MG TABLET 4
46.	CEPODEM 200 MG TABLET 10
47.	CHYMORAL FORTE 100000 IU TABLET 20
48.	CIDMUS 24/26 MG TABLET 14
49.	CILACAR 10 MG TABLET 15
50.	CIPREMI 100 MG INJECTION 1
51.	CLARIBID 500 MG TABLET 10
52.	CLAVAM 500/125 MG TABLET 10
53.	CLEXANE 40 MG INJECTION 0.4 ML

S No.	Brand name of the formulation
54.	CLEXANE 60 MG INJECTION 0.6 ML
55.	COBADEX CZS TABLET 15
56.	CODISTAR 4/10 MG SYRUP 100 ML
57.	COMBIFLAM 400/325 MG TABLET 20
58.	CONCOR 5 MG TABLET 10
59.	COREX DX 4/10 MG SYRUP 100 ML
60.	CREMAFFIN PLUS SF 1.25 ML/3.75ML/3.33MG LIQUID 225 ML
61.	CYPON 275/2 MG SYRUP 200 ML
62.	CYRA D 30/20 MG TABLET SR 10
63.	DALACIN C 300 MG CAPSULE 10
64.	DECA DURABOLIN 50 MG INJECTION 1
65.	DEFCORT 6 MG TABLET 10
66.	DERIPHYLLIN 25.3/84.7 MG INJECTION 2 ML
67.	DEROBIN 1.15/1.15/5.3 % OINTMENT 30 GM
68.	DEXONA (VIAL) 4 MG INJECTION 2 ML
69.	DEXORANGE 160 MG/0.5MG/7.5MCG SYRUP 200 ML
70.	DOLO 650 MG TABLET 15
71.	DOLONEX 20 MG TABLET DT 15
72.	DOXINATE 10/10 MG TABLET 30
73.	DOXT SL 100 MG/5BIU CAPSULE 10
74.	DOXY 1 FORTE L DR 100 MG/5BIU CAPSULE 10
75.	DULCOFLEX 5 MG TABLET 10
76.	DUOLIN 3 1.25 MG/500MCG RESPULES 3 ML
77.	DUPHASTON 10 MG TABLET 10
78.	DYDROBOON 10 MG TABLET 10
79.	DYNAPAR AQ 75 MG INJECTION 1 ML
80.	EASY SIX PREFILLED SYRINGE 0.5 ML
81.	ECOSPRIN AV 10/75 MG CAPSULE 15
82.	ECOSPRIN GOLD 75/20/75 MG TABLET 15
83.	ELAXIM 40 MG INJECTION 1
84.	ELECTRAL SACHET 21.8 GM
85.	ELIQUIS 2.5 MG TABLET 10
86.	ELIQUIS 5 MG TABLET 10
87.	ELTROXIN 100 MCG TABLET 120
88.	ENTEROGERMINA 2 BIU ORAL SUSPENSION 5 ML
89.	EXHEP 40 MG PREFILLED SYRINGE 0.4 ML
90.	FABIFLU 200 MG TABLET 34
91.	FABIFLU 400 MG TABLET 17
92.	FABIFLU COPACK 800 MG TABLET 18
93.	FARONEM 200 MG TABLET 10
94.	FARONEM 300 MG TABLET ER 10
95.	FORACORT 20/500 MCG RESPULES 2 ML
96.	FORACORT 6/200 MCG ROTACAP 30

S No.	*Brand name of the formulation*
97.	FORACORT 6/400 MCG ROTACAP 30
98.	FORXIGA 10 MG TABLET 14
99.	GABAPIN NT 400/10 MG TABLET 15
100.	GALVUS 50 MG TABLET 15
101.	GALVUS MET 50/1000 MG TABLET 15
102.	GALVUS MET 50/500 MG TABLET 15
103.	GEFTINAT 250 MG TABLET 30
104.	GELUSIL MPS 250/50/250 MG LIQUID 200 ML
105.	GEMCAL 500 MG/0.25MCG/7.5MG CAPSULE 15
106.	GEMER 2/500 MG TABLET 10
107.	GIBTULIO 25 MG TABLET 10
108.	GLUCONORM-G 2/500 MG TABLET 15
109.	GLYCOMET GP 1/500 MG TABLET 15
110.	GLYCOMET GP 2/500 MG TABLET SR 15
111.	GLYNASE MF 5/500 MG TABLET 10
112.	GLYXAMBI 25/5 MG TABLET 10
113.	GRILINCTUS 60/2.5/5/50 MG SYRUP 100 ML
114.	GUDCEF 200 MG TABLET 10
115.	GUDCEF CV 200/125 MG TABLET 10
116.	HCQS 200 MG TABLET 15
117.	HEXAXIM INJECTION 0.5 ML
118.	HUCOG HP 5000 IU INJECTION 1 ML
119.	HUMINSULIN 30/70 100 IU CARTRIDGE 3 ML
120.	INFANRIX HEXA INJECTION 0.5 ML
121.	ISTAMET 50/500 MG TABLET 15
122.	IVABRAD 5 MG TABLET 15
123.	IVERMECTOL NEW 12 MG TABLET 2
124.	JALRA M 50/500 MG TABLET 15
125.	JANUMET 50/1000 MG TABLET 15
126.	JANUMET 50/500 MG TABLET 15
127.	JANUVIA 100 MG TABLET 7
128.	JARDIANCE 10 MG TABLET 10
129.	JARDIANCE 25 MG TABLET 10
130.	KABIMOL 1000 MG INFUSION 100 ML
131.	KARVOL PLUS CAPSULE 10
132.	KENACORT 40 MG INJECTION 1 ML
133.	KETOROL 10 MG TABLET DT 15
134.	KETOSTERIL TABLET 20
135.	LANTUS 100 IU CARTRIDGE 3 ML
136.	LANTUS SOLOSTAR 100 IU DISPOSABLE PEN 3 ML
137.	LEVERA 500 MG TABLET 15
138.	LEVIPIL 500 MG TABLET 10
139.	LIBRAX 2.5/5 MG TABLET 20

S No.	Brand name of the formulation
140.	LIMCEE CHEW ORANGE 500 MG TABLET 15
141.	LIPAGLYN 4 MG TABLET 10
142.	LMWX 40 MG INJECTION 0.4 ML
143.	LOBATE GM NEO 0.05/0.5/2 % CREAM 15 GM
144.	LONOPIN 40 MG INJECTION 0.4 ML
145.	LOSAR 50 MG TABLET 15
146.	LOSAR H 50/12.5 MG TABLET 15
147.	MACBERY XT 50/1.25/4 MG SYRUP 100 ML
148.	MAGNEX FORTE 1000/500 MG INJECTION 1
149.	MANFORCE 100 MG TABLET 4
150.	MANFORCE 50 MG TABLET 9
151.	MAXTRA 5/2 MG SYRUP 60 ML
152.	MEFTAL SPAS 10/250 MG TABLET 10
153.	MEGALIS 20 MG TABLET 4
154.	MEGANEURON OD PLUS 1500 MCG CAPSULE 10
155.	MENACTRA INJECTION 0.5 ML
156.	MERO 1000 MG INJECTION 1
157.	MEROMAC 1000 MG INJECTION 1
158.	MERONEM 1000 MG INJECTION 1
159.	MEROZA 1000 MG INJECTION 1 ML
160.	MIFEGEST KIT 200 MG/200MCG TABLET 1
161.	MIKACIN 500 MG INJECTION 2 ML
162.	MINIPRESS XL 5 MG TABLET XL 30
163.	MIXTARD HM PENFILL 30/70 100 IU INJECTION 3 ML
164.	MIXTARD HUMAN 30/70 40 IU INJECTION 10 ML
165.	MIXTARD HUMAN 50/50 40 IU INJECTION 10 ML
166.	MONOCEF 1000 MG INJECTION 5 ML
167.	MONOCEF O 200 MG TABLET 10
168.	MONOCEF SB 1000/500 MG INJECTION 1
169.	MONTAIR LC 10/5 MG TABLET 15
170.	MONTAZ 1000/125 MG INJECTION 1
171.	MONTEK-LC 10/5 MG TABLET 10
172.	MONTICOPE 10/5 MG TABLET 10
173.	MOX 500 MG CAPSULE 15
174.	MOX CV 500/125 MG TABLET 10
175.	MOXCLAV 500/125 MG TABLET 10
176.	MOXIKIND CV 500/125 MG TABLET 10
177.	MUCAINE MINT 10/291/98 MG GEL 200 ML
178.	MUCINAC SF ORANGE 600 MG TABLET 10
179.	NEBICARD 5 MG TABLET 10
180.	NEFROSAVE 150/500 MG TABLET 15
181.	NEUROBION FORTE TABLET 30
182.	NEXPRO 40 MG TABLET 15

S No.	Brand name of the formulation
183.	NEXPRO RD 30/40 MG CAPSULE 10
184.	NIKORAN 5 MG TABLET 20
185.	NISE 100 MG TABLET 15
186.	NITROCONTIN 2.6 MG TABLET CR 30
187.	NOVOMIX 100 IU CARTRIDGE 3 ML
188.	NOVOMIX 30/70 MG FLEXPEN 3 ML
189.	NOVORAPID 100 IU CARTRIDGE 3 ML
190.	NUROKIND LC 500 MG/1.5MG/1500MCG TABLET 15
191.	NUROKIND PLUS RF 1500 MCG CAPSULE 10
192.	O2 200/500 MG TABLET 10
193.	OMEZ 20 MG CAPSULE 20
194.	OMEZ D 30/20 MG CAPSULE SR 15
195.	OMNIKACIN 500 MG INJECTION 2 ML
196.	ONDERO 5 MG TABLET 10
197.	ONDERO MET 2.5/500 MG TABLET 10
198.	OROFER FCM INJECTION 10 ML
199.	OROFER-XT 100/1.5 MG TABLET 10
200.	OROFER-XT PLUS 30 MG/500MCG/500MCG SUSPENSION 200 ML
201.	OTRIVIN OXY FAST RELIEF 0.05 % SPRAY 10 ML
202.	OVRAL L 0.03/0.15 MG TABLET 21
203.	OXRA 10 MG TABLET 14
204.	PAN 40 MG TABLET 15
205.	PAN D 30/40 MG CAPSULE 15
206.	PANDERM PLUS PLUS 0.05/0.5/2 % CREAM 15 GM
207.	PANTIN IV 40 MG INJECTION 10 ML
208.	PANTOCID 40 MG TABLET 15
209.	PANTOCID DSR 30/40 MG CAPSULE 15
210.	PANTODAC 40 MG TABLET 15
211.	PANTODAC DSR 30/40 MG CAPSULE 15
212.	PANTOP 40 MG INJECTION 10 ML
213.	PANTOP 40 MG TABLET 15
214.	PANTOP D 10/20 MG CAPSULE 10
215.	PANTOP D SR 30/40 MG CAPSULE SR 10
216.	PHENSEDYL COUGH LINCTUS 4/10 MG SYRUP 100 ML
217.	PIPZO 4000/500 MG INJECTION 10 ML
218.	PRACTIN 4 MG TABLET 10
219.	PREGA NEWS KIT 6
220.	PREVENAR 13 INJECTION 0.5 ML
221.	R.B TONE SYRUP 200 ML
222.	RABLET-D 30/20 MG CAPSULE 10
223.	RANTAC 150 MG TABLET 30
224.	RAZO 20 MG TABLET 15
225.	RAZO D 30/20 MG TABLET 15

S No.	*Brand name of the formulation*
226.	REFRESH TEARS 0.5 % EYE DROPS 10 ML
227.	REJUNEX-CD3 TABLET 10
228.	REMDAC 100 MG INJECTION 1
229.	ROSUVAS 10 MG TABLET 15
230.	ROSUVAS 20 MG TABLET 10
231.	RYZODEG 2.56/1.05 MG PENFILL 3 ML
232.	SARIDON 250/50/150 MG TABLET 10
233.	SEROFLO 50/250 MCG ROTACAP 30
234.	SHELCAL 500 MG/250IU TABLET 15
235.	SHELCAL XT 500 MG/2000IU/1500MCG/1MG/20MG TABLET 15
236.	SILODAL 8 MG TABLET 10
237.	SILODAL D 8/0.5 MG TABLET 10
238.	SINAREST 125/5/1 MG SYRUP 60 ML
239.	SINAREST NEW 500/10/2 MG TABLET 10
240.	SINAREST NEW 500/10/2 MG TABLET 15
241.	SKINLITE 2/0.1/0.025 % CREAM 25 GM
242.	SOMPRAZ D 30/40 MG CAPSULE 15
243.	SPASMO PROXYVON PLUS 10/325/50 MG CAPSULE 8
244.	SPEGRA 50/200/25 MG TABLET 30
245.	STAMLO 5 MG TABLET 30
246.	STAMLO BETA 50/5 MG TABLET 15
247.	STEMETIL 5 MG TABLET MD 15
248.	SUCRAFIL O 1000/20 MG GEL 200 ML
249.	SUMO 100/325 MG TABLET 15
250.	SUMO L IV 1000 MG INFUSION 100 ML
251.	SUPRADYN TABLET 15
252.	SYNFLORIX INJECTION 1
253.	T BACT 2 % OINTMENT 15 GM
254.	T BACT 2 % OINTMENT 5 GM
255.	TARGOCID 400 MG INJECTION 1 ML
256.	TAXIM O 200 MG TABLET 10
257.	TAZOMAC 4000/500 MG INJECTION 2 ML
258.	TELEKAST-L 10/5 MG TABLET 15
259.	TELMA 40 MG TABLET 30
260.	TELMA AM 40/5 MG TABLET 15
261.	TELMA H 40/12.5 MG TABLET 15
262.	TELMIKIND 40 MG TABLET 10
263.	TELMIKIND AM 40/5 MG TABLET 10
264.	TELMIKIND H 40/12.5 MG TABLET 10
265.	THROMBOPHOB OINTMENT 20 GM
266.	THYRONORM 100 MCG TABLET 120
267.	THYRONORM 25 MCG TABLET 120
268.	THYRONORM 50 MCG TABLET 120

S No.	*Brand name of the formulation*
269.	TOSSEX NEW 4/10 MG SYRUP 100 ML
270.	TRAJENTA 5 MG TABLET 10
271.	TRESIBA FLEXTOUCH 100 IU DISPOSABLE PEN 3 ML
272.	TUSQ DX 5/2/15 MG SYRUP 100 ML
273.	UDILIV 150 MG TABLET 15
274.	UDILIV 300 MG TABLET 15
275.	ULTRACET 325/37.5 MG TABLET 15
276.	UNIENZYME TABLET 15
277.	UNWANTED 72 1.5 MG TABLET 1
278.	UNWANTED KIT 200 MG/200MCG TABLET 1
279.	UPRISE D3 60000 IU CAPSULE 8
280.	URIMAX 0.4 MG CAPSULE 20
281.	URIMAX D 0.4/0.5 MG TABLET 15
282.	URSOCOL 300 MG TABLET 15
283.	VARILRIX INJECTION 0.5 ML
284.	VELOZ D 30/20 MG CAPSULE SR 10
285.	VELPANAT 400/100 MG TABLET 28
286.	VERTIN 16 MG TABLET 15
287.	VOLINI 1.16 % SPRAY 40 GM
288.	VORIER 200 MG TABLET 4
289.	VOVERAN SR 100 MG TABLET SR 15
290.	VYMADA 24/26 MG TABLET 14
291.	WYSOLONE 10 MG TABLET DT 15
292.	WYSOLONE 5 MG TABLET DT 15
293.	XONE 1000 MG INJECTION 5 ML
294.	ZAVICEFTA 2000/500 MG VIAL 10 ML
295.	ZEDEX 4/5/50 MG SYRUP 100 ML
296.	ZERODOL P 100/325 MG TABLET 10
297.	ZERODOL SP 100/325/15 MG TABLET 10
298.	ZIFI 200 MG TABLET 10
299.	ZORYL-M 2/500 MG TABLET 20
300.	ZOSTUM 1000/500 MG INJECTION 1.]

[1128][SCHEDULE I

(Omited]

[1129][SCHEDULE J

(See rule 106)

DISEASES AND AILMENTS (BY WHATEVER NAME DESCRIBED) WHICH A DRUG MAY NOT PURPORT TO PREVENT OR CURE OR MAKE CLAIMS TO PREVENT OR CURE.

1. AIDS
2. Angina Pectoris
3. Appendicitis
4. Arteriosclerosis
5. Baldness
6. Blindness
7. Bronchial Asthma
8. Cancer and Benign tumour
9. Cataract
10. Change in colour of the hair and growth of new hair.
11. Change of foetal sex by drugs.
12. Congenital malformations
13. Deafness
14. Diabetes
15. Diseases and disorders of uterus.
16. Epilepticfits and psychiatric disorders
17. Encephalitis
18. Fairness of the skin
19. Form, structure of breast
20. Gangrene
21. Genetic disorders
22. Glaucoma
23. Goitre
24. Hernia
25. High/low Blood Pressure
26. Hydrocele
27. Insanity
28. Increase in brain capacity and improvement of memory
29. Improvement in height of children/adults
30. mprovement in size and shape of the sexual organ and in duration of sexual performance
31. improvement in the strength of the natural teeth
32. Improvement in vision
33. Jaundice/Hepatitis/Liverdisorders
34. Leukaemia
35. Leucoderma
36. Maintenance or improvement of capacity of the human being for sexual pleasure.
37. Mental retardation, subnormalities and growth
38. Myocardial infarction
39. Obesity
40. Paralysis
41. Parkinsonism
42. Piles and Fistulae
43. Power to rejuvenate
44. Premature ageing
45. Premature greying of hair
46. Rheumatic Heart diseases
47. Sexual Impotence, Premature ejaculation and spermatorrhoea
48. Spondylitis
49. Stammering
50. Stones in gall-bladder, kidney, bladder
51. Varicose vein]

SCHEDULE K

(See rule 123)

Class of Drugs	*Extent and Conditions of Exemptions*
1. Drugs falling under clause (b)(i) of section 3 of the Drugs and Cosmetics Act, not intended for medicinal use.	All the provisions of Chapter IV of the Act and the rules thereunder, subject to the conditions that the drug is not sold for medicinal use or for use in the manufacture of medicines and that each container is labelled conspicuously with the words "NOT FOR MEDICINAL USE".
2. [1130][***]	
[1131][2A.Quinine and other antimalarial drugs.]	[1132][Persons selling the drugs by retail under arrangements made by State Government for sale and distribution of the drugs will be exempted from the requirements to take out licences for retail sale under clause (c) of section 18 of the Act.]
3.[1133][***	
4. ***]	
[1134][5. Drugs supplied by a registered medical practitioner to his own patient or any drug specified in Schedule C supplied by a registered medical practitioner at the request of another such practitioner if it is specially prepared with reference to the condition and for the use of an individual patient provided the registered medical practitioner is not (a) keeping an open shop or (b) selling across the counter or (c) engaged in the importation, manufacture, distribution or sale of drugs in India to a degree which render him liable to the provisions of Chapter IV of the Act and the rules thereunder.]	All the provisions of Chapter IV of the Act and the rules made thereunder, subject to the following conditions:— [1134][(1) The drugs shall be purchased only from a dealer or a manufacturer licensed under these rules, and records of such purchases showing the names and quantities of such drugs, together with their batch numbers and names and addresses of the manufacturers shall be maintained. Such records shall be open to inspection by an Inspector appointed under the Act, who may, if necessary, make enquiries about purchases of the drugs and may also take samples for test.] (2) In the case of medicine containing a substance specified in [1135][Schedule G, H or X] the following additional conditions shall be complied with:— (a) the medicine shall be labelled with the name and address of the registered medical

	practitioner by whom it is supplied; (b) If the medicine is for external application, it shall be labelled with the words [1136][***] "For external use only" or, if it is for internal use with the dose; (c) the name of the medicine or ingredients of the preparation and the quantities thereof, the dose prescribed, the name of the patient and the date of supply and the name of the person who gave the prescription shall be entered at the time of supply in register to be maintained for the purpose; (d) the entry in the register shall be given a number and that number shall be entered on the label of the container; (e) the register and the prescription, if any, on which the medicines are issued shall be preserved for not less than two years from the date of the last entry in the register or the date of the prescription, as the case may be. [1137][(3) The drug will be stored under proper storage conditions as directed on the label.] [1138][(4) No drug shall be supplied or dispensed after the date of expiration of potency recorded on its container, label or wrapper or in violation of any statement or direction recorded on such container, label or wrapper.]
[1139][5A. Drugs supplied by a hospital or dispensary maintained or supported Government or local body [1140][***	The provisions of Chapter IV of the Act and the Rules thereunder which require them to be covered by a sale licence, subject to the following conditions : (1) The dispensing and supply of drugs shall be carried out by or under the supervision of a qualified person; (2) The premises where drugs are supplied or stocked shall be open to inspection by an Inspector appointed under the Drugs and

	Cosmetics Act who can, if necessary, take samples for test; (3) The drugs shall be stored under proper storage conditions. [1141][(4) The drugs shall be purchased from a manufacturer or a dealer licensed under these rules or received as transferred stocks from hospital stores for distribution. Records of such purchases or receipts shall be maintained.] [1142][(5) No drug shall be supplied or dispensed after the date of expiration of potency recorded on its container, label or wrapper or in violation of any statement or direction recorded on such container, label or wrapper.]
[1143][5B. Whole Human Blood IP and / or its components stored for transfusion by a First Referral Unit, Community Health Centre, Primary Health Centre and a Hospital.	The provisions of Chapter IV of the Act and the rules made thereunder which require obtaining of a licence for operation of a [1144][blood centre] or processing Whole Human Blood and / or its components, subject to the following conditions, namely: - (1) The First Referral Unit, Community Health Centre, Primary Health Centre and / or any Hospital shall be approved by the State / Union Territory Licensing Authority after satisfying the conditions and facilities through inspection. (2) [1145][***] (3) The Whole Human Blood and/or its components shall be procured only from Government [1146][Blood centre] and/or Indian Red Cross Society Blood Bank and/or Regional Blood Transfusion Centre duly licensed. (4) The approval shall be valid for a period of two years from the date of issue unless sooner suspended or cancelled and First Referral Unit, Community Health Centre, Primary Health Centre or the Hospital shall apply for renewal to the State Licensing Authority three months prior to the date of expiry of the approval. (5) The First Referral Unit, Community

	Health Centre, Primary Health Centre and/or any Hospital shall have the following technical staff for storage of blood or its components:— (a) A trained Medical Officer for proper procurement, storage and cross matching of blood and/or its components. He/ she shall also be responsible for identifying haemolysed blood and ensure non-supply of date expired blood or its components. (b) A [1146][blood centre] Technician with the qualification and experience as specified in Part XII B of Schedule F or an experienced laboratory technician trained in blood grouping and cross matching. (6) The First Refereral Unit, Community Health Centre, Primary Health Centre and Hospital shall have an area of 10 sq. meters. It shall be well lighted, clean and preferably air-conditioned. [1146][Blood Centre] refrigerator of appropriate capacity fitted with alarm device and temperature indicator with regular temperature monitoring shall be provided to store blood units between 2°C to 8°C and if the components are proposed to be stored specialised equipments as specified in Part XII B of Schedule F shall also be provided. (7) The First Referral Unit, Community Health Centre, Primary Health Centre and Hospital shall maintain records and registers including details of procurement of Whole Human Blood I.P. and/or blood components, as required under Part XII B of Schedule F. (8) The First Referral Unit, Community Health Centre, Primary Health Centre and Hospital shall store samples of donors blood as well as patients sera for a period of seven days after transfusion.]
[1147][6.* * *]	
7.Quinine Sulphate	The provisions of sub-section (a) (i) of Section 18 of the Act to the following extent- (i) the colour of the drug may be pink, owiing to its being coloured with an edible pink colouring matter;

	(ii) the B.P. tests for readily carbonisable substances produce a yellow colour of an intensity about four times the colour produced with quinine sulphate conforming to the B.P. standard; (iii) other Cinchona alkaloids present shall not exceed six per cent; and (iv) the residue on incineration shall not exceed 0.14 per cent.
[1148][8.* * *]	
[1149][9. Magnesium Sulphate.	The provisions of sub-clause (i) of clause (a) of Section 18 of the Act to the following extent:- Chlorides present in the salt shall not exceed 0.12 per cent in the case of the produce prepared from sea water.]
[1150][10.The following substances which are used both as articles of food as well as drugs: (i) all condensed or powdered milk whether pure, skimmed or malted, fortified with vitamins and minerals or otherwise. (ii) Farex, Oats, [1151][***] and all other similar cereal preparations whether fortified with vitamins or otherwise excepting those for parenteral use. (iii) Virol, Bovril, Chicken essence and all other similar predigested foods. [1152][(iv) Ginger, Pepper, Cumin, Cinnamon and all other similar spices and condiments unless they are specially labelled as conforming to the standards in the Indian Pharmacopoeia or the Official Pharmacopoeias and official compendia of drug standards prescribed under the Act and rules made thereunder.]]	All provisions of Chapter IV of the Act and the Rules thereunder
[1153][11.* * *]	
[1154][12. Substances intended to be used for destruction of vermin or insects which cause disease in human beings or animals, *vis.* Insecticides and Disinfectants.	The provision of Chapter IV of the Act and Rules thereunder, which require them to be covered by a sale licence [1155][subject to the condition that provision of condition (17) of Rule 65 of the Drugs and Cosmetics Rules, 1945 are complied with by the person

	stocking or selling such substances.]
[1156][13. The following household remedies, namely:— [1157][(1) Aspirin tablets] [1158][(2) Paracetamol Tablets] (3) Analgesic Balms. (4) Antacid preparations. (5) Gripe Water for use of infants. (6) Inhalers, containing drugs for treatment of cold and nasal congestion. (7) Syrups, lozenges, pills and tablets for cough. (8) Liniments for external use. (9) Skin ointments and ointments for bums. (10) Absorbent cotton wool, bandages absorbent gauze and adhesive plaster. (11) Castor Oil, Liquid Paraffin and Epsom salt. (12) Eucalyptus Oil. (13) Tincture Iodine, Tincture Benzoin Co. and Mercurochrome in containers not exceeding 100 ml. (14) Tablets of Quinine Sulphate I.P. (15) Tablets of lodochlorohydroxy quinoline 250 mg.]	The provisions of Chapter IV of the Act and rules thereunder, which require them to be covered with a sale licence in Form 20A subject to the following conditions:— (a) The drugs are sold only in a village having population of not more than one thousand persons and where there is no licensed dealer under the Drugs and Cosmetics Act. (b) The drugs do not contain any substance specified in [1159][Schedules G, H or X.] (c) The drugs are sold in the original unopened containers of the licensed manufacturers. (d) When the drugs are sold under clause (a) condition 3 under "Conditions of licence" of Form 20-B shall not apply.
[1160][14. Mechanical Contraceptives	The provisions of Chapter IV of the Act and rules thereunder, which require them to be covered by a sale licence [1161][subject to the condition that the provisions of condition (17) of Rule 65 of the Drugs Rules, 1945, are complied with by the person stocking or selling mechanical contraceptives.]
[1162][14A. Vaginal contraceptive pessaries containing Nonoxynol.	The provisions of Chapter IV of the Act and the rules made thereunder which require them to be covered by a sale licence subject to the condition that the provisions of clause (17) of rule 65 of the Drugs Rules, 1945 are complied with by the person stocking or selling this contraceptive.]
[1163][15.Chemical contraceptive having the following composition per tablet: (1) DL-Norgestrel — 0.30 mg. Ethinyloestradiol — 0.30 mg. (2) Levonorgestrel — 0.15 mg. Ethinyloestradiol — 0.03 mg. (3) Centchroman — 30 mg. [1164][(4) Desogestrel — 0.150 mg.	The provisions of Chapter IV of the Act and the rules made thereunder which required them to be covered by a sale licence.]

Ethinyloestradiol - 0.030 mg. (5) Levonorgestrel — 0.1 mg. Ethinyloestradiol — 0.02 mg.]	
[1165][16. ***]	
[1166][17. Ophthalmic ointments of the Tetracycline group of drugs.	Persons authorised by the Government to distribute or sell the drugs under the National Trachoma Control Programme shall be exempted from the provisions of Chapter IV of the Act and the rules made thereunder, which require the drugs to be covered by a sale licence.]
[1167][18.* * *]	
[1168][19.Hair Fixers, namely mucilagenous preparations containing gums, used by men for fixing beard.	The provisions of Chapter IV of the Act and the rules thereunder.]
[1169][20. Radio Pharmaceuticals.	All the provisions of Chapter IV of the Act and the Rules made thereunder.]
[1170][21. Tablets of Chloroquine Salts.	The provisions of Chapter IV of the Act and rules thereunder, which require them to be covered by a sale licence, provided the drug in strip pack is sold under the Commercial Distribution Scheme of the National Malaria Eradication Programme and duly labelled as "National Malaria Eradication Programme—Ministry of Health and Family Welfare Government of India."]
[1171][22. Sales form restaurant cars of trains and from coastal ships of household remedies, which do not require the supervision of a qualified person for their sale.	The provisions of Chapter IV of the Act and rules thereunder which require them to be covered by a sale licence, subject to be following conditions namely:— (a) The records of purchase and sale of drugs shall be maintained by the person-in-charge of sale of such drugs, which shall be available for inspection by an Inspector appointed under the Act; (b) The place where such drugs are stocked shall be open to inspection by an Inspector appointed under the Act who can, if necessary, take samples for test.]
[1172][23. Drags supplied by (i) Multipurpose Workers attached to Primary Health Centres/Sub-Centres, (ii) Community Health	The provisions of Chapter IV of the Act and the rules thereunder, which require them to be covered by a sale licence, provided the drugs are supplied under the Health or

Volunteers under the Rural Health Scheme, (iii) Nurses, Auxiliary Nurses, Midwives and Lady Health Visitors attached to Urban Family Welfare Centres/ Primary Health Centres/Sub-Centres [1173][(iv) Anganwadi Workers; and (v) Community Health Officers at Ayushman Bharat Health and Wellness Centres.]	Family Welfare Programme of the Central or State Government.]
[1174][24. Homoeopathic medicines supplied by a registered Homeopathic medical practitioner to his own patient or Homoeopathic medicines supplied by a registered Homoeopathic medical practitioner at the request of another such practitioner provided the registered Homoeopathic medical practitioner is not (a) keeping an open shop, or (b) selling across the counter or, (c) engaged in the importation, manufacture, distribution or sale of Homoeopathic medicines in India to a degree which renders him liable to the provisions of Chapter IV of the Act and the Rules made thereunder.	All the provisions of Chapter IV of the Act and rules made thereunder subject to the following conditions:— (1) The Homoeopathic medicines shall be purchased only from a dealer or a manufacturer licensed under the Drugs and Cosmetics Rules, 1945. (2) The premises where the Homoeopathic medicines are stocked shall be open to inspection by an Inspector appointed under the Act, who may, if necessary, take samples for test.]
[1175][25. Preparations applied to human body for the purpose of repelling insects like mosquitoes.	The provisions of Chapter IV of the Act and rules thereunder which require them to be covered by a sale licence subject to the conditions that such a product has been manufactured under a valid drug manufacturing licence.
[1176][26. Medicated Dressings and Bandages for First Aid.]	The provisions of Chapter IV of the Act and rules thereunder which require them to be covered by a sale licence, subject io the conditions that such a product has been manufactured under a valid drug manufacturing licence.]
[1177][27. [1178][Oral Rehydration Salts (Manufactured as per the following formula):-Composition of the formulation in terms of the amount in g, to be dissolved in sufficient water to produce 1000 ml. • Sodium Chloride 2.6 • Dextrose (anhydrous) or 13.5 • Dextrose mono-hydrate 14.85 • Potassium chloride 1.5 • Sodium Citrate 2.9]	The provisions of Chapter IV of the Act and rules thereunder which required them to be covered by a sale licence, subject to the conditions that such a product has been manufactured under a valid drug manufacturing Licence.]
[1179][28. White or Yellow Petroleum Jelly I.P. (Non-	The Provisions of Chapter IV of the Act and the rules made thereunder which require them to be covered by a sale licence subject

perfumed)	to the conditions that such a product has been manufactured under a valid drug manufacturing licence.]
[1180][29. Morphine Tablets	The Provisions of Chapter IV of the Act and the rules made thereunder which require them to be covered by a sale licence, subject to the following conditions, namely:— (i) The drug shall be supplied by the Palliative Care Centres approved by the State Government to terminally ill cancer patients. (ii) The drug shall be kept under the custody of the Medical Officer-in-charge of the said Centre. (iii) The drug shall be purchased from a dealer or a manufacturer who holds licence under these rules, and records of such purchases showing the names and quantities together with their batch numbers, and names and addresses of the manufacturers or dealers and the names and addresses of the patients to whom supplies have been made shall be maintained. Such records shall be open to inspection by an Inspector appointed under the Act, who may also take samples for test.
30. Whole Human Blood collected and transfused by Centres run by Armed Forces Medical Services in border areas, small mid-zonal hospitals including peripheral hospitals, Field Ambulances, Mobile medical units including blood supply units in border, sensitive and field areas.	All the provisions of Chapter IV of the Act and rules made thereunder which require them to be covered by a licence to operate a 1181[Blood Centre] for collection, storage and processing of whole human blood for sale or distribution subject to the following conditions:— (i) These Centres shall collect, process and transfuse blood in emergent situations which require life saving emergency surgeries/or transfusion. (ii) The Centres shall be under the active direction and personal supervision of a qualified Medical Officer, possessing the qualifications and experiences specified in condition (i) of rule 122G. (iii) Each blood unit shall be tested before use for freedom from HIV I and II antibodies, Hepatitis B surface antigen, malarial parasites and other tests specified under the monograph "Whole Human

	Blood" in current edition of Indian Pharmacopoeia. (iv) These Centres shall have adequate infrastructure facilities for storage and transportation of blood. (v) The blood collected and tested by such Centres shall be transfused by the Centre itself and may be made available for use of other peripheral Armed Forces hospitals or centres during operational circumstances.]
[1182][31. Homoepathic Medicines	The provisions of Chapter IV of the Act and the rules made thereunder which relates to sale licence in Form 20C, subject to the following conditions:— (i) These medicines shall be sold in the original sealed small quantity packings of the licensed manufacturers; (ii) Medicines shall be stocked and sold by retail dealers of medicines licensed under rule 61; (iii) Medicines shall be stored separately from other allopathic drugs; (iv) Medicines shall be purchased front a manufacturer or a dealer licensed under these rules; and (v) Purchase and sale records of medicines shall be maintained by the dealer for a minimum period of three years.]
[1183][32. First Aid kit supplied along with motor vehicle by the manufacturer or its distributor at the time of first sale of vehicle.	The provisions of Chapter IV of the Act and rules made thereunder which require them to be covered by a sale licence, subject to the condition that the drug items are procured from a manufacturer or a dealer licensed under the rules.]
[1184][33. Nicotine gum [1185][and Lozenges] containing upto 2 mg. of nicotine	The provisions of Chapter IV of the Act and the Rules made thereunder which require them to be covered by a sale licence subject to the condition that such a product has been manufactured under a valid drug manufacturing licence.]
[1186][34. Production of Oxygen 93 per cent. USP or Oxygen 93 per cent. IP, produced from air by the molecular sieve process or Oxygen 93 per cent,	The provisions of Chapter IV of the Act and the rules made thereunder which require them to be covered by manufacturing licence under the rules, provided that the production

supplied from liquid Oxygen, by a hospital or medical institute for their captive consumption.	facilities shall be open to inspections by an Inspector appointed under the Act, who can, if necessary, take samples for test.]
[1187][35. Homeopathic hair oils having active ingredients up to 3X potency only.	The provisions of Chapter IV of the Act and the rules made thereunder which require them to be regulated with a sale license subject to the condition that such products have been manufactured under a valid manufacturing license and sold in the original sealed packing of the licensed manufacturers.
36. Custom made devices.	All provisions of Chapter IV of the Act and the rules made thereunder, subject to the condition that the device being specifically made in accordance with a duly qualified medical practitioner's written prescription under his responsibility, in accordance with specific design, characteristics and the same is intended for the sole use of a particular patient and the label contain the words 'custom made device' . Explanation.—Mass produced devices, which only need adoption to meet the specific requirement of a medical practitioner or any other professional user, shall not be considered as custom made device.
37. Zinc sulphate tablets and oral solutions having 10 mg and 20 mg of elemental zinc.	The provisions of Chapter IV of the Act and rules thereunder which require them to be covered by a sale licence, subject to the condition that such a product has been manufactured under a valid drug manufacturing licence.]
[1188][38. Sterile solutions intended for parenteral administration with 100 ml in one container of the finished dosage form for single use manufactured for export only.	The provisions of Chapter IV of the Act and rules made thereunder which require them to obtain a licence in Form 28D or 28DA from the Central Licence Approving Authority subject to the condition that such drugs have been manufactured for export purpose only under a licence granted by the State Licensing Authority.]

[1334][39. Liquid Antiseptics for household use	The provisions of Chapter IV of the Act and rules made thereunder, which require them to be covered with a sale license in Form 20 or Form 20A, subject to the following conditions, namely:— (a) The drugs are manufactured by licensed manufacturers; (b) the drugs do not contain any substance specified in Schedule G, H, H1 or X; (c) the drugs are sold in the original unopened containers of the licensed manufacturer; (d) the drugs are purchased from a licensed wholesaler or a licensed manufacturer.] [1337][Provided that the condition specified in clause (d) shall not be applicable for the drugs manufactured on or before the 30th November, 2022.]

[1189][***]

[1190]***[SCHEDULE L-I***

(See rules 74, 78 and 150E)

GOOD LABORATORY PRACTICES AND REQUIREMENT OF PREMISES AND EQUIPMENTS

1. General Requirements:

(a) The laboratory or the organisation of which it is a part must be an entity that is legally authorised to function and can be held legally responsible.

(b) It is the responsibility of the management to ensure that the laboratory carry out its testing, calibration, validation, and all other technical activities in such a way as to meet Good Laboratory Practices (GLP) requirements.

(c) Laboratory management shall have a qualified individual to be known as quality manager or technical manager for carrying out all technical activities and for the implementation of documented quality system and shall report to the top management directly.

(d) The quality manager shall prepare a schedule for technical audit of the laboratory for GLP compliance by an expert or experts appointed by the top-management other than the in-charge of the laboratory and shall

ensures the maintenance of documented quality system as per quality, manual.

2. Premises:

(a) (i) the laboratories shall be designed, constructed and maintained so as to prevent entry of insects and rodents besides cross contamination;

(ii) interior surface (walls, floor, and ceilings) shall be smooth and free from cracks, and permit easy cleaning and disinfection;

(iii) adequate provision is made not only for space and equipment for carrying out necessary test but also for utilities like water, power and gas;

(iv) air ventilation system shall ensure dust free environment.

(b) The laboratories shall be provided with adequate lighting and ventilation and if necessary, air-conditioning to maintain satisfactory temperature and relative humidity that will not adversely affect the testing and storage of drugs or the accuracy of the functioning of the laboratory equipments or instruments.

(c) The drainage system facilities shall be such as to facilitate proper maintenance and prevent water logging in the laboratory.

(d) Tabletops shall be constructed with acid, alkali and solvent resistant material and shall be smooth and free from crevices as far as possible.

(e) All bio-medical laboratory waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 1996.

(f) Adequate space with proper storage conditions in the laboratory shall be provided for keeping reference and working standards and be maintained by the quality control department. Standard Operating Procedure (SOP) for the maintenance of reference standards and

evaluation of Working and Secondary standards shall be prepared by the laboratory.

(g) The air circulation is maintained in the area where sterility test is carried out as per Schedule 'M',

(h) Bio-burden shall be routinely maintained in the controlled and uncontrolled area. *(e.g.,* air locks)

(i) Animal House:

(i) Animal House shall have the approval of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

(ii) Designed in such a way that there is an arrangement to quarantine the new animals procured or purchased and have a provision for clean corridor and dirty corridor.

(iii) In case of a diseased animal proper diagnosis shall be done and proper record of treatment shall be maintained.

(iv) Different types of animals shall be housed separately with proper identification.

(v) A Standard Operating Procedure shall be prepared for breeding and care of animals, maintenance, cleaning or sanitation with suitable schedule for cleaning of animal cages, racks, floor and other equipments.

(vi) The animal house shall have proper air-conditioning (temperature and humidity) with proper lighting and be monitored regularly and documented periodically.

3. Personal:

(a) Staff iii the laboratory shall possess necessary qualification, proper training and shall have adequate, experience for the assigned duties.

(b) A training record of all the personnel shall be maintained.

(c) Head of the laboratory must be of high professional standing with experience in drug analysis and laboratory management who is responsible for—

(i) ensuring the control and maintenance of documents including the quality system as per the requirements of regulatory authorities which involves all raw data, SOPs, documentation exhibits, protocols, training charts, etc;

(ii) planning and organising the audit of the quality system and initiation as well as follow up action of the corrective actions, if any;

(iii) investigation of technical complaints;

(iv) taking final responsibilities for recommending any regulatory action in the event of non-compliance of tested samples.

4. Equipments:

(a) The laboratory shall be furnished with all types of equipments as may be necessary for carrying out the different activities within the laboratory.

(b) The analytical instruments shall be housed in dust-tree environment and whenever required, conditions of temperature and humidity shall be maintained and periodic checks on temperature and humidity be made and recorded.

(c) The instruments, instrument bench and surrounding areas shall be kept clean and tidy at all times,

(d) Instruments requiring calibration shall be calibrated at regular intervals and records of such calibration or maintenance be maintained and there shall be written instructions in the form of Standard Operating Procedures for the operation, maintenance and calibration of instruments.

(e) Equipment records shall be maintained and such records shall contain the following:—

(i) name of equipment or machine or apparatus;
(ii) manufacturer's name, model number and type of identification;
(iii) serial number;
(iv) date on which equipment was received in laboratory;
(v) current location;
(vi) condition when received *(e.g.*, new, used, re-conditioned);
(vii) copy of the manufacturer's operating instructions;
(viii) frequency of calibration;
(ix) frequency of maintenance;
(x) log Book (day-to-day entry including status of the equipment)
(xi) staff responsible for monitoring the calibration and maintenance status of the equipment;
(xii) calibrating records;
(xiii) list of authorised users or operators, if any;
(xiv) history of any damage, malfunction, modification or upgradation, repair and calibration;
(xv) list of spares and accessories, if any.

(f) A progress register for non-functional equipments and action for procurement of spares and accessories, monitoring thereof, shall be maintained.

(g) A Standard Operating Procedure for preventive maintenance of machine or equipment or apparatus shall be prepared by the laboratory.

(h) Other equipments such as burettes, pipettes, volumetric flasks, weight boxes, thermometers, etc., shall be thoroughly checked for accuracy of calibration before acceptance for use.

(i) Maintenance procedure in the form of Standard Operating Procedures must be prepared and regular servicing must be performed by the maintenance engineer or specialist.

(j) Equipments, instruments giving anomalous results or defective must be labeled as 'out-of-order' till they are repaired and after instrument is repaired it should be calibrated before use.

(k) The maintenance of equipments for services like electricity, gas, water, steam, and compressed gas shall be handled by competent person.

(1) Autoclaves must meet the requirements described for operations, safety and validation procedures, and the validation carried out by the laboratory shall be recorded.

(m) Fume Cupboards. Work involving the evolution of harmful and obnoxious vapours shall be carried out in a fume cupboard. The exhaust system of the fume cupboard shall be checked frequently to ensure that it is in order. There should be a water drainage system inside the fume cupboard and shall be checked frequently to ensure that there is no water logging and it is in order.

5. Chemicals and Reagents:

(a) The storage and handling of chemicals and reagents shall be done in a manner considering the physicochemical properties of these substances and the hazards involved in their use.

(b) All reagents and solutions in the laboratory shall be property identified with a label.

(c) A standardisation register shall be maintained by the laboratory along with its raw data and Standard Operating Procedure for preparation and standardisation on stock solutions, standard solutions, volumetric solutions must be prepared for the guidance of staff.

(d) Containers of stock solutions and of standard solutions shall bear the following details:—

(i) name of analytical chemist who prepared the solution;

(ii) date of preparation;

(iii) Each volumetric solution shall have "use before date" depending upon the stability of the solution; and

(iv) standardisation records.

(e) The transfer of hazardous chemicals and regents from one container to another container shall be carried out with suitable equipment by taking the care of safety and no make-shift or hazardous methods must be resorted to.

6. Good house keeping and safety:

(a) General and specific written down instructions for safety shall be circulated to each staff member and the instructions be revised periodically as appropriate *(e.g.,* poster displays, audio-visual material and by seminars/conferences).

(b) Standard Operating Procedure for safety, house-keeping and loss prevention shall be prepared in accordance with the various rules, and regulations of the Government of India and include the following requirements, namely:—

(i) safety data sheets must be made available to staff before testing is carried out;

(ii) drinking, eating and smoking shall riot be permitted in the laboratories; food for human consumption shall not be kept in working or storage areas; food meant for test animals shall be handled by the workers under the guidance of a veterinary doctor or qualified person. In the animal house, the facilities for collection and disposal of animal waste or safe sanitary storage of waste before removal from testing be provided;

(iii) staff must wear laboratory coats or other protective clothing including gloves and face masks and eye protection wherever required;

(iv) the laboratories shall have adequate first aid kit and fire fighting equipments located at the right places and the staff must be familiar and trained with the use of fire fighting equipment including fire extinguishers, fire blankets and gas masks;

(v) operators carrying out sterility tests shall wear sterilised garments including headgear, face masks and shoes;

(vi) the staff must be educated in the first aid techniques, emergency care and use of antidotes; and

(vii) safety rules in handling cylinders of compressed gases must be observed and staff must be familiar with relevant colour identification codes;

(c) Protective precautions to be taken in Laboratories—

(i) water showers shall be installed at appropriate places in the laboratory;

(ii) rubber suction bulbs must be used on manual pipettes and siphons;

(iii) warnings, precautions, and written instructions must be given for work with violent, uncontrollable or dangerous reactions *(e.g.,* mixing water and acids, biological such as infectious agents, etc.);

(iv) appropriate facilities for the collection, storage, and disposal of wastes shall be made available;

(v) staff must be aware of methods for safe disposal of corrosive or dangerous products by neutralisation or deactivation and of the need for complete disposal of mercury and its salts;

(vi) staff must also be aware about the safety precautions to be adopted while handling potassium cyanide and cyanogen bromide;

(vii) a Standard Operating Procedure for handling, collection, disposal of chemical and biological wastes be prepared.

7. Maintenance, calibration and validation of equipments:

(a) All equipments, instruments and other devices used in the laboratory shall use appropriate methods and procedures for all tests or

calibrations and they shall be regularly calibrated and validated. The frequency of calibration may differ from instrument to instrument.

(b) The original equipment manufacturer's recommendations along with the experience of the laboratory staff and the use of equipment per day may also be considered while fixing the frequency of calibration.

(c) For most of the equipments and instruments, Standard Operating Procedures for calibration and calibration schedule be prepared by the laboratory and a logbook shall also be prepared by each laboratory for proper documentation of calibration results.

8. Reference materials:

(a) Reference materials are necessary for the testing and, or calibration, validation or verification of a sample or of equipment, instruments or other devices and all such materials shall be traceable to agency authorised by Government of India or any other International body.

(b) The laboratory shall prepare working standard by comparing with the reference standards and shall be routinely checked for their purity by selecting parameters such as identity, loss on drying or on water, impurity and assay, etc.

(c) Whenever, any new reference material is received by the laboratory, a code number shall be assigned and this code number shall be quoted on the laboratory note book and analytical work sheet. The working standard shall also be provided with identification code.

(d) A register pertaining to reference and working materials must be maintained by the laboratory. The following details may be mentioned in the register:—

(i) source of supply;
(ii) code number of the reference material;
(iii) date of receipt;
(iv) batch number or identification number of the supplying agency;

(v) details like assay value, water content or any other information provided;

(vi) storage condition of the material; and

(vii) date of expiry, if any and date of manufacturing if possible.

(e) All working standards shall be checked at appropriate intervals or before use to ensure that it has not deteriorated or decomposed during storage. These observations be recorded in a register. All the reference and working standards shall be stored at appropriate storage condition; those requiring storage between 2-8°C shall be stored in a refrigerator. Wherever recommended the material may not be allowed to be frozen.

9. Microbiological Cultures:

(a) Standard Operating Procedure for maintenance of microbial culture and subculture must be prepared by the laboratories.

(b) If the cultures have become non-viable or mutant, proper procedure shall be followed to destroy these cultures by autoclaving under an authorised personnel for biological testing. Preferably not more than five passages may be prepared.

(c) All activities be carried out in a aseptic area by authorised person.

(d) The laboratories shall perform standard biochemical tests on the sub-culture as given in literature to ensure their viability,

10. Quality system:

The quality system shall be designed to ensure the following objectives:—

(a) the measurements and calibrations shall fully conform to the compendial requirements and the methods demonstrably based on validation protocols are followed;

(b) it shall be effective in providing necessary assurance that the activities or processes or techniques or practices comply with planned arrangements;

(c) it helps in early detection and correction of non-conformities;

(d) remedial action on the observations by internal and external audits are taken appropriately; and

(e) it shall have a documented quality policy for the organisation.

11. Internal quality system audits:

(a) Internal audits are done to assure the integrity of the analysis and such audits shall be conducted periodically with a predetermined schedule and procedure with appropriate checklist, to verify that the operations continue to comply with the requirements of quality system and requirements of regulator authorities. Internal quality audits shall be carried out by trained and qualified personnel who are independent of the activity to be audited.

(b) The periodicity of quality audit shall be fixed by the Head of the laboratory so that each activity is audited at least once in a year.

(c) Head of the laboratory will be responsible for initiation of the corrective action arising from audits and verification of corrective action.

(d) Whenever any non-compliance or any diversion is noticed by the team in implementing quality policy or quality system, protocols, the same will be attended by the Quality Manager. The problem will be analysed and necessary actions will be taken with proper documentation.

(e) The Quality Manager shall maintain all the records of the analysis being conducted which includes test system, the type of analysis, date on which analysis, is done, etc., and quality Manager shall also maintain copies of all protocols pertaining to different activities being checked by the audit team.

12. Management review:

Quality system reviews shall be conducted by the top management atleast once in every twelve months and the agenda of review shall generally cover the following:—

(i) report or input of internal audits;
(ii) matter arising from previous reviews;
(iii) report of external audits, if any;
(iv) surveillance report, if any;
(v) result of proficiency testing;
(vi) complaints or feedback received from users of laboratory services;
(vii) details of in-house quality control checks;
(viii) need of amendment of the quality system and documentation;
(ix) induction training of new staff; and
(x) any other requirements of the laboratory.

13. Standard Operating Procedures:

(a) Standard Operating Procedures are written procedures for different activities being conducted in a laboratory and shall include the following characteristics:—

(i) they shall be written in a chronological order listing different steps leading to an analysis of drugs or calibration of an instrument;

(ii) testing laboratories shall have Standard Operative Procedure manuals and have its periodic review;

(iii) it shall be user friendly documents and shall include designation of the person responsible for intended activity.

(b) Standard Operating Procedures in addition to those recommended under various activities shall also be prepared to the minimum in respect of the following:—

(i) sample handling and accountability;
(ii) receipt identification, storage, mixing and method sampling of the test and control articles;
(iii) record keeping, reporting, storage and retrieval of data;
(iv) coding of different studies, handling of data including use of computerized data system;

(v) operation of technical audit personnel in performing and reporting audits, inspections and final report reviews;
(vi) routine inspection of cleaning, maintenance, testing, calibration and standardisation of instruments;
(vii) action to be taken in respect of equipment failure;
(viii) analytical data methods;
(ix) the raw data;
(x) data handling and storage retrieval;
(xi) health and safety protection;
(xii) animal room preparations;
(xiii) animal care;
(xiv) storage and maintenance of microbial cultures;
(xv) maintenance of sterility room *(i.e.,* constant maintenance and monitoring of Aseptic condition of sterility room);
(xvi) use and storage of reference standards;
(xvii) procurement of stores and equipment;
(xviii) monitoring of testing of samples;
(xix) method of retention of unexpended sample, their location, maintenance and disposal;
(xx) document control;
(xxi) redressal of technical complaints;
(xxii) housing-keeping;
(xxiii) corrective and preventive action;
(xxiv) working procedure (test methods);
(xxv) calibration Manual; and
(xxvi) training manual.

14. Protocols and specifications archive:

(a) Every laboratory shall have a specification archive and current versions of all necessary specifications shall be kept as per the requirements of the Act and the rules made thereunder and the National Pharmacopoeia (Indian Pharmacopoeia).

(b) All updates and corrections must be noted in the mas ter volumes of Pharmacopoeias to prevent the use of obsolete sections; supplement and addendum shall also be made available in the laboratory.

(c) The specification archive shall contain the following:—

(i) list of all the pharmacopoeias;

(ii) a file on patent and proprietary medicines (non-pharmacopoeial) test methods to specifications prepared and validated by the manufacturer or by the laboratory itself. The test methods shall be submitted to the concerned Drug Control Authority. The validated test methods developed by the manufacturer or the laboratory shall stand to the requirements of compendial parameters in regard to its precision, accuracy, reproducibility, specificity, linearity, and ruggedness, etc.

15. Raw data:

(a) Raw data refers to the laboratory work sheet, note books or analysis sheet, records, memorandum, notes or extract copies thereof that may be the results of general observations and other activities and such raw data shall include hand written notes, photographs, software, drawings, computer printouts, spectral charts, dictated observations or recorded data from automated equipments. The raw data also includes record on receipt of animals, result of environmental monitoring, calibration, records of equipments, integrator output from analytical equipment, including work-sheet used to read a note, information from Light Emitting Diode (LED) display of any equipment.

(b) A single line shall strike through the data being changed; the correct information shall be recorded along with the old data and the reason of change. The analyst making the change shall be identified by his signature with date. In case of automated data collection system, the person responsible shall be identified at the time of data output. The original entry must be saved and the system shall have audit trail for all the data.

(c) Data integrity and security shall be maintained and the data shall not be accessible to any unauthorised person.

16. Storage and archival:

(a) The residual sample shall be retained in proper storage condition, for a period of one year after the final report.

(b) The laboratory must establish and maintain procedures for the identification collection, indexing, retrieval, storage, maintenance, and disposal of all quality documents.

(c) All the raw data, documentation, Standard Operative Procedures, protocols, and final reports are to be retained and there shall be archives for orderly storage and expeditious retrieval of all raw data, documentation, protocols, interim and final report. The archive shall provide a suitable environment that will prevent modification, damage, or deterioration and/or loss.

(d) The condition under which the original documents are stored must ensure their security and confidentiality.

(e) Paper documents shall not be kept for long periods under high humidity and raw data in the form of tape and discs are to be preserved with care.

(f) In case of storage of only optical disc, the life of disc shall be longer than the storage time.

(g) Raw data on thermal paper might fade away with time; therefore, a photocopy of the thermal paper shall also be retained in the archive.

(h) Time for which records are retained shall be prescribed in the document.]

[1191][SCHEDULE M

[See rules 71, 74, 76 and 78]

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR PHARMACEUTICAL PRODUCTS

Note.—To achieve the objectives listed below, each licensee shall evolve appropriate methodology, systems and procedures which shall be documented and maintained for inspection and reference; and the manufacturing premises shall be used exclusively for production of drugs and no other manufacturing activity shall be undertaken therein.

PART I

GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS: MAIN PRINCIPLES

1. Pharmaceutical Quality System (PQS):

1.1. The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the licence and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in different departments and at all levels within the company, the company's suppliers and the distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented pharmaceutical quality system incorporating Good Manufacturing Practices (GMP) and Quality Risk Management (QRM).

1.2. Senior management has the ultimate responsibility to ensure that an effective pharmaceutical quality system is in place, is adequately resourced, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the pharmaceutical quality system is essential. This shall ensure the support and commitment of staff at all levels and sites within the organisation to the pharmaceutical quality system.

1.3. Quality management is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality management, therefore, incorporates Good Manufacturing Practices and other factors, including those outside the scope of this

Part, such as product design and development.

1.4. Good Manufacturing Practices applies to the life-cycle stages from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, until the product discontinuation. The product quality system can extend to the pharmaceutical development life-cycle stages and shall facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. All parts of the product quality system shall be adequately resourced and maintained, including being provided with sufficient competent personnel, suitable premises, equipment and facilities.

1.5. The product quality system appropriate to the manufacture of pharmaceutical products shall ensure that—

(a) product realisation is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

(b) product and process knowledge is managed throughout all lifecycle stages;

(c) pharmaceutical products are designed and developed in a way that takes into account, the requirements of GMP and other GXPs such as those of Good Laboratory Practices (GLP) and Good Clinical Practices (GCP);

(d) production and quality control operations shall be clearly specified in a written form and GMP requirements are adopted;

(e) managerial responsibilities are clearly specified in the job descriptions;

(f) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;

(g) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out;

(h) the finished product is correctly processed and checked, according to the defined procedures;

(i) pharmaceutical products are not sold or supplied before the authorised

persons have certified that each production batch has been produced and controlled in accordance with the requirements of the licence and other applicable regulations relevant to the production, control and release of pharmaceutical products;

(j) processes are in place to ensure the management of outsourced activities;

(k) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;

(l) there is a procedure for self-inspection or quality audit that regularly appraises the effectiveness and applicability of the product quality system;

(m) product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviations occurring in the future;

(n) arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to their implementation, taking into account regulatory notification and approval where required. After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;

(o) regular reviews of the quality of pharmaceutical products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;

(p) a state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;

(q) continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;

(r) there is a system for QRM; and

(s) deviations, suspected product defects and other problems are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations. The most likely root causes shall be identified and appropriate corrective and preventive actions shall be identified and taken. The effectiveness of corrective and

preventive actions shall be monitored.

1.6. There shall be periodic management reviews, with the involvement of senior management, of the operation of the product quality system to identify opportunities for continual improvement of products, processes and the system itself. Unless otherwise justified, such reviews shall be conducted at least annually.

1.7. The product quality system shall be defined and documented. A quality manual or an equivalent documentation shall be established and shall contain a description of the quality management system including management responsibilities.

2. Quality Risk Management (QRM):

2.1. Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

2.2. Quality Risk Management shall ensure that the-

(a) evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

(b) level of effort, formality and documentation of the QRM process is commensurate with the level of risk.

2.3. Product quality review-

2.3.1. Regular, periodic or rolling quality reviews of all pharmaceutical products, including products for export only, shall be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

2.3.2. Such reviews shall normally be conducted and documented annually, taking into account previous reviews, and shall include at least,-

(a) review of starting materials and packaging materials used for the product, especially those from new sources and in particular the review of supply chain traceability of active substances;

(b) a review of critical in-process controls, and finished product results;
(c) a review of all batches that failed to meet established specifications and their investigation;
(d) a review of all significant deviations or non-conformity, the related investigations and the effectiveness of resultant corrective and preventive actions taken;
(e) a review of all changes made to the processes or analytical methods;
(f) a review of dossier variations submitted, granted or refused;
(g) a review of the results of the stability monitoring programme and any adverse trends;
(h) a review of all quality related returns, complaints and recalls and the investigations performed at the time;
(i) a review of adequacy of any other previous corrective actions on product processes or equipment;
(j) post marketing commitments for new dossiers and variations to the dossiers;
(k) the qualification status of relevant equipment and utilities, e.g., heating, ventilation, and air conditioning, water or compressed gases and a review of the results of monitoring the output of such equipment and utilities; and
(l) a review of technical agreements to ensure that they are up to date.

2.3.3. The manufacturer shall evaluate the results of the review and an assessment shall be made as to whether corrective and preventive actions or any revalidation shall be undertaken, under the product quality system. Corrective and preventive actions shall be completed in a timely and effective manner, according to documented procedures. There shall be procedures for the on-going management and review of these actions, and the effectiveness of these procedures shall be verified during self-inspection. Quality reviews may be grouped by product type e.g., solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified. There shall be a technical agreement in place between the various parties that

defines their respective responsibilities in producing the quality review. The authorised person responsible for final batch certification shall ensure that the quality review is performed in a timely manner and is accurate.

3. Good manufacturing practices for pharmaceutical products:

3.1. Good manufacturing practices is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use as required by the conditions of licence, clinical trial permission or product specifications. Good manufacturing practices are concerned with both production and quality control. Good manufacturing practices are aimed primarily at managing and minimising the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products. Under Good manufacturing practices—

(1) all manufacturing processes are clearly defined, systematically reviewed for associated risks in the light of scientific knowledge and experience and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;

(2) qualification and validation are performed;

(3) all necessary resources are provided, including the following, namely-

(a) sufficient and appropriately qualified and trained personnel;

(b) adequate premises and space;

(c) suitable equipment and services;

(d) appropriate materials, containers and labels;

(e) approved procedures and instructions;

(f) suitable storage and transport;

(g) adequate personnel, laboratories and equipment are in process controls; and

(h) books necessary for ensuring compliance with the requirements relating to product development, manufacturing and quality control testing such as the Drugs and Cosmetics Act, 1940, the Drugs Rules, 1945, the Indian Pharmacopoeia (Current Edition) and other relevant books and guidance documents officially issued by the Ministry of Health and Family Welfare, Government of India;

(4) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
(5) procedures are carried out correctly and personnel are trained to do so;
(6) records are made (manually or by recording instruments or by both) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive action is implemented;
(7) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
(8) the proper storage and distribution of the products which minimises any risk to their quality;
(9) a system is available to recall any batch of product from sale or supply; and
(10) complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures are taken in respect of the defective products to prevent recurrence.

4. Sanitation and hygiene:

A high level of sanitation and hygiene shall be practiced in every aspect of the manufacture of drugs. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection and anything that could become a source of contamination to the product. Potential sources of contamination shall be eliminated through an integrated comprehensive programme of sanitation and hygiene.

5. Qualification and validation:

5.1. In accordance with GMP, each pharmaceutical company shall identify what qualification and validation work is required to prove that the critical aspects of their particular operation is controlled.
5.2. The key elements of a qualification and validation programme of a company shall be clearly defined and documented in a validation master plan.

5.3. Qualification and validation shall establish and provide documentary evidence that—

(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for good manufacturing practices [design qualification (DQ)];

(b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications [installation qualification (IQ)];

(c) the premises, supporting utilities and equipment operate in accordance with their design specifications [operational qualification (OQ)];

(d) a specific process shall consistently produce a product meeting its predetermined specifications and quality attributes [process validation (PV), also called performance qualification (PQ)].

5.4. Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, shall be qualified and validated.

5.5. Qualification and validation shall not be considered as one-off exercises. An on-going programme shall follow their first implementation and shall be based on a periodic review.

5.6. The commitment to maintain continued validation status shall be stated in the relevant company documentation, such as the quality manual or validation master plan.

5.7. The responsibility for performing validation shall be clearly defined.

5.8. Validation studies are an essential part of good manufacturing practices and shall be conducted in accordance with predefined and approved protocols.

5.9. A written report summarising the results recorded and the conclusions reached shall be prepared and stored.

5.10. Processes and procedures shall be established on the basis of the results of the validation performed.

5.11. Particular attention shall be paid to the validation of analytical test methods, automated systems and cleaning procedures.

5.12. The premises, equipment or process system, facility qualification and validation shall be carried out.

6. Complaints and adverse reaction:

6.1. All complaints and other information concerning potentially defective products shall be carefully reviewed according to the written procedures and corrective action shall be taken.

6.2. A person responsible for handling the complaints and deciding the measures to be taken shall be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorised person, the latter shall be made aware of any complaint, investigation or recall.

6.3. There shall be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

6.4. Special attention shall be given to establishing that the product that gave rise to a complaint was defective.

6.5. Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control (QC) shall normally be involved in the review of such investigations.

6.6. If a product defect is identified or suspected in a batch, consideration shall be given as to whether other batches shall be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch shall be investigated.

6.7. Where necessary, appropriate follow-up action, possibly including product recall, shall be taken after investigation and evaluation of the complaint.

6.8. All decisions made and measures taken as a result of a complaint shall be recorded and referenced to the corresponding batch records.

6.9. Complaint records shall be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

6.10. The licensing authorities shall be informed if a manufacturer is considering action following the faulty manufacture, product deterioration, a suspect product or any other serious quality problems with a product.

6.11. The licensee shall have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the adverse drug reactions emerging

from the use of drugs manufactured or marketed by the licensee.

7. Product recalls:

7.1. There shall be a system to recall from the market, products known or suspected to be defective.

7.2. The authorised person shall be responsible for the execution and coordination of recalls. He or she shall have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

7.3. There shall be established written procedures, which are regularly reviewed and updated, for the organisation of any recall activity. Recall operations shall be capable of being initiated at the required level in the distribution chain.

7.4. An instruction shall be included in the written procedures to store recalled products in a secure segregated area.

7.5. The licensing authorities shall be informed of any intention to recall the product because it is, or is suspected of being, defective.

7.6. The distribution records shall be readily available to the authorised person, and they shall contain sufficient information on wholesalers and directly supplied customers to permit an effective recall.

7.7. The progress of the recall process shall be monitored and recorded. Records shall include the disposition of the product. A final report shall be issued, including reconciliation between the delivered and recovered quantities of the products.

7.8. The effectiveness of the arrangements for recall shall be tested and evaluated from time to time.

7.9. A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard.

7.10. There shall be an established written procedure in the form of Standard Operating Procedure for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated, so as to effectively reach at the level of each distribution channel.

7.11. The distribution records shall be readily made available to the persons designated for recall.

7.12. The designated person shall record a final report issued, including

reconciliation between the delivered and the recovered quantities of the products.

7.13. The effectiveness of the arrangements for recall shall be evaluated from time to time.

7.14. The recalled products shall be stored separately in a secured segregated area pending final decision on them.

8. Change control:

8.1. A formal change control system shall be established to evaluate all changes that may affect the production and control of the product.

8.2. Written procedures shall cover the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

8.3. Any proposals for relevant changes to GMP shall be drafted, reviewed and approved by the appropriate organisational units and reviewed and approved by the quality units.

8.4. The potential impact of the proposed change on the quality of the intermediate or Active Pharmaceutical Ingredient (API) or finished product shall be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on their nature and extent and the effect of these changes may have on the process. Scientific judgement shall be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.

8.5. When implementing the approved changes, measures shall be taken to ensure that all the documents are affected by the changes as revised.

8.6. After the change has been implemented there shall be an evaluation of the first batch produced or tested under the change.

8.7. The potential for critical changes to affect established retest or expiry dates shall be evaluated. If necessary, samples of the intermediate or API or finished product produced by the modified process can be placed on an accelerated stability programme or can be added to the stability monitoring programme or both.

9. Production under loan licence or contract and contract analysis and other activities:

9.1. **Principle-** Production under loan licence or contract and contract analysis and any other activity covered by good manufacturing practices must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

9.2. **General-**

9.2.1. All arrangements for production under loan licence or contract and analysis, including technology transfer and any proposed changes in technical or other arrangements, shall be in accordance with the licence for the product concerned.

9.2.2. The contract shall permit the loan licensee or contract giver to audit the facilities and activities of the manufacturing facility provider or contract acceptor or mutually agreed sub-contractors.

9.2.3. In the case of contract analysis, the final approval for release must be given by the authorised person in accordance with good manufacturing practices and the licence as specified in the contract.

9.3. **Loan licensee or contract giver-**

9.3.1. The product quality system of the loan licensee or contract giver shall include the control and review of any outsourced activities. The contract giver is responsible for assessing the legality, suitability and competence of the manufacturing facility provider or contract acceptor to successfully carry out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of good manufacturing practices incorporating quality risk management principles are followed.

9.3.2. The loan licensee or contract giver shall provide the manufacturing facility provider or contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the licence and any other legal requirements. The loan licensee or contract giver shall ensure that the manufacturing facility provider or contract acceptor is fully aware of any hazards associated with the product, work or tests that might pose a risk to premises, equipment, personnel, other

materials or other products.

9.3.3. The loan licensee or contract giver shall review and assess the records and results related to the outsourced activities. The contract giver shall ensure that all the products and materials delivered by the manufacturing facility provider or contract acceptor have been processed in accordance with good manufacturing practices and the licence; comply with their specifications and that the product has been released by the authorised person in accordance with good manufacturing practices and the licence.

9.3.4. The loan licensee or contract giver shall monitor and review the performance of the manufacturing facility provider or contract acceptor including the implementation of any needed improvements and their effectiveness.

9.3.5. The loan licensee or contract giver is responsible for ensuring that the manufacturing facility provider or contract acceptor understands that his or her activities may be subject to inspection by the competent authorities.

9.4. **Manufacturing facility provider or contract acceptor-**

9.4.1. The manufacturing facility provider or contract acceptor must have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work ordered by the loan licensee or contract giver. Contract manufacture shall be undertaken only by a manufacturer who holds a valid manufacturing licence.

9.4.2. The manufacturing facility provider or contract acceptor shall not pass to a third party any of the work entrusted to him or her under the contract without the loan licensee or contract giver's prior evaluation and approval of the arrangements. Arrangements made between the manufacturing facility provider or contract acceptor and any third party shall ensure that information and knowledge, including that from assessments of the suitability of the third party, are made available in the same way as between the original loan licensee or contract giver and contract acceptor.

9.4.3. The manufacturing facility provider or contract acceptor shall refrain from any activity (including unauthorised changes outside the terms of the contract) that may adversely affect the quality of

the product manufactured oranalysed or both for the loan licensee or contract giver.

9.5. **Contract-**

9.5.1. There must be a written contract between the loan licensee or contract giver and the manufacturing facility provider or contract acceptor which clearly establishes the responsibilities of each party, covering the outsourced activities, the products or operations to which they are related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it.

9.5.2. The contract must clearly state the way in which the authorised person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the licence.

9.5.3. Technical aspects of the contract shall be drawn up by competent persons with suitable knowledge of pharmaceutical technology, analysis and good manufacturing practices.

9.5.4. All arrangements for production and analysis must be in accordance with the licence and agreed by both parties.

9.5.5. The contract shall clearly describe who is responsible for contracted activities e.g., knowledge management, technology transfer, supply chain, sub-contracting, testing and releasing materials and undertaking production and quality control, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract shall state whether or not the manufacturing facility provider or contract acceptor shall take samples at the premises of the manufacturer.

9.5.6. Manufacturing, analytical and distribution records, and reference samples, shall be kept by, or be available to, the loan licensee or contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect, or to investigating a suspected product or laboratory fraud, must be accessible and specified in the procedures of the loan licensee or contract giver.

9.5.7. The contract shall describe the handling of starting materials,

intermediate, bulk and finished products, if they are rejected. It shall also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

10. Self-inspection, quality audits and suppliers' audits and approval:

10.1. The purpose of self-inspection is to evaluate the manufacturer's compliance with good manufacturing practices in all aspects of production and QC. The self-inspection programme shall be designed to detect any shortcomings in the implementation of good manufacturing practices and to recommend the necessary corrective actions. Self-inspections shall be performed routinely, and may be, in addition, performed on special occasions e.g., in the case of product recall or repeated rejections, or when an inspection by the regulatory authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of good manufacturing practices objectively. All recommendations for corrective action shall be implemented. The procedure for self-inspection shall be documented and there shall be an effective follow-up programme.

10.2. **Items for self-inspection**-Written instructions for self-inspection shall be established to provide a minimum and uniform standard of requirements. These may include questionnaires on good manufacturing practices requirements covering at least the following items, namely:-

(a) personnel;
(b) premises including personnel facilities;
(c) maintenance of buildings and equipment;
(d) storage of starting materials and finished products;
(e) equipment;
(f) production and in-process controls;
(g) quality control (QC);
(h) documentation;
(i) sanitation and hygiene;
(j) validation and revalidation programmes;
(k) calibration of instruments or measurement systems;
(l) recall procedures;
(m) complaints management;

(n) labels control; and

(o) results of previous self-inspections and any corrective steps taken.

10.3. **Self-inspection team-** Management shall appoint a self-inspection team consisting of experts in their respective fields who are familiar with GMP. The members of the team may be appointed from inside or outside the company.

10.4. **Frequency of self-inspection-** The frequency with which self-inspections are conducted may depend on company requirements but shall be at least once in a year. The frequency shall be stated in the procedure.

10.5. **Self-inspection report-** A report shall be made at the completion of a self-inspection. The report shall include the following, namely:-

(a) self-inspection results;

(b) evaluation and conclusions; and

(c) recommended corrective actions.

10.6. **Follow-up action-** There shall be an effective follow-up programme. The company management shall evaluate both the self-inspection report and the corrective actions as necessary.

10.7. **Quality audit-** It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

10.8. **Suppliers' audits and approval-**

10.8.1. The person responsible for quality control shall have responsibility, together with other relevant departments, for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

10.8.2. Before suppliers are approved and included in the approved suppliers' list or specifications, they shall be evaluated. The evaluation shall take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it shall determine the supplier's ability to conform with good manufacturing practices standards.

11. Personnel:

11.1. Principle- The establishment and maintenance of a satisfactory system of Quality Assurance (QA) and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities shall be clearly defined and understood by the persons concerned and recorded as written descriptions.

11.2. General-

11.2.1. The manufacturer shall have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual shall not be so extensive as to present any risk to quality.

11.2.2. Responsible staff shall have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities. Its duties may be delegated to designated deputies with a satisfactory level of qualifications. There shall be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of good manufacturing practices. The manufacturer shall have an organisation chart.

11.2.3. All personnel shall be aware of the principles of good manufacturing practices that affect them and receive initial and continuing training, including hygiene instruction, relevant to their needs. All personnel shall be motivated to support the establishment and maintenance of high quality standards.

11.2.4. Steps shall be taken to prevent unauthorised people from entering production, storage and QC areas. Personnel who do not work in these areas shall not use them as a passageway.

11.3. Key personnel-

11.3.1. Key personnel include the heads of production, the heads of quality units and the authorised person. The quality units typically comprise the QA and QC functions. In some cases, these could be combined in one department. The authorised person may also be responsible for one or more of these quality units. Normally, key posts shall be occupied by full-time personnel. The heads of production and quality units shall be

independent of each other. In large organisations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

11.3.2. Key personnel responsible for supervising the production and quality units for pharmaceutical products shall possess the qualifications and experience as specified under the rules. Their education shall include the study of an appropriate combination of the following, namely:-

(a) chemistry (analytical or organic) or biochemistry;
(b) chemical engineering;
(c) microbiology;
(d) pharmaceutical sciences and technology;
(e) pharmacology and toxicology;
(f) physiology; or
(g) other related sciences.

They shall also have adequate practical experience in the manufacture and QA of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they shall perform their duties under professional guidance. The scientific education and practical experience of experts shall be such, so as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and QC of pharmaceutical products.

11.3.3. The heads of the production and the quality units shall have shared, or jointly exercised, responsibilities relating to quality. They may include the following, namely:-

(a) authorisation of written procedures and other documents, including amendments;
(b) monitoring and control of the manufacturing environment;
(c) plant hygiene;
(d) process validation and calibration of analytical apparatus;
(e) training, including the application and principles of QA;
(f) approval and monitoring of suppliers of materials;
(g) approval and monitoring of contract manufacturers;

(h) designation and monitoring of storage conditions for materials and products;
(i) performance and evaluation of in-process controls;
(j) retention of records;
(k) monitoring of compliance with good manufacturing practices requirements; and
(l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.

11.3.4. The head of production has the following responsibilities, namely:-
(a) to ensure that products are produced and stored in accordance with the appropriate documentation in order to obtain the required quality;
(b) to approve the instructions relating to production operations, including the in-process controls and to ensure their strict implementation;
(c) to ensure that the production records are evaluated and signed by a designated person;
(d) to check the maintenance of the department, premises and equipment;
(e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports are made available; and
(f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

11.3.5. The heads of the quality units generally have the following responsibilities, namely:-
(a) to approve or reject starting materials, packaging materials and intermediate, bulk and finished products in relation to their specifications;
(b) to evaluate batch records;
(c) to ensure that all necessary testing is carried out;
(d) to approve sampling instructions, specifications, test methods and other QC procedures;
(e) to approve and monitor analysis carried out under contract;
(f)to check the maintenance of the department, premises and

equipment;

(g) to ensure that the appropriate validations, including those of analytical procedures and calibrations of control equipment are carried out;

(h) to ensure that the required initial and continuing training of quality unit personnel is carried out and adapted according to need;

(i) establishment, implementation and maintenance of the quality system;

(j) supervision of the regular internal audits or self-inspections;

(k) participation in external audit (vendor audit); and

(l) participation in validation programmes.

11.3.6. The authorised person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval for the release of finished product for sale or supply.

11.3.7. Assessment of finished products shall embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product and an examination of the finished pack.

11.3.8. No batch of product is to be released for sale or supply prior to certification by the authorised persons.

11.3.9. The authorised person responsible for approving a batch for release shall always ensure that the following requirements have been met:-

(a) the licence and the approval requirements for the product have been met for the batch concerned;

(b) the principles and guidelines of GMP, as laid down in this Part, have been followed;

(c) the principal manufacturing and testing processes have been validated;

(d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;

(e) any planned changes or deviations in manufacturing or QC have been notified in accordance with a well-defined

reporting system before any product is released. Such changes may need notification and approval by the licensing authority;

(f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;

(g) all necessary production and QC documentation has been completed and endorsed by supervisors trained in appropriate disciplines;

(h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;

(i) approval has been given by the head of quality control; and

(j) all relevant factors have been considered, including the factor associated with the output batch directly under review (e.g., sub-division of output batches from a common input, factors associated with continuous production runs).

11.3.10. The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

11.4. Training-

11.4.1. The manufacturer shall provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into the control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

11.4.2. Besides basic training on the theory and practice of good manufacturing practices, newly recruited personnel shall receive training appropriate to the duties assigned to them. Continuous training shall also be given, and its practical effectiveness be assessed periodically. Approved training programmes shall be available. Training records shall be kept.

11.4.3. Personnel working in areas where contamination is a hazard e.g., clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, shall be given specific

training.

11.4.4. The concept of quality assurance and all the measures which aid its understanding and implementation shall be fully discussed during the training sessions.

11.4.5. Visitors or untrained personnel shall preferably not be taken into the production and quality control areas. If this is unavoidable, they shall be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They shall be closely supervised.

11.4.6. Consultant and contract staff shall be qualified for the services they provide. Evidence of this shall be included in the training records.

11.5. Personal hygiene-

11.5.1. All personnel, prior to and during employment, as appropriate, shall undergo health checkups. Personnel conducting visual inspections shall also undergo periodic eye checkups.

11.5.2. All personnel shall be trained in the practices of personal hygiene. A high level of personal hygiene shall be observed by all those concerned with manufacturing processes. In particular, personnel shall be instructed to wash and sanitise their hands before entering production areas. Signs to this effect shall be posted and instructions are complied with.

11.5.3. Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle starting materials, packaging materials, in-process materials or drugs until his or her health condition is no longer judged to be a risk.

11.5.4. All employees shall be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.

11.5.5. Direct contact shall be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk products.

11.5.6. To ensure protection of the product from contamination,

personnel shall wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, shall be stored in a separate closed containers until properly laundered and, if necessary, disinfected or sterilised.

11.5.7. Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines shall not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.

11.5.8. Personal hygiene procedures, including the wearing of protective clothing, shall apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g., contractors' employees, visitors, senior managers and inspectors.

12. Premises:

12.1. **Principle-** Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. They shall conform to the conditions as laid down in the Factories Act, 1948 (63 of 1948).

12.2. **General-**

12.2.1. The layout and design of premises must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products.

12.2.2. Where dust is generated (e.g., during sampling, weighing, mixing and processing operations or packaging of powder), measures shall be taken to avoid cross-contamination and facilitate cleaning.

12.2.3. Premises shall be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.2.4. Premises used for the manufacture of finished products shall be suitably designed and constructed to facilitate good sanitation.

12.2.5. Premises shall be carefully maintained, and it shall be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.2.6. Premises shall be cleaned and, where applicable, disinfected according to detailed written procedures and records shall be maintained.

12.2.7. Electrical supply, lighting, temperature, humidity and ventilation shall be appropriate and they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage or the accurate functioning of equipment.

12.2.8. The design, installation, qualification and maintenance of the Heating, Ventilation, Air Conditioning (HVAC) systems of the manufacturing plant shall be carried out.

12.2.9. Premises shall be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There shall be a procedure for rodent and pest control.

12.2.10. Premises shall be designed to ensure the logical flow of materials and personnel.

12.3. **Ancillary areas-**

12.3.1. Rest and refreshment rooms shall be separate from manufacturing and control areas.

12.3.2. Facilities for changing and storing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the number of users. Toilets shall not communicate directly with production or storage areas.

12.3.3. Maintenance workshops shall, if possible be separated from production areas. Whenever parts and tools are stored in the production area, they shall be kept in rooms or lockers reserved for that use.

12.3.4. Animal houses shall be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

12.4. **Storage areas-**

12.4.1. Storage areas shall be of sufficient capacity to allow orderly storage of the various categories of materials and products with

proper separation and segregation; starting and packaging materials, intermediates, bulk and finished products, products in quarantine and released, rejected, returned or recalled products.

12.4.2. Storage areas shall be designed or adapted to ensure good storage conditions. In particular, they shall be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature, humidity) they shall be provided, controlled, monitored and recorded, where appropriate.

12.4.3. Receiving and dispatch bays shall be separated and shall protect the materials and products from the weather. Receiving areas shall be designed and equipped to allow containers of incoming materials to be cleaned, if necessary, before storage.

12.4.4. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine shall give equivalent security.

12.4.5. Segregation shall be provided for the storage of rejected, recalled or returned materials or products.

12.4.6. Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion shall be stored in safe and secure areas.

12.4.7. Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention shall be paid to sampling and the safe and secure storage of these materials.

12.4.8. There shall normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it shall be conducted in such a way so as to prevent contamination or cross-contamination.

12.5. **Weighing areas-**The weighing of starting materials and the estimation of yield by weighing shall be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

12.6. **Production areas-**

12.6.1. In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitising materials (e.g., penicillins) or biological preparations (e.g., live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and non-pharmaceutical products, shall not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, shall not be allowed in premises used for the manufacture of pharmaceutical products.

12.6.2. Premises shall preferably be laid out in such a way so as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

12.6.3. The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

12.6.4. Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks and open joints, shall not shed particulate matter and shall permit easy and effective cleaning and, if necessary, disinfection.

12.6.5. Pipework, light fittings, ventilation points and other services shall be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they shall be accessible from outside the manufacturing areas.

12.6.6. Drains shall be of adequate size and designed and equipped to prevent back-flow. Open channels shall be avoided where possible, but if they are necessary they shall be shallow to facilitate cleaning and disinfection.

12.6.7. Production areas shall be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas shall be regularly monitored during both production and non-production periods so as to ensure compliance with their design specifications.

12.6.8. Premises for the packaging of pharmaceutical products shall be specifically designed and laid out so as to avoid mix ups, contamination or cross-contamination.

12.6.9. Production areas shall be well lit, particularly where visual online controls are carried out.

12.7. **Quality Control (QC) areas-**

12.7.1. QC laboratories shall be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed shall be separated from each other.

12.7.2. QC laboratories shall be designed to suit the operations to be carried out in them. Sufficient space shall be given to avoid mix ups and cross-contamination. There shall be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

12.7.3. The design of the laboratories shall take into account the suitability of construction materials, prevention of fumes, and ventilation. There shall be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

12.7.4. A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors or where it is

necessary to isolate the instruments.

13. Equipment:

13.1. Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

13.2. Equipment shall be installed in such a way so as to minimise any risk of error or of contamination.

13.3. Fixed pipework shall be clearly labelled to indicate the contents and, where applicable, the direction of flow.

13.4. All service pipework and devices shall be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

13.5. Balances and other measuring equipment of an appropriate range and precision shall be available for production and control operations and shall be calibrated according to a fixed schedule.

13.6. Production equipment shall be thoroughly cleaned according to a fixed schedule.

13.7. Laboratory equipment and instruments shall be suited to the testing procedures undertaken.

13.8. Washing, cleaning and drying equipment shall be chosen and used so as not to be a source of contamination.

13.9. Production equipment shall not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to an extent that would affect the quality of the product.

13.10. Defective equipment shall be removed from production and QC areas. If this is not possible, it shall be clearly labelled as defective to prevent use.

13.11. Closed equipment shall be used whenever appropriate. Where open equipment is used or equipment is opened, precautions shall be taken to minimize the contamination.

13.12. Non-dedicated equipment shall be cleaned according to validated cleaning procedures between being used for production of different

pharmaceutical products to prevent cross-contamination.

13.13. Current drawings of critical equipment and support systems shall be maintained.

14. Materials:

14.1. The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2. Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

14.3. No materials used for operations such as cleaning, lubrication of equipment and pest control shall come into direct contact with the product. Where possible, such materials shall be of a suitable grade (e.g., food grade) to minimise health risks.

14.4. All incoming materials and finished products shall be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5. All materials and products shall be stored under the appropriate conditions established by the manufacturer, and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule.

14.6. Water used in the manufacture of pharmaceutical products shall be suitable for its intended use. There shall be validated system for treatment of water drawn from own or any other source to render it potable in accordance with the standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce purified water conforming to Pharmacopoeial specification. Purified Water so produced shall only be used for all the operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf. Good manufacturing practices regarding the design, installation and operation of pharmaceutical water systems including guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients and dosage forms, shall be ensured.

14.7. The purchase of starting materials is an important operation that shall involve staff who has a particular and thorough knowledge of the products and suppliers.

14.8. Starting materials shall be purchased only from the approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is beneficial for all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, to be contractually agreed between the manufacturer and the supplier.

14.9. For each consignment, at a minimum, the containers shall be checked at least for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10. All incoming materials shall be checked to ensure that the consignment corresponds to the order. Containers shall be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information shall not be lost.

14.11. Damage to containers and any other problem that might adversely affect the quality of a material shall be recorded and reported to the QC Department and investigated.

14.12. If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

14.13. Starting materials in the storage area shall be appropriately labelled. Labels shall bear at least the following information, namely:—

(a) the designated name of the product and the internal code reference where applicable;

(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;

(c) the status of the contents (e.g., in quarantine, on test, released, rejected, returned or recalled); and

(d) where appropriate, an expiry date or a date beyond which retesting is necessary. When fully validated computerised storage systems

are used, not all of the above information need be in a legible form on the label.

14.14. Only raw materials which have been released by the QC Department and which are within their shelf-life shall be used.

14.15. The raw materials other than APIs, if released by QC Department without specific batch testing, for use in manufacturing, it shall be based on vendor approval and statistical data analysis of earlier test results of such material for release.

14.16. There shall be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn shall be identified.

14.17. Only starting materials released by the QC Department and within their shelf-life shall be used.

14.18. Starting materials shall be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

14.19. Each dispensed material and its weight or volume shall be independently checked and recorded.

14.20. Materials dispensed for each batch of the final product shall be kept together and conspicuously labelled as such.

14.21. The purchase, handling and control of primary and printed packaging materials shall as for starting materials.

14.22. Particular attention shall be paid to printed packaging materials. They shall be stored in secure conditions so as to exclude the possibility of unauthorised access. Roll feed labels shall be used wherever possible. Cut labels and other loose printed materials shall be stored and transported in separate closed containers so as to avoid mix ups. Packaging materials shall be issued for use only by designated personnel following an approved and documented procedure.

14.23. Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.

14.24. Out-dated or obsolete primary packaging material or printed packaging material shall be destroyed and its disposal shall be recorded.

14.25. All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity and

conformity with the packaging instructions.

14.26. All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validated test methods, sample sizes, specifications, cleaning procedure and sterilisation procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used.

14.26.1. Whenever bottles are being used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, they shall be rinsed with purified water or water for injection, as the case may be.

14.26.2. The requirements mentioned in this Part do not include requirements of machinery, equipment and premises required for preparation of containers and closures for different dosage forms and categories of drugs. The suitability and adequacy of the machinery, equipment and premises shall be examined taking into consideration the requirements of each licensee in this respect.

14.26.3. Packaging material to be used for pharmaceutical products shall be in accordance with the requirements prescribed in Indian Pharmacopoeia (IP).

14.27. Intermediate and bulk products shall be kept under appropriate conditions.

14.28. Intermediate and bulk products purchased shall be handled on receipt as they were starting materials.

14.29. Finished products shall be held in quarantine until their final release, after which they shall be stored as usable stock under conditions established by the manufacturer.

14.30. The evaluation of finished products and the documentation necessary for release of a product for sale are described in paragraph 19.

14.31. Rejected materials and products shall be clearly marked and stored separately in restricted areas. They shall either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken shall be approved by the authorised personnel and recorded.

14.32. The reworking or recovery of rejected products shall be exceptional.

It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. A record shall be kept of the reworking or recovery. A reworked batch shall be given a new batch number.

14.33. The introduction of all or part of earlier batches, conforming to the required quality standards, into a batch of the same product at a defined stage of manufacture shall be authorised beforehand. This recovery shall be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery shall be recorded.

14.34. The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, shall be considered by the QC Department.

14.35. Recalled products shall be identified and stored separately in a secure area until a decision is taken and the decision shall be made as soon as possible.

14.36. Products returned from the market shall be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the QC function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued shall be taken into account in the assessment. Where any doubt arises over the quality of the product, it shall not be considered suitable for reissue or reuse. Any action taken shall be appropriately recorded.

14.37. There shall be records for the receipt and preparation of reagents and culture media.

14.38. Reagents made up in the laboratory shall be prepared according to the written procedures and appropriately labelled. The label shall indicate the concentration, standardisation factor, shelf-life, the date when re-standardisation is due and the storage conditions. The label shall be signed and dated by the person preparing the reagent.

14.39. Both positive and negative controls shall be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls shall be appropriate to

the sensitivity required.

15. Reference Standards:

15.1. Whenever official reference standards exist, they shall be used.

15.2. Indian Pharmacopoeia reference standards shall be procured from Indian Pharmacopoeia Commission.

15.3. Official reference standards shall only be used for the purpose described in the appropriate monograph.

15.4. Reference standards prepared by the manufacturer shall be tested, released and stored in the same way as official standards. They shall be kept under the responsibility of a designated person in a secure area.

15.5. Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardisation.

15.6. Reference standards shall be properly labelled with at least the following information, namely-

(a) name of the material;
(b) batch or lot number and control number;
(c) date of preparation;
(d) shelf-life;
(e) potency; and
(f) storage conditions.

15.7. All in-house working standards or secondary standards shall be standardised against an official reference standard, when available, initially and at regular intervals thereafter.

15.8. All reference standards shall be stored and used in a manner that will not adversely affect their quality.

16. Waste materials:

16.1. Provision shall be made for the proper and safe storage of waste materials waiting disposal. Toxic substances and flammable materials shall be stored in suitably designed, separate, enclosed cupboards.

16.2. Waste material shall not be allowed to accumulate. It shall be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

16.3. The disposal of sewage and effluents (solid, liquid and gas) from the

manufacturing area shall be in conformity with the requirements of the guidelines issued by the Environmental Pollution Control Board.

16.4. All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 2016.

16.5. Rodenticides, insecticides, fumigating agents and sanitising materials shall not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

17. Documentation:

17.1. **Principle-**Good documentation is an essential part of the quality assurance system and, as such, shall exist for all aspects of good manufacturing practices. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorised persons have all the information necessary to decide whether or not to release a batch of a drug for sale; to ensure the existence of documented evidence, traceability and to provide records and an audit trial that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described in this paragraph may be brought together, but they will usually be separate.

17.2. **General-**

17.2.1. Documents shall be designed, prepared, reviewed and distributed with care. They shall comply with the relevant Parts of the manufacturing and licences.

17.2.2. Documents shall be approved, signed and dated by the responsible persons. No document shall be changed without authorisation and approval.

17.2.3. Documents shall have unambiguous contents; the title, nature and purpose shall be clearly stated. They shall be laid out in an orderly manner and be easy to check. Reproduced documents shall be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

17.2.4. Documents shall be regularly reviewed and kept up to date. When a document has been revised, a system shall exist to prevent inadvertent use of the superseded version. Superseded documents shall be retained for a specific period of time.

17.2.5. Where documents require the entry of data, these entries shall be clear, legible and indelible. Sufficient space shall be provided for such entries.

17.2.6. Any alteration made to a document shall be signed and dated; the alteration shall be done in such a way so as to permit the reading of the original information. Where appropriate, the reason for the alteration shall be recorded.

17.2.7. Records shall be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records shall be retained for at least one year after the expiry date of the finished product.

17.2.8. Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed SOPs relating to the system in use shall be available and the accuracy of the records shall be checked. If documentation is handled by electronic data-processing methods, only authorised persons shall be able to enter or modify data in the computer system, and there shall be a record of changes and deletions; access shall be restricted by passwords or other means and the entry of critical data shall be independently checked. Batch records stored electronically shall be protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is particularly important that, during the period of retention, the data are readily available.

17.2.9 The site master file shall be prepared and maintained up to date as per the Appendix-I this Part.

17.3. **Documents Required:**

17.3.1. **Labels-**

17.3.1.1. Labels applied to containers, equipment or premises shall be clear, unambiguous and in the company's

agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g., quarantined, accepted, reject0ed and clean).

17.3.1.2. All finished drugs shall be identified by labelling bearing at least the following information, namely:-

(a) the name of the drugs;

(b) a list of the active ingredients [if applicable, with the International Nonproprietary Names (INN)], showing the amount of each present and a statement of the net contents (e.g., number of dosage units, weight and volume);

(c) the batch number assigned by the manufacturer;

(d) the expiry date and date of manufacture in an uncoded form;

(e) any special storage conditions or handling precautions that may be necessary;

(f) directions for use, and warnings and precautions that may be necessary; and

(g) the name and address of the manufacturer or the company and the person responsible for placing the product on the market.

17.3.1.3. For reference standards, the label or accompanying document or both shall indicate potency or concentration, date of manufacture, expiry date, date the closure if it is first opened, storage conditions and control number, as appropriate.

17.3.2. **Specifications and testing procedures**

17.3.2.1. Testing procedures described in documents shall be validated in the context of available facilities and equipment before they are adopted for routine testing.

17.3.2.2. There shall be appropriately authorised and dated specifications, including tests on identity, content, purity and quality for starting and packaging materials and for finished products; where appropriate, they shall also be available for intermediate or bulk products. Specifications for water, solvents and

reagents (e.g., acids and bases) used in production shall be included.

17.3.2.3. Each specification shall be approved, signed and dated, and maintained by the QC or QA units. Specifications for starting materials, intermediates, bulk, finished products and packaging materials.

17.3.2.4. Periodic revisions of the specifications may be necessary to comply with new editions of the Indian pharmacopoeia or other official pharmacopoeia.

17.3.2.5. Pharmacopoeias, reference standards, reference spectra and other reference materials shall be available in the QC laboratory.

17.3.3. **Specifications for starting and packaging materials-**

17.3.3.1. Specifications for starting, primary and printed packaging materials shall provide, if applicable, a description of the materials, including—

(a) the designated name (if applicable, the INN) and internal code reference;

(b) the reference, if any, to a pharmacopoeial monograph; and

(c) qualitative and quantitative requirements with acceptance limits.

17.3.3.2. Depending on the company's practice other data may be added to the specification, namely:-

(a) the supplier and the original producer of the materials;

(b) a specimen of printed materials;

(c) directions for sampling and testing, or a reference to procedures;

(d) storage conditions and precautions; and

(e) the maximum period of storage before re-examination.

17.3.3.3. Packaging material shall conform to the specifications and shall be compatible with the material or with the drugs or both it contains. The material shall be examined for compliance with the specification, and

for defects as well as for the correctness of identity markings.

17.3.3.4. Documents describing testing procedures shall state the required frequency for re-assaying each starting material, as determined by its stability.

17.3.4. **Specifications for intermediate and bulk products-** Specifications for intermediate and bulk products shall be available. The specifications shall be similar to specifications for starting materials or for finished products, as appropriate.

17.3.5. **Specifications for finished products-** Specifications for finished products shall include the following, namely:—

(a) the designated name of the product and the code reference, where applicable;

(b) the designated names of the active ingredients (if applicable, with the INNs);

(c) the formula or a reference to the formula if provided in any pharmacopoeia;

(d) a description of the dosage form and package details;

(e) directions for sampling and testing or a reference to procedures;

(f) the qualitative and quantitative requirements, with acceptance limits;

(g) the storage conditions and precautions, where applicable; and

(h) the shelf-life.

17.3.6. **Master formula records-**

17.3.6.1. A formally authorised master formula shall exist for each product and batch size to be manufactured.

17.3.6.2. The master formula records shall include the following, namely:-

(a) the name of the product, with a product reference code relating to its specification;

(b) a description of the dosage form, strength of the product and batch size;

(c) a list of all starting materials to be used (if

applicable with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention shall be made of any substance that may disappear in the course of processing);

(d) a statement of the expected final yield with the acceptable limits and of relevant intermediate yields, where applicable;

(e) a statement of the processing location and the principal equipment to be used;

(f) the methods or reference to the methods to be used for preparing and operating the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilising, use;

(g) detailed step-wise processing instructions (e.g., checks on materials, pre-treatments, sequence for adding materials, mixing times and temperatures);

(h) the instructions for any in-process controls with their limits;

(i) where necessary, the requirements for storage of the products, including the container, the labelling and any special storage conditions;

(j) any special precautions to be observed; and

(k) the hold time permitted for intermediate and in process material.

17.3.7. **Packaging instructions-** Formally authorised packaging instructions shall exist for each product, pack size and type. These shall normally include or make reference to the following, namely:—

(a) the name of the product;

(b) a description of its pharmaceutical form, strength and, where applicable, method of application;

(c) the pack size expressed in terms of the number, weight or volume of the product in the final container;

(d) a complete list of all the packaging materials required for a

standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;

(e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;

(f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;

(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used; and

(h) details of in-process controls with instructions for sampling and acceptance limits.

17.3.8. **Batch processing records-**

17.3.8.1. A batch processing record shall be kept for each batch processed. It shall be based on the relevant Parts of the currently approved specifications on the record. The method of preparation of such records shall be designed to avoid errors. (copying or validated computer programmes are recommended. Transcribing from approved documents shall be avoided.)

17.3.8.2. Before any processing begins a check shall be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check shall be recorded.

17.3.8.3. During processing, the following information shall be recorded at the time each action is taken, and after completion of the record shall be dated and signed by the person responsible for the processing operations, namely:-

(a) the name of the product;

(b) the number of the batch being manufactured;
(c) dates and time of commencement of significant intermediate stages and of completion of production;
(d) the name of the person responsible for each stage of production;
(e) the initials of the operators of different significant steps of production and, where appropriate, of the persons who checked each of these operations (e.g., weighing);
(f) the batch number or analytical control number or both and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
(g) any relevant processing operation or event and the major equipment used;
(h) the hold time permitted for intermediate and in process material;
(i) the in-process controls performed, the initials of the persons carrying them out, and the results obtained;
(j) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield; and
(k) notes on special problems including details, with signed authorisation for any deviation from the master formula.

17.3.9. **Batch packaging records-**

17.3.9.1. A batch packaging record shall be kept for each batch or part batch processed. It shall be based on the relevant Parts of the approved packaging instructions and the method of preparing such records shall be designed to avoid errors. (copying or validated computer programmes are recommended. Transcribing

from approved documents shall be avoided.)

17.3.9.2. Before any packaging operation begins, checks shall be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations and that equipment is clean and suitable for use. These checks shall be recorded.

17.3.9.3. The following information shall be recorded at the time each action is taken, and the date and the person responsible shall be clearly identified by signature or electronic password, namely:-

(a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;

(b) the date and time of packaging operations;

(c) the name of the responsible person carrying out the packaging operation;

(d) (d) the initials of the operators of the different significant steps;

(e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product if it is unpacked or a record of returning product that has not been packaged to the storage area;

(g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;

(h) notes on any special problems, including the details of any deviation from the packaging

instructions, with written authorisation by an appropriate person; and

(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

17.3.10. **Standard operating procedures and records:**

17.3.10.1. Standard Operating Procedures (hereinafter to be referred as SOPs) and associated records of actions taken or, where appropriate, conclusions reached shall be available for the following, namely-

(a) equipment assembly and validation;
(b) analytical apparatus and calibration;
(c) maintenance, cleaning and sanitisation;
(d) personnel matters including qualifications, training, clothing and hygiene;
(e) environmental monitoring;
(f) pest control;
(g) complaints;
(h) recalls; and
(i) returns.

17.3.10.2. There shall be SOPs and records for the receipt of each delivery of starting material and primary and printed packaging material.

17.3.10.3. The records of the receipts shall include the following, namely-

(a) the name of the material on the delivery note and the containers;
(b) the "in-house" name or code or both of material, if different from clause (a);
(c) the date of receipt;
(d) the supplier's name and, if possible, manufacturer's name;
(e) the manufacturer's batch or reference number;
(f) the total quantity and number of containers

received;

(g) the batch number assigned after receipt; and

(h) any relevant comment (e.g. state of the containers).

17.3.10.4. There shall be SOPs for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

17.3.10.5. SOPs shall be available for each instrument and piece of equipment (e.g., use, calibration, cleaning and maintenance) and placed in close proximity to the equipment.

17.3.10.6. There shall be SOPs for sampling, which specify the persons authorised to take samples.

17.3.10.7. The sampling instructions shall include-

(a) the method of sampling and the sampling plan;

(b) the equipment to be used;

(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;

(d) the amount of samples to be taken;

(e) instructions for any required sub-division of the sample;

(f) the type of sample containers to be used, and whether they are for aseptic sampling or for normal sampling and labelling; and

(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

17.3.10.8. There shall be an SOPs describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

17.3.10.9. The SOPs for batch numbering that are applied to the processing stage and to the respective packaging stage shall be related to each other.

17.3.10.10. The SOPs for batch numbering shall ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

17.3.10.11. Batch-number allocation shall be immediately recorded, e.g. in a logbook. The record shall include at least the date of allocation, product identity and size of batch.

17.3.10.12. There shall be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed shall be recorded.

17.3.10.13. Analysis records shall include at least the following data, namely-

(a) the name of the material or product and, where applicable, dosage form;

(b) the batch number and, where appropriate, the manufacturer and supplier;

(c) references to the relevant specifications and testing procedures;

(d) test results, including observations and calculations, and reference to any specifications (limits);

(e) date and reference number of testing;

(f) the initials of the persons who performed the testing;

(g) the date and initials of the persons who verified the testing and the calculations, where appropriate; and

(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated person.

17.3.10.14. Written release and rejection procedures shall be available for materials and products and in particular for the release for sale of the finished product by an authorised person.

17.3.10.15. Records shall be maintained regarding the

distribution of each batch of a product in order, for example, to facilitate the recall of the batch, if necessary.

17.3.10.16. Records shall be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning or repair operations, including dates and the identity of the people who carried out these operations.

17.3.10.17. The use of major and critical equipment and the areas where products have been processed shall be appropriately recorded in chronological order.

17.3.10.18. There shall be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned and such written procedures shall be followed.

18. Good practices in production:

18.1. **Principle-** Production operations must follow clearly defined procedures in accordance with manufacturing and licences, with the objective of obtaining products of the requisite quality.

18.2. **General-**

18.2.1. All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution shall be done in accordance with written procedures or instructions and, where necessary, recorded.

18.2.2. Deviation from instructions or procedures shall be avoided as far as possible. If deviations occur, they shall be in accordance with an approved procedure. The authorisation of the deviation shall be approved in writing by a designated person, with the involvement of the QC Department, when appropriate.

18.2.3. Checks on yields and reconciliation of quantities shall be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

18.2.4. Operations on different products shall not be carried out

simultaneously or consecutively in the same room or area unless there is no risk of mix up or cross-contamination.

18.2.5. At all times during processing, all materials, bulk containers, major items of equipment, and, where appropriate, the rooms and packaging lines being used, shall be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication shall also mention the stage of production. In some cases, it may be useful to also record the name of the previous product that has been processed.

18.2.6. Access to production premises shall be restricted to authorised personnel.

18.2.7. Non-medicinal products shall not be produced in areas or with equipment destined for the production of pharmaceutical products.

18.2.8. In-process controls are usually performed within the production area. The performance of such in-process controls shall not have any negative effect on the quality of the product or another product (e.g., cross-contamination or mix up).

18.3. **Prevention of cross-contamination and bacterial contamination during production-**

18.3.1. When dry materials and products are used in production, special precautions shall be taken to prevent the generation and dissemination of dust. Provision shall be made for proper air control (e.g., supply and extraction of air of suitable quality).

18.3.2. Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitising materials, biological preparations such as living organisms,

certain hormones, cytotoxic substances and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses or over a long time or both. Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure areas. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authorities.

18.3.3. Cross-contamination shall be avoided by taking appropriate technical or organisational measures, namely:-

(a) carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, cytotoxic, sex hormones, spore forming, live vaccines, live bacterial preparations and certain other biologicals);

(b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;

(c) providing appropriately designed airlocks, pressure differentials and air supply and extraction systems;

(d) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

(e) wearing protective clothing where products or materials are handled;

(f) using cleaning and decontamination procedures of known effectiveness;

(g) using a closed system in production;

(h) testing for residues; and

(i) using cleanliness status labels on equipment.

18.3.4. Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to SOPs.

18.3.5. Production areas where susceptible products are processed shall undergo periodic environmental monitoring (e.g., for microbiological and particulate matter, where appropriate).

18.4. **Processing operations-**

18.4.1. Before any processing operation is started, steps shall be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

18.4.2. Any necessary in-process controls and environmental controls shall be carried out and recorded.

18.4.3. Means shall be instituted of indicating failures of equipment or of services (e.g., water and gas) to equipment. Defective equipment shall be withdrawn from use until the defect has been rectified. After use, production equipment shall be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

18.4.4. Time limits for storage of process materials and equipment, after cleaning and before use, shall be stated and based on relevant data.

18.4.5. Containers for filling shall be cleaned before filling. Attention shall be given for avoiding and removing any contaminants such as glass fragments and metal particles.

18.4.6. Any significant deviation from the expected yield shall be recorded and investigated.

18.4.7. Checks shall be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another area are connected in the correct manner.

18.4.8. Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes shall be sanitised and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

18.4.9. Measuring, weighing, recording and control equipment and instruments shall be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments shall be checked daily or prior to use for performing analytical tests. The date of calibration and

servicing and the date when recalibration is due shall be clearly indicated on a label attached to the instrument.

18.4.10. Repair and maintenance operations shall not present any hazard to the quality of the products.

18.5. **Packaging operations:**

18.5.1. When the programme for packaging operations is being set up, particular attention shall be given to minimising the risk of cross-contamination, mix ups or substitutions. Different products shall not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

18.5.2. Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance shall be performed according to an appropriate procedure and checklist and shall be recorded.

18.5.3. The name and batch number of the product being handled shall be displayed at each packaging station or line.

18.5.4. Normally, filling and sealing shall be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures shall be applied to ensure that no mix ups or mislabelling can occur.

18.5.5. The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging shall be checked and recorded. Attention shall be paid to printing by hand, which shall be rechecked at regular intervals.

18.5.6. Special care shall be taken when cut labels are used and when overprinting is carried out off-line and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix ups. Online verification of all labels by automated electronic means can be helpful in preventing mix ups, but checks shall be made to ensure that any electronic code readers, label counters or similar devices

are operating correctly. When labels are attached manually, in-process control checks shall be performed more frequently.

18.5.7. Printed and embossed information on packaging materials shall be distinct and resistant to fading or erasing.

18.5.8.1. Regular online control of the product during packaging shall include at a minimum checks on—

(a) the general appearance of the packages;

(b) whether the packages are complete;

(c) whether the correct products and packaging materials are used;

(d) whether any overprinting is correct; and

(e) the correct functioning of line monitors.

18.5.8.2. Samples taken away from the packaging line shall not be returned.

18.5.9. Products that have been involved in an unusual event during packaging shall be reintroduced into the process only after special inspection, investigation and approval by the authorised personnel. A detailed record shall be kept of this operation.

18.5.10. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated, satisfactorily accounted for and recorded before release.

18.5.11. Upon completion of a packaging operation, any unused batch-coded packaging materials shall be destroyed and the destruction shall be recorded. A documented procedure requiring checks to be performed before returning unused materials shall be followed, if uncoded printed materials are returned back to the stock.

18.5.12. Production records shall be reviewed as part of the approval process of batch release before transfer to the authorised person. Any divergence or failure of a batch to meet production specifications shall be thoroughly investigated. The investigation shall, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written

record of the investigation shall be made and shall include the conclusion and follow-up action.

19. Good practices in quality control:

19.1. Quality control is the part of good manufacturing practices concerned with sampling, specifications and testing and with the organisation and documentation which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the requirements. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

19.2. The independence of QC from production is considered fundamental.

19.3. Each manufacturer shall have a QC function. The QC function shall be independent of other Departments and under the authority of a person with appropriate qualifications and experience. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out. The basic requirements for QC are as follows—

(a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials and intermediate, bulk and finished products and where appropriate for monitoring environmental conditions for good manufacturing practices purposes;

(b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved by the QC Department;

(c) qualification and validation;

(d) records must be made (manually or by recording instruments or both) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;

(e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the licence; the ingredients must be of the required purity, in their proper container and correctly labelled;

(f) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against

specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

(g) sufficient samples of starting materials and products must be retained to permit future examination of the product, if necessary; the retained product must be kept for the appropriate time in its final pack unless the pack is exceptionally large, in which case one that is equivalent to the marketed packaging system may be used.

19.4.1. Other QC responsibilities include the following, namely:-

(a) establishing, validating and implementing all QC procedures;

(b) evaluating, maintaining and storing reference standards for substances;

(c) ensuring the correct labelling of containers of materials and products;

(d) ensuring that the stability of the active pharmaceutical ingredients and products are monitored;

(e) participating in the investigation of complaints related to the quality of the product;

(f) participating in environmental monitoring; and

(g) participation in quality risk management programme.

19.4.2. These activities shall be carried out in accordance with written procedures and, where necessary, recorded.

19.5. Quality control personnel shall have access to the production areas for sampling and investigation as appropriate.

19.6. **Control of starting materials and intermediate, bulk and finished products-**

19.6.1. All tests shall follow the instructions given in the relevant written test procedure for each material or product. The result shall be checked by the supervisor before the material or product is released or rejected.

19.6.2. Samples shall be representative of the batches of material from which they are taken in accordance with the approved written procedure.

19.6.3. Sampling shall be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled shall be marked accordingly and carefully resealed after sampling.

19.6.4. Care shall be taken during sampling to guard against contamination or mix up of, or by, the material being sampled. All sampling equipment that comes into contact with the material shall be clean. Hazardous or potent materials may require special precautions.

19.6.5. Sampling equipment shall be cleaned and, if necessary, sterilised before and after each use and stored separately from other laboratory equipment.

19.6.6. Each sample container shall bear a label indicating-

(a) the name of the sampled material;

(b) the batch or lot number;

(c) the number of the container from which the sample has been taken;

(d) the number of the sample;

(e) the signature of the person who has taken the sample; and

(f) the date of sampling.

19.6.7. Out-of-specification results obtained during testing of materials or products shall be investigated in accordance with an approved procedure and record shall be maintained.

19.7. **Test requirements-**

19.7.1. Before releasing a starting or packaging material for use, the QC in-charge shall ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

19.7.2. An identity test shall be conducted on a sample from each container of starting material. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.

19.7.2.1. The above validation shall take account of at least the following aspects, namely:-

(a) the nature and status of the manufacturer and of the supplier and their understanding of the good manufacturing practices requirements;

(b) the QA system of the manufacturer of the starting material;

(c) the manufacturing conditions under which the starting material is produced and controlled; and

(d) the nature of the starting material and the medicinal products in which it will be used.

19.7.2.2. Under such a system it is possible that a validated procedure for exemption from the requirement for identity testing of each incoming container of starting material could be accepted for the following, namely-

(a) starting materials coming from a single product manufacturer or plant; or

(b) starting materials coming directly from a manufacturer, or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's QA system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

19.7.2.3. It is improbable that such a procedure could be satisfactorily validated for either-

(a) starting materials supplied by intermediaries, such as brokers, where the source of manufacture is unknown or not audited; or

(b) starting materials for use in parenteral products.

19.7.3. Each batch (lot) of printed packaging materials shall be examined following its receipt.

19.7.4. In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities. Certificates must be originals and not photocopies or otherwise have their authenticity assured. Certificates must contain at least the following information, namely:—

(a) identification (name and address) of the issuing supplier;

(b) signature of the competent official and

statement of his or her qualifications;

(c) the name of the material tested;

(d) the batch number of the material tested;

(e) the specifications and methods used;

(f) the test results obtained; and

(g) the date of testing.

19.7.5. In-process control records shall be maintained and form part of the batch records.

19.7.6. For each batch of drugs, there shall be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to its release.

19.7.7. Products failing to meet the established specifications or any other relevant quality criteria shall be rejected.

19.8. **Batch record review:**

19.8.1. Quality control records shall be reviewed as part of the approval process of batch release before transfer to the authorised person. Any divergence or failure of a batch to meet its specifications shall be thoroughly investigated. The investigation shall, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusion and follow-up action.

19.8.2. Retention samples from each batch of finished product shall be kept for at least one year after the expiry date. Finished products shall usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials shall be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases and water) shall be retained for a minimum of two years, if their stability allows. Retention samples of materials and products shall be of a size sufficient to permit at least two

full re-examinations.

19.9. **Stability studies-**

19.9.1. QC shall evaluate quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

19.9.2. QC shall establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

19.9.3. A written programme for on-going stability determination shall be developed and implemented to include elements such as —

(a) a complete description of the drug involved in the study;

(b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;

(c) provision for the inclusion of a sufficient number of batches;

(d) the testing schedule for each drug;

(e) provision for special storage conditions;

(f) provision for adequate sample retention; and

(g) a summary of all the data generated, including the evaluation and the conclusion of the study.

19.9.4. Stability shall be determined prior to marketing and following any significant changes, for example, in processes, equipment or packaging materials.

20. Computerised systems:

20.1. GMP-related computerised systems shall be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.

20.2. Appropriate installation qualification and operational qualification shall demonstrate the suitability of computer hardware and software to perform assigned tasks.

20.3. Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at the time of installation, a retrospective validation could be

conducted, if appropriate documentation is available.

20.4. Computerised systems shall have sufficient controls to prevent unauthorised access or changes to data. There shall be controls to prevent omissions in data (e.g., the system being turned off and data not captured). There shall be a record of any data change made, the previous entry, the person who made the change and when the change was made.

20.5. Written procedures shall be available for the operation and maintenance of computerised systems.

20.6. Where critical data are being entered manually, there shall be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.

20.7. Incidents related to computerised systems that could affect the quality of products or the reliability of records or test results shall be recorded and investigated.

20.8. Changes to the computerised system shall be made according to a change procedure and shall be formally authorised, documented and tested. Records shall be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records shall demonstrate that the system is maintained in a validated state.

20.9. A back-up system shall be provided so that there is no permanent loss of records due to system breakdown or failure. Means of ensuring data protection shall be established for all computerised systems.

20.10. Data may be recorded by other means in addition to the computer system.

Appendix-I

Site Master File

The licensee shall prepare a succinct document in the form of 'Site Master File' containing specific and factual Good Manufacturing Practices about the production or control or both of pharmaceutical manufacturing preparations carried out at the licensed premises. It shall contain the following, namely-

1. General information:-

(a) brief information of the firm;

(b) pharmaceutical manufacturing activities as permitted by the licensing

authority;

(c) other manufacturing activities, if any, carried out in the premises;
(d) type of products licensed for manufacture with flow charts mentioning procedure and process flow;
(e) number of employees engaged in the production, quality control, storage and distribution;
(f) use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
(g) products details registered with foreign countries.
(h) short description of the Quality Management System of the firm;
(i) pharmaceutical Quality System; and
(j) quality risk assessment.

2. Personnel:-

(a) organisational chart showing the arrangement for quality assurance including production and quality control;
(b) qualifications, experience and responsibilities of key personnel;
(c) outline for arrangements for basic and in-service training and how the records are maintained;
(d) health requirements for personnel engaged in production; and
(e) personnel hygiene requirements, including clothing.

3. Premises:-

(a) simple plan or description of manufacturing areas drawn to scale;
(b) nature of construction and fixtures or fittings;
(c) brief description of ventilation systems. More details shall be given for critical areas with potential risk of airborne contamination (schematic drawing of systems). Classification of the rooms used for the manufacture of sterile products shall be mentioned;
(d) special areas for the handling of the highly toxic, hazardous and sensitising materials;
(e) brief description of water system (schematic drawings of systems), including sanitation; and
(f) description of planned preventive maintenance programmes for premises and of the recording system.

4. Equipment:-

(a) brief description of major equipment used in production and Quality Control Laboratories (a list of equipment required);
(b) description of planned preventive maintenance programmes for equipment and of the recording system; and
(c) qualification and calibration including the recording systems and arrangements for computerised systems validation.

5. Sanitation:-availability of written specifications and procedures for cleaning manufacturing areas and equipment.

6. Documentation:-

(a) arrangements for the preparation, revision and distribution of;
(b) necessary documentation for the manufacture; and
(c) any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls about air and water).

7. Production:-

(a)brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters;
(b)arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage;
(c)arrangements for the handling of rejected materials and products; and
(d)brief description of general policy for process validation.

8. Quality Assurance and Control:-

(a) documentation system;
(b) change control;
(c) master validation plan and validation policy;
(d) product quality review; and
(e) description of the quality control system and of the activities of the QC Department. Procedures for the release of the finished products.

9. Manufacture under loan licence and licensee:- description of the way in which compliance of GMP by the loan licensee shall be assessed.

10. Distribution, complaints and product recall:-

(a) arrangements and recording system for distribution; and
(b) arrangements for the handling of complaints and product recalls.

11. Self-inspection:- short description of the self-inspection system indicating whether an outside, independent and experienced external expert was involved in evaluating the manufacturer's compliance with GMP in all aspects of production.

12. Export of drugs:-

(a) products exported to different countries; and
(b) complaints and product recall, if any.

Note.-The guidelines published by the World Health Organization (WHO) on following aspects relating to GMP through their Technical Report Series from time to time may be considered for general guidance purposes:-

(1) Guidelines on the principles of airflow directions, air filtration standards, temperature, humidity and related parameters.
(2) GMP guidelines regarding the design, installation and operation of pharmaceutical water systems including guidance about which quality of water to use for specific applications, such as the manufacture of APIs and dosage forms.
(3) Guidelines on design, installation, qualification and maintenance of the HVAC systems of the manufacturing plant.
(4) GMP guidelines for validation.
(5) Guidelines on packaging of pharmaceutical products.

PART II

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF STERILE PRODUCTS, PARENTERAL PREPARATIONS (SMALL VOLUME INJECTABLES AND LARGE VOLUME PARENTERALS) AND STERILE OPHTHALMIC PREPARATIONS

Note.-Good Manufacturing Practices for pharmaceutical products:- Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of sterile products, parenteral preparations (small volume injectables and large volume parenterals) and sterile ophthalmic

preparations. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General considerations:-

1.1. The production of sterile preparations shall be carried out in clean areas, entry shall be through airlocks for personnel or for equipment and materials or both. Clean areas shall be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2. The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilisation shall be carried out in separate areas within the clean area. These areas are classified into four grades as described in paragraph of this Part.

1.3. Manufacturing operations are divided here into two categories, namely:-

(I) those, where the product is terminally sterilised; and

(II) those, which are conducted aseptically at some or all stages.

2. Quality control:-

2.1. The sterility test applied to the finished product shall only be regarded as the last in a series of control measures by which sterility is assured. The test shall be validated for the product concerned.

2.2. Samples taken for sterility testing shall be representative of the whole of the batch but shall, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example-

(i) for products that have been filled aseptically, samples shall include containers filled at the beginning and end of the batch and after any significant interruption of work;

(ii) for products that have been heat sterilised in their final containers, consideration shall be given to taking samples from that part of the load that is potentially the coolest.

2.3. The sterility of the finished product is assured by validation of the sterilisation cycle in the case of terminally sterilised products, and by "media simulation" or "media fill" runs for aseptically processed products. Batch-processing records and, in the case of aseptic processing, environmental quality records, shall be examined in conjunction with the results of the sterility tests. The sterility test procedure shall be validated for a given product. Pharmacopoeial

methods shall be used for the validation and performance of the sterility test. In those cases where parametric release has been authorised in place of sterility testing, special attention shall be paid to the validation and the monitoring of the entire manufacturing process.

2.4. For injectable products, the water for injection and the intermediate, if appropriate and finished products shall be monitored for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume parenterals, such monitoring of water or intermediates shall always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of the failure shall be investigated and necessary action shall be taken.

2.5. The use of rapid microbiological methods to replace the traditional microbiological methods, and to obtain earlier results on the microbiological quality of, for example, water, the environment or bio burden, could be considered if appropriately validated and a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method.

3. Sanitation:-

3.1. The sanitation of clean areas is particularly important. They shall be cleaned frequently and thoroughly in accordance with an approved written programme. Where disinfectants are used, more than one type shall be employed. Monitoring shall be regularly undertaken to detect contamination or the presence of an organism against which the cleaning procedure is ineffective. Interactions between different cleaning materials shall be validated. Appropriate cleaning validation shall be carried out to ensure disinfectant residuals can be detected and are removed by the cleaning process.

3.2. Disinfectants and detergents shall be monitored for microbial contamination; dilutions shall be kept in previously cleaned containers and shall only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grade A and B areas shall be sterile before use.

3.3. A disinfectant programme shall also include a sporicidal agent since many common disinfectants are ineffective against spores. The effectiveness of cleaning and disinfectant procedures shall be

demonstrated.

3.4. Fumigation of clean areas may be useful for reducing microbial contamination in inaccessible places.

4. Manufacture of sterile preparations:-

4.1. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate level of environmental cleanliness in the operational state to minimise the risk of particulate or microbial contamination of the product or materials being handled.

4.2. Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc., is not given in this Part. International Organization for Standardisation (ISO) standards shall be used for classification of cleanliness according to concentration of airborne particles (determination of number of sample locations, calculation of sample size and evaluation of classification from the data obtained). Table 1 shall also be used to define the levels to be used as the basis for monitoring clean areas for airborne particles.

4.3. For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:-

Grade A: The local zone for high-risk operations, e.g., filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems shall provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level shall not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow shall be demonstrated by undertaking airflow visualisation tests.

Grade B: In aseptic preparation and filling, this is the background environment for the Grade A zone.

Grades C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e., aseptic connection with aseptic connectors and operations in a closed system).

A unidirectional airflow and lower velocities may be used in closed isolators and glove boxes.

Explanation.- For the purpose of classification of grade C and grade D clean areas, the parameters provided in paragraph 4.6, 4.7, 4.9, and 4.11of this Part shall be applied.

4.4. In order to reach the B, C and D air grades the number of air changes shall be appropriate for the size of the room and the equipment and personnel present in it.

4.5. High-efficiency particulate air (hereinafter to be referred as HEPA) filters shall be subjected to an installed filter leakage test in accordance with ISO standards at a recommended interval of every six months, but not exceeding twelve months. The purpose of performing regular leak tests is to ensure the filter media, filter frame and filter seal are free from leaks. The aerosol selected for HEPA leak testing shall not support microbial growth and shall be composed of a sufficient number or mass of particles. HEPA filter patching is allowed at the filter manufacturer and in situ operation provided that the patch sizes and procedures follow the recommendations of ISO standards.

4.6. Clean rooms and clean-air devices shall be classified in accordance with ISO standards.

4.6.1. Classification shall be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each Grade is given in Table 1 below.

Table 1

Maximum permitted airborne particle concentrate

Grade	**Maximum permitted number of particles per m^3 greater than or equal to the tabulated size**			
	At rest		**In operation**	
	0.5 µm	**5.0 µm**	**0.5 µm**	**5.0 µm**
A	3520	20	3520	20
B	3520	29	352000	2900

C	352000	2900	3520000	29000
D	3 520000	29000	Not defined	Not defined

The "at rest" state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

The "in operation" state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems shall be designed to achieve both the "at rest" and "in operation" states.

4.6.2. For classification purposes in Grade A zones, a minimum sample volume of 1 m^3 shall be taken per sample location. Referring to Table 1, for Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥ 5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both particle sizes considered. For Grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8, respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes ISO standards methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest particle size considered and the method of evaluation of the data collected. The sample volume shall be determined according to ISO standards. However, for lower grades (Grade C in operation and Grade D at rest) the sample volume per location shall be at least two litres and the sample time per location shall be not less than one minute.

4.6.3. Portable particle counters with a short length of sample tubing shall be used for classification purposes to avoid the loss of particles ≥ 5.0 µm. Isokinetic sample heads shall be used in unidirectional airflow systems.

4.6.4. "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. ISO standards provide information on testing to demonstrate continued compliance

with the assigned cleanliness classification.

4.7. Clean rooms and clean-air devices shall be routinely monitored while in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms or clean-air devices or both.

4.7.1. For Grade A zones, particle monitoring shall be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards. In such cases monitoring during routine equipment set-up operations shall be undertaken before exposure to the risk. Monitoring during simulated operations shall also be performed. The Grade A zone shall be monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

4.7.2. It is recommended that a similar system be used for Grade B zones, although the sample frequency may be decreased. The importance of the particle monitoring system shall be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone shall be monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded.

4.7.3. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or multiple small particle counters located near monitoring points and networked to a data acquisition system. Combination of systems can also be used. The system selected shall be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing shall

be considered in the context of particle losses in the tubing. The selection of the monitoring system shall take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.

4.7.4. The sizes of samples taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean-air devices.

4.7.5. The airborne particle conditions given in Table 1 for the "at rest" state shall be achieved in the absence of the operating personnel after a short "clean-up" or "recovery" period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 1 for Grade A "in operation" shall be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. The "clean-up" or "recovery" test shall demonstrate a change in particle concentration by a factor of 100 within the prescribed time as per the ISO standards.

4.7.6. In order to demonstrate control of the cleanliness of the various clean areas during operation, they shall be monitored for airborne particles and microbial contamination. In addition to "at rest" and "in operation" classification, airborne particles shall be monitored periodically "in operation" at critical locations. The sampling plan need not be the same as that used for classification. Locations and sample sizes shall be determined based on an assessment of the process and contamination risk.

4.7.7. The monitoring of Grade C and D areas in operation shall be performed in accordance with the principles of QRM. The requirements and alert or action limits will depend on the nature of the operations carried out, but the recommended "clean-up period" shall be attained.

4.7.8. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters shall not interfere with the defined cleanliness standard.

4.7.9. Examples of operations to be carried out in the various

Grades are given in the Table 2 below:

Table 2

Examples of operations to be carried out in the various Grades

Grade	Examples of operations for terminally sterilised products
A	Filling of products, which are unusually at risk
C	Placement of filling and sealing machines, preparation of solutions, when (usually at risk). Filling of product when usually at risk.
D	Moulding, blowing (pre forming) operations of solutions and components for subsequent filling.

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
B	Background room conditions for activities requiring Grade A
C	Preparation of solutions to be filtered
D	Handling of components after washing

4.8. To control the microbiological cleanliness of Grades A to D in-operation, the clean areas shall be monitored. Where aseptic operations are performed, monitoring shall be frequent using methods such as settle plates, volumetric air and surface sampling (e.g., swabs and contact plates). Sampling methods used in operation shall not interfere with zone protection. Results from monitoring shall be considered when reviewing batch documentation for finished product release. Surfaces and personnel shall be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g., after validation of systems, cleaning and sanitisation.

4.9. Levels of detection of microbial contamination shall be established for the purpose of setting alert and action limits and for monitoring the trends in environmental cleanliness in the facility. Limits expressed in Colony-Forming Units(CFU) for the microbiological monitoring of clean areas in operation are given in Table 3 below. The sampling

methods and numerical values included in the said Table are not intended to represent specifications, but are for information only.

Table
Recommended limits for microbial contamination

Grade	Air sample (CFU/m3)	Settle plates (diameter 90 mm)(CFU/4 hours)	Contact plates (diameter 55 mm)(CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

These are average values.
Individual settle plates may be exposed for less than four hours.

4.10. Appropriate alert and action limits shall be set for the results of particulate and microbiological monitoring. If the action limits are exceeded or a trend is identified in the alert limits, investigation shall be initiated and the appropriate corrective actions shall be taken, as prescribed in the operating procedures.

4.11. The area Grades specified in this Part shall be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g., aseptic media fills or others types of process simulations) are used to establish processing hold times and a maximum fill duration. The determination of an appropriate process area environment and a time limit shall be based on the microbial contamination (bio burden) found.

4.11.1. **Terminally sterilised products**

4.11.1.1. Components and products shall be prepared in at least a Grade D zone to ensure low microbial bio burden and particulate counts prior to filtration and sterilisation. Where the product is at unusual risk of microbial contamination (e.g., because it actively supports microbial growth, must be held for a long period before sterilisation, or is necessarily processed mainly in open

vessels), the preparation shall generally be done in a Grade C zone.

4.11.1.2. The filling of products for terminal sterilisation shall generally be done in at least a Grade C environment.

4.11.1.3. Where the product is at unusual risk of contamination from the environment (e.g., because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling shall be done in a Grade A zone with at least a Grade C background.

4.11.1.4. The preparation and filling of ointments, creams, suspensions and emulsions shall generally be done in a Grade C zone before terminal sterilisation.

4.11.2. **Aseptic preparation-**

4.11.1.5. Components after washing shall be handled in at least Grade D zone. The handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a microorganism-retaining filter later in the process, shall be undertaken in a Grade A zone with Grade B background.

4.11.1.6. The preparation of solutions which are to be sterile-filtered during the process shall be undertaken in Grade C zone (unless a closed system is used, in which Grade D zone may be justifiable). If not sterile-filtered (therefore an aseptic manipulation) the preparation of materials and products shall be undertaken in Grade A zone with Grade B background.

4.11.1.7. The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, shall be undertaken in Grade A zone with Grade B background.

4.11.1.8. The transfer of partially closed containers, as used in freeze-drying, before stoppering is completed, shall be undertaken either in Grade A zone with Grade B background or in sealed transfer trays in Grade B zone.

4.11.1.9. The preparation and filling of sterile ointments, creams, suspensions and emulsions shall be undertaken in Grade

A zone with Grade B background when the product is exposed and is not subsequently filtered.

5. Processing:

5.1. Precautions to minimise contamination shall be taken during all processing stages, including the stages before sterilisation.

5.2. In general, preparations containing live micro-organisms shall not be made, nor shall containers be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live micro-organisms, the use of multi-product facilities may be justifiable. Vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers in the same premises as other sterile pharmaceutical products, provided that the inactivation procedure has been properly validated. When multi-product facilities are used to manufacture sterile preparations containing live microorganisms and other sterile pharmaceutical products, the manufacturer shall demonstrate and validate the effective decontamination of the live micro-organisms, in addition to precautions taken to minimise contamination.

5.3. Validation of aseptic processing shall include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium shall be based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.

5.4. The process simulation test shall imitate as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.

5.5. Process simulation tests shall be performed as part of validation by running three consecutive satisfactory simulation tests. These tests shall be repeated at defined intervals and after any significant modification to the HVAC system, equipment or process. Process simulation tests shall incorporate activities and interventions known to occur during normal production as well as in the worst-case situations. The process simulation tests shall be representative of each shift and shift changeover to address any time-related and operational features.

5.6. The number of containers used for media fills shall be sufficient to enable a valid evaluation. For small batches the number of containers

for media fills shall at least equal to the size of the product batch. The target shall be zero growth and the following shall apply:

(a) when filling fewer than 5000 units, no contaminated units shall be detected;

(b) when filling 5000–10000 units -

(i) one contaminated unit shall result in an investigation, including consideration of a repeat media fill;

(ii) two contaminated units are considered cause for revalidation following investigation;

(c) when filling more than 10000 units -

(i) one contaminated unit shall result in an investigation;

(ii) two contaminated units are considered cause for revalidation following investigation.

5.7. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that shall be investigated. Investigation of gross failures shall include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

5.8. Care shall be taken to ensure that any validation does not compromise the processes.

5.9. Water sources, water-treatment equipment and treated water shall be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records shall be maintained of the results of the monitoring and of any action taken.

5.10. Activities in clean areas, especially when aseptic operations are in progress, shall be kept to a minimum and the movement of personnel shall be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. As far as possible, personnel shall be excluded from Grade A zones. The ambient temperature and humidity shall not be uncomfortably high because of the nature of the garments worn and to reduce the risk of contamination liberated from the personnel.

5.11. The presence of containers and materials liable to generate fibres shall be minimised in clean areas and avoided completely when aseptic work is in progress.

5.12. Components, bulk-product containers and equipment shall be handled

after the final cleaning process in such a way so as to ensure that they are not re-contaminated. The stage of processing of components as well as the bulk-product containers and equipment shall be properly identified.

5.13. The interval between the washing and drying and the sterilisation of components, bulk-product containers and equipment, as well as between sterilisation and use, shall be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

5.14. The time between the start of the preparation of a solution and its sterilisation or filtration through a bacteria-retaining filter shall be as short as possible. A maximum permissible time shall be set for each product that takes into account its composition and the prescribed method of storage.

5.15. Any gas that is used to purge a solution or blanket a product shall be passed through a sterilising filter.

5.16. The bio burden shall be monitored before sterilisation. There shall be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bio burden assay shall be performed on each batch for both aseptically filled products and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bio burden might be monitored only at suitable scheduled intervals. For parametric release systems, bio burden assay shall be performed on each batch and considered as an in-process test. Where appropriate, the level of endotoxins shall be monitored. All solutions, in particular large-volume infusion fluids, shall be passed through a microorganism-retaining filter, if possible sited immediately before filling.

5.17. Components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress, shall be sterilised and wherever possible passed into the area through double-ended sterilisers sealed into the wall. Other procedures that prevent the introduction of contamination may be acceptable in some circumstances.

5.18. The efficacy of any new processing procedure shall be validated and the validation shall be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

6. Sterilisation:

6.1. Whenever possible products intended to be sterile shall be terminally sterilised by heat in their final container. Where it is not possible to carry out terminal sterilisation by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g., plastic eye-dropper bottles), a decision shall be taken to use an alternative method of terminal sterilisation following filtration or aseptic processing or both.

6.2. Sterilisation can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilisation), by ethylene oxide (or other suitable gaseous sterilising agents), or by filtration with subsequent aseptic filling of sterile final containers. Each method has its advantages and disadvantages. Where possible and practicable, heat sterilisation is the method of choice. In any case the sterilisation process shall be in accordance with the marketing and manufacturing authorisations.

6.3. The microbial contamination of starting materials shall be minimal and their bio burden shall be monitored before sterilisation. Specifications shall include requirements for microbiological quality when the need for this has been indicated by monitoring.

6.4. All sterilisation processes shall be validated. Particular attention shall be paid when the adopted sterilisation method is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions.

6.5. Before any sterilisation process is adopted, its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed shall be demonstrated by physical measurements and by biological indicators, where appropriate. The validity of the process shall be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records shall be kept of the results.

6.6. For effective sterilisation the whole of the material shall be subjected to the required treatment and the process shall be designed to ensure that it is achieved.

6.7. Biological indicators shall be considered only as an additional method of monitoring the sterilisation process. They shall be stored and used

according to the manufacturer's instructions and their quality checked by positive controls. If they are used, strict precautions shall be taken to avoid any transfer of microbial contamination from them.

6.8. There shall be a clear means of differentiating products that have not been sterilised from those which have. Each basket, tray, or other carrier of products or components shall be clearly labelled with the name of the material, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the batch is in fact sterile.

6.9. Validated loading patterns shall be established for all sterilisation processes.

6.10. Sterilisation records shall be available for each sterilisation run. They shall be approved as part of the batch-release procedure.

6.11.1. **Terminal sterilisation-**

6.11.1.1. Each heat-sterilisation cycle shall be recorded by means of appropriate equipment of suitable accuracy and precision, e.g., on a time or temperature chart with a suitably large scale. The temperature shall be recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature shall preferably be checked against a second independent temperature probe located at the same position. Sterilisation records shall be available for each sterilisation run and shall be approved as part of the batch release procedure. Chemical or biological indicators may also be used but shall not take the place of physical controls.

6.11.1.2. Sufficient time shall be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time is started. This time shall be determined for each type of load to be processed.

6.11.1.3. After the high-temperature phase of a heat sterilisation cycle, precautions shall be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product shall be sterilised.

6.11.1.4. Both temperature and pressure shall be used to monitor the

process. Control instrumentation shall normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they shall be validated to ensure that critical process requirements are met. System and cycle faults shall be registered by the system and observed by the operator. The reading of the independent temperature indicator shall be routinely checked against the reading on the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilisation period. There shall be regular leak tests on the chamber when a vacuum phase is part of the cycle.

6.11.1.5. The items to be sterilised, other than products in sealed containers, shall be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilisation. Specially designed autoclavable stainless steel containers, that allow steam to enter and air to leave, can also be used. All parts of the load shall be in contact with water or saturated steam at the required temperature for the required time.

6.11.1.6. Care shall be taken to ensure that the steam used for sterilisation is of suitable quality chemical, microbiological and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat and non-condensable gases) and does not contain additives at a level that could cause contamination of the product or equipment. Steam used for sterilisation shall be tested regularly.

6.11.1.7. Sterilisation by dry heat may be suitable for non-aqueous liquids or dry-powder products. The process used shall include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied it shall be passed through a microorganism-retaining filter (e.g., a HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins are required as part of the validation.

6.11.1.8. Sterilisation by radiation is used mainly for heat-sensitive

materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilisation.

6.11.1.9. If sterilisation by radiation is done by an outside contractor, the manufacturer is responsible for ensuring that the requirements of paragraph 6.8 are met and that the sterilisation process is validated.

6.11.1.10. During the sterilisation procedure the radiation dose shall be measured. The dosimeters used for this purpose shall be independent of the dose rate and shall provide a quantitative measurement of the dose received by the product itself. Dosimeters shall be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used they shall be used within the time-limit of their calibration. Dosimeter absorbance shall be read shortly after exposure to radiation. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilisation. The information obtained shall constitute part of the batch record.

6.11.1.11. Validation procedures shall ensure that consideration is given to the effects of variations in the density of the packages.

6.11.1.12. Material-handling procedures shall prevent any mix-up of irradiated and non-irradiated materials. Each package shall carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

6.11.1.13. The total radiation dose shall be administered within a predetermined period.

6.11.1.14. Sterilisation by gases and fumigants shall only be used for finished products where there is no suitable alternative.

6.11.1.15. Various gases and fumigants may be used for sterilisation (e.g., ethylene oxide and hydrogen peroxide vapour). Ethylene oxide shall be used only when no other method is practicable.

During process validation, it shall be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits shall be incorporated in the specifications.

6.11.1.16. Direct contact between gas and microorganisms is essential; precautions shall, therefore, be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

6.11.1.17. Before exposure to the gas, materials shall be brought into equilibrium with the humidity and temperature required by the process. This requirement shall be balanced against the need to minimise the waiting time before sterilisation.

6.11.1.18. Each sterilisation cycle shall be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information thus obtained shall form part of the batch record.

6.11.1.19. Biological indicators shall be stored and used according to the manufacturer's instructions and their performance checked by positive controls.

6.11.1.20. For each sterilization cycle, records shall be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration. The pressure and temperature shall be recorded on a chart throughout the cycle. The records shall form part of the batch record.

6.11.1.21. After sterilisation, the load shall be stored in a controlled manner in ventilated conditions to allow concentration of residual gas and reaction products to fall to their prescribed levels. This process shall be validated.

6.11.2. **Aseptic processing and sterilisation by filtration:-**

6.11.2.1. The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilised by one of the above

methods.

6.11.2.2. The operating conditions shall be to prevent microbial contamination.

6.11.2.3. In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to the following namely:-

(a) the environment;

(b) personnel;

(c) critical surfaces;

(d) container or closure sterilisation and transfer procedures;

(e) the maximum holding period of the product before filling into the final container; and

(f) the sterilising filter.

6.11.2.4. Certain solutions and liquids that cannot be sterilised in the final container can be filtered through a sterile filter of nominal pore size 0.22 µ (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilised container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration shall be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilisation in the final container is possible. Of the methods currently available, steam sterilisation is preferred.

6.11.2.5. Owing to the potential additional risks of the filtration method as compared with other sterilisation processes, a double-filter layer or second filtration through a further sterilised microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration shall be carried out as close as possible to the filling point.

6.11.2.6. The fibre-shedding characteristics of filters shall be minimal (virtually zero). Asbestos-containing filters shall not be used under any circumstances.

6.11.2.7. The integrity of the sterilised filter shall be verified before use and shall be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or

pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter shall be determined during validation and any significant difference from these during routine manufacturing shall be noted and investigated. Results of these checks shall be included in the batch record. The integrity of critical gas and air vent filters shall be confirmed after use. The integrity of other filters shall be confirmed at appropriate intervals. Consideration shall be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g., the circulation of high-temperature air.

6.11.2.8. The same filter shall not be used for more than one working day unless such use has been validated.

6.11.2.9. The filter shall not affect the product either by removing ingredients from it or by releasing substances into it.

6.11.3. **Isolator technology-**

6.11.3.1. The use of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbial contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment shall be designed so that the required air quality for each zone can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from single-door to double-door designs to fully-sealed systems incorporating sterilisation mechanisms.

6.11.3.2. The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high-risk manipulations, although it is recognised that unidirectional airflow may not exist in the working zone of all isolators and transfer devices.

Explanation.- For the purpose of this paragraph "local zone" means an area inside the isolator for high risk manipulation.

6.11.3.3. The air classification required for the background environment depends on the design of the isolator and its application. It shall be controlled, and for aseptic processing it shall be at least Grade D.

6.11.3.4. Isolators shall be introduced only after appropriate validation. Validation shall take into account all critical factors of isolator technology, for example, the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.

6.11.3.5. Monitoring shall be done routinely and shall include frequent leak testing of the isolator and the glove or sleeve system.

6.11.4. **Blow, Fill-Seal technology-**

6.11.4.1. Blow, Fill-Seal units are purpose-built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow, Fill-Seal equipment used for aseptic production which is fitted with an effective Grade A air shower may be installed in at least a Grade C zone, provided that Grade A or B clothing is used. The environment shall comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow, Fill-Seal equipment used for the production of products which are terminally sterilised shall be installed in at least a Grade D zone.

6.11.4.2. Because of this special technology, particular attention shall be paid to at least the following, namely:-

(a) equipment design and qualification;

(b) validation and reproducibility of cleaning-in-place and sterilisation-in-place;

(c) background clean room environment in which the equipment is located;

(d) operator training and clothing; and

(e) interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

7. Personnel:-

7.1. Only the minimum number of personnel required shall be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls shall be conducted from outside such areas.

7.2. All personnel (including those concerned with cleaning and maintenance) employed in such areas shall receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g., building or maintenance contractors) need to be brought in, particular care shall be taken over their instruction and supervision.

7.3. Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process shall not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

7.4. High standards of personal hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations shall be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbial hazards shall be decided by a designated competent person.

7.5. Changing and washing shall follow a written procedure designed to minimise the contamination of clean-area clothing or the carry-through of contaminants to clean areas. The clothing and its quality shall be appropriate for the process and the grade of the working area. It shall be worn in such a way so as to protect the product from contamination.

7.6. Outdoor clothing shall not be brought into changing rooms leading to Grade B and C rooms. For every worker in a Grade A or B area, clean sterile (sterilised or adequately sanitized) protective garments shall be

provided at each work session. Gloves shall be regularly disinfected during operations. Masks and gloves shall be changed at least every working session. Operators working in Grade A and B zone shall wear sanitised goggles.

7.7. Wrist-watches, cosmetics and jewellery shall not be worn in clean areas.

7.8. The clothing required for each grade is as follows:

(i) Grade D: The hair and, where relevant, beard and moustache shall be covered. Protective clothing and appropriate shoes or overshoes shall be worn. Appropriate measures shall be taken to avoid any contamination from outside the clean area.

(ii) Grade C: The hair and, where relevant, beard and moustache shall be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes shall be worn. The clothing shall shed virtually no fibres or particulate matter.

(iii) Grades A and B: Entry of personnel into Grade A zone shall be minimised. Headgear shall totally enclose the hair and, where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and with a high neck, shall be worn. The headgear shall be tucked into the neck of the suit. A facemask shall be worn to prevent the shedding of droplets. Sterilised, non-powdered gloves of appropriate material and sterilised or disinfected footwear shall be worn. Trouser bottoms shall be tucked inside the footwear and garment sleeves into the gloves. The protective clothing shall shed virtually no fibres or particulate matter and shall retain particles shed by the body.

7.9. Clothing used in clean areas shall be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilisation, there may be an increased risk of shedding particles. Washing and sterilisation operations shall follow standard operating procedures.

8. Premises:

8.1. All premises shall as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A and B zone shall be designed so that all operations can be observed from

outside.

8.2. In clean areas all exposed surfaces shall be smooth, impervious and unbroken to minimise the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

8.3. To reduce the accumulation of dust and to facilitate cleaning, there shall be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors shall be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors shall open to the high pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements.

8.4. False ceilings shall be sealed to prevent contamination from the void space above them.

8.5. Pipes and ducts and other utilities shall be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings shall be used and threaded pipe connections shall be avoided.

8.6. Sinks and drains shall be avoided wherever possible and shall be excluded from Grade A and B zone where aseptic operations are carried out. Where installed they shall be designed, located and maintained so as to minimise the risks of microbial contamination; they shall be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels shall be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants.

8.7. Changing rooms shall be designed as airlocks and used to provide physical separation of the different stages of changing tominimise microbial and particulate contamination of protective clothing. They shall be flushed effectively with filtered air. The final stage of the changing room shall, in the at rest state, be the same Grade as the zone into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities shall be provided only in the first stage of the changing rooms. There shall not be a change of more than one Grade between airlocks or passages and changing rooms, i.e., a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads

to a Grade B clean room. Changing rooms shall be of a sufficient size to allow for ease of changing. Changing rooms shall be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room.

8.8. Airlock doors shall not be opened simultaneously. An interlocking system and a visual or audible or both warning system shall be operated to prevent the opening of more than one door at a time.

8.9. A filtered air supply shall be used to maintain a positive pressure and the airflow relative to surrounding areas of a lower Grade under all operational conditions; it shall flush the area effectively. Adjacent rooms of different Grades shall have a pressure differential of approximately 10 to 15 Pascal (guidance value). Particular attention shall be paid to the protection of the zone of greatest risk, i.e., the immediate environment to which the product and the cleaned components in contact with it are exposed. The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

8.10. It shall be demonstrated that airflow patterns do not present a contamination risk; for example, care shall be taken to ensure that particles from a particle generating person, operation or machine are not conveyed to a zone of higher product risk.

8.11. A warning system shall be operated to indicate failure in the air supply. Indicators of pressure differentials shall be fitted between areas where this difference is important, and the pressure differentials shall be regularly recorded and failure alarmed.

8.12. Consideration shall be given to restricting unnecessary access to critical filling areas e.g., Grade A filling zones, by means of a physical barrier.

9. Equipment:

9.1. A conveyor belt shall not pass through a partition between a Grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilised (e.g., in a sterilising tunnel).

9.2. Whenever possible, equipment used for processing sterile products

shall be chosen so that it can be effectively sterilised by steam or dry heat or other methods.

9.3. As far as possible, equipment fittings and services shall be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance shall be re-sterilised after complete reassembly, wherever possible.

9.4. When equipment maintenance is carried out within a clean area, clean instruments and tools shall be used and the area shall be cleaned and disinfected again, where appropriate, before processing recommences, if the required standards of cleanliness or asepsis or both have not been maintained during the maintenance work.

9.5. All equipment such as sterilisers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems shall be subject to validation and planned maintenance; their return to use shall be approved.

9.6. Water-treatment plants and distribution systems shall be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They shall not be operated beyond their designed capacity. Consideration shall be given to include a testing programme in the maintenance of a water system. Water for injection shall be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g., by constant circulation at a temperature above 70 °C or not more than 4 °C.

10.Finishing of sterile products:-

10.1. Containers shall be closed by appropriately validated methods. Containers closed by fusion, e.g., glass or plastic ampoules, shall be subject to 100 percent integrity testing. Samples of other containers shall be checked for integrity according to appropriate procedures.

10.2. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap shall, therefore, be performed as soon as possible after stopper insertion.

10.3. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment shall be located at a separate station equipped with adequate air extraction.

10.4. Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials shall be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials shall be protected with a Grade A air supply until the cap has been crimped.

10.5. Vials with missing or displaced stoppers shall be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology shall be used to prevent direct contact with the vials and to minimise microbial contamination.

10.6. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.

10.7. Containers sealed under vacuum shall be tested for maintenance of that vacuum after an appropriate, predetermined period.

10.8. Filled containers of parenteral products shall be inspected individually for extraneous contamination or other defects. When inspection is carried out visually this shall be done under suitable and controlled conditions of illumination and background. Operators doing the inspection shall pass regular eyesight checks, using personal corrective lenses (e.g., spectacles or contact lenses) as required, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process shall be validated and the performance of the equipment shall be checked at intervals. Results shall be recorded.

PART III

SPECIFIC REQUIREMENTS FOR MANUFACTURING OF PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES SUCH AS SEX HORMONES, STEROIDS (ANABOLIC, ANDROGENIC) OR CYTOTOXIC SUBSTANCES

Note.-Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I Schedule shall be complied with, *mutatis mutandis,* for the manufacture of hazardous substances such as certain sex hormones, steroids (anabolic, androgenic) or cytotoxic substances. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Introduction:-

The areas to which this Part applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. Wherever possible products shall be manufactured in closed systems.

1.1. Facilities shall be designed and operated in accordance with the main good manufacturing practices principles, as follows:-

(a) to ensure quality of product;

(b) to protect the operators from possible harmful effects of products containing hazardous substances; and

(c) to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

1.2. The production of certain products containing hazardous substances shall generally be conducted in separate, dedicated, self-contained facilities. These self-contained facilities may be in the same building as another facility but shall be separated by a physical barrier and have e.g., separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services shall be determined by risk assessment.

1.3. In general these manufacturing facilities shall be regarded as containment facilities.

1.4. The effective operation of a facility may require the combination of some or all of the following, namely:-

(a) appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;

(b) manufacturing process controls including adherence to SOPs;

(c) appropriately designed Environmental Controls Systems (ECS) or HVAC;

(d) extraction systems;

(e) Personal Protective Equipment (PPE);

(f) appropriate de-gowning and decontamination procedures;

(g) industrial hygiene (monitoring staff exposure levels);

(h) medical surveillance (monitoring staff exposure levels);

and

(i) administrative controls.

2. Risk assessment:-

2.1. Not all products containing hazardous substances are equally potent and risk assessments shall be carried out to determine the potential hazards to operators and to the environment. The risk assessment shall also determine which phase of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment shall include airborne contamination as well as liquid effluent contamination.

2.2. Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators or to the public or to the environment, the guidelines to be followed for the design and operation of the facility shall be as detailed in this Schedule.

2.3. The toxicological data available, such as permissible occupational exposure levels (OEL) for the product, shall be taken into account when conducting the risk assessment.

2.4. The risk assessment shall take into account occupational health and safety requirements for OELs in the work environment.

3. Product protection:- The requirement for producing quality products, with respect to protection from contamination and cross-contamination, clean room class of air, temperature and humidity shall be as for other pharmaceutical products.

4. Personal Protection Equipment and breathing air systems:-

4.1. The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. In case of the facility and equipment design is not providing adequate product containment, operator protection shall be provided. If facility and equipment design are adequate, a spillage or non-routine incident could cause a hazardous situation, in which case PPE shall be available. Unless otherwise specified in the material safety data sheet, operators shall be protected from exposure with an appropriate method, such as by wearing-

(a) flash-spun, high-density polyethylene fibre material suits or

impervious washable protective suits. Integral hoods may be required depending on the respirator type used;

(b) flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;

(c) suitable single-use, disposable gloves. Double gloves shall be worn where direct active contact with the product cannot be avoided. Gloves shall be taped or sealed on to the protective suit sleeves; and

(d) respirator eye and face protection with associated breathing air systems.

4.2. Where breathing air systems are used, these shall be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel shall be appropriately trained and assessed in the use of these systems before they enter the area. The breathing air systems shall comprise a protective face mask, which shall form an integral part of a protective suit. The breathing air systems could be any of the systems described below-

(a) a central air supply system which connects to the operator's facemask by means of flexible hoses and quick coupling sockets, also called an Airline Respirator (AR). The air connection shall incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply shall be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it shall be of the oil-free type or have suitable oil removal filters fitted;

(b) a Self-Contained Breathing Apparatus (SCBA) or Powered Air Purifying Respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;

(c) for zones with lower contamination levels, a half-mask High Efficiency Particulate Air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.

4.3. The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified Protection Factor (PF).

4.4. The air supplies shall be filtered through a final filter, which shall be a

HEPA filter rated as an H13 filter according to European norms. The supply of breathing air in to the face mask or protective suit or both shall result in the interior of the mask and suit being at a positive pressure relative to the facility environment.

4.5. Central breathing air supply systems shall have a one hundred percent back-up system in the event of the main system failing. This could be in the form of a gas bottle system with atleast five minutes supply. Change over from the normal supply to the back-up supply shall be automatic. The system shall have a monitoring system and send alarm signals to a permanently manned location in the following situations, namely:-

(i) failure of main air supply;
(ii) temperature out of specification (OOS);
(iii) humidity OOS;
(iv) carbon dioxide (CO_2) OOS;
(v) carbon monoxide (CO) OOS; and
(vi) sulfur dioxide (SO_2) OOS.

4.6. Breathing air shall be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO standards and European norms.

4.7. Where air is delivered through a central system the piping shall not cause any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters shall be as close as possible to the operator connection points. The operator hose connection to the air supply shall be a dedicated connection specific to the breathing air system to avoid inadvertent connection to a different gas system.

5. Environmental protection:-

5.1. Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues shall be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

5.2. The external atmosphere and the public in the vicinity of the facility shall be protected from possible harm from hazardous substances.

5.3. If liquid effluent poses a safety or contamination risk, the effluent shall be treated before being discharged to a municipal drain.

5.4. Exhaust air filtration to ensure environmental protection shall be as per paragraph 11.

6. Facility layout:-

6.1. The premises shall be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention shall be paid to the level of containment provided by the equipment.

6.2. The link between the interior and exterior of the premises shall be through airlocks [Personnel Airlock (PAL), Material Airlock (MAL)], changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel shall have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

6.3. The changing rooms shall have an arrangement with a step-over- bench. The facilities on the exit side shall incorporate showers for the operators.

6.4. The premises shall be laid out and designed so as to facilitate the required pressure cascades and containment.

6.5. The premises and equipment shall be appropriately designed and installed to facilitate cleaning and decontamination.

6.6. The manufacturing site and buildings shall be described in sufficient detail by means of plans and written explanations to ensure that the designation and conditions of use of all the rooms are correctly shown.

6.7. The flow of people and products shall be clearly marked on the layouts and plans.

6.8. The activities carried out in the vicinity of the site shall be indicated.

6.9. Plans shall describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

6.10. The facility shall be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

6.11. Areas of the facility where exposed product presents a risk shall be maintained at a negative air pressure relative to the environment.

7. Air-handling systems:-

7.1. The HVAC system shall be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.

7.2. Facilities and premises dealing with hazardous substances shall have the following basic air-handling characteristics, namely:-

(i) there shall be no direct venting of air to the outside;

(ii) air-conditioning or ventilation shall result in a negative pressure relative to the outside. Air pressure differentials shall be such that there is no uncontrolled flow of air between the work area and the external environment;

(iii) appropriate air pressure alarm systems shall be provided to warn of any pressure cascade reversal or loss of design pressure status. The appropriate design, alert and action limits shall be in place. System redundancies shall be in place to respond appropriately to pressure cascade failure;

(iv) the starting and stopping of the supply and exhaust air fan shall be synchronized so that the premises remain at a negative pressure during start-up and shut-down;

(v) the air pressure cascade within the facility, shall comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection;

(vi) visual indication of the status of room pressures shall be provided in each room;

(vii) air shall be exhausted to the outside through HEPA filters and not be re-circulated except to the same area, and provided that a further HEPA filtration stage is applied to the return air. Where HEPA filters are mentioned in the Schedule, this refers to HEPA filters with a minimum rating of H13 according to European norms;

(viii) where possible, single-pass air-handling systems with no recirculation shall be provided;

(ix) exhaust air or return air shall be filtered through a safe-change or bag- in-bag-out filter housing. The filter housing shall contain pre-filters and HEPA filters, both of which shall be removable with the safe bagging system;

(x) changing rooms shall be supplied with air filtered to the same standard as that for the work area they serve;

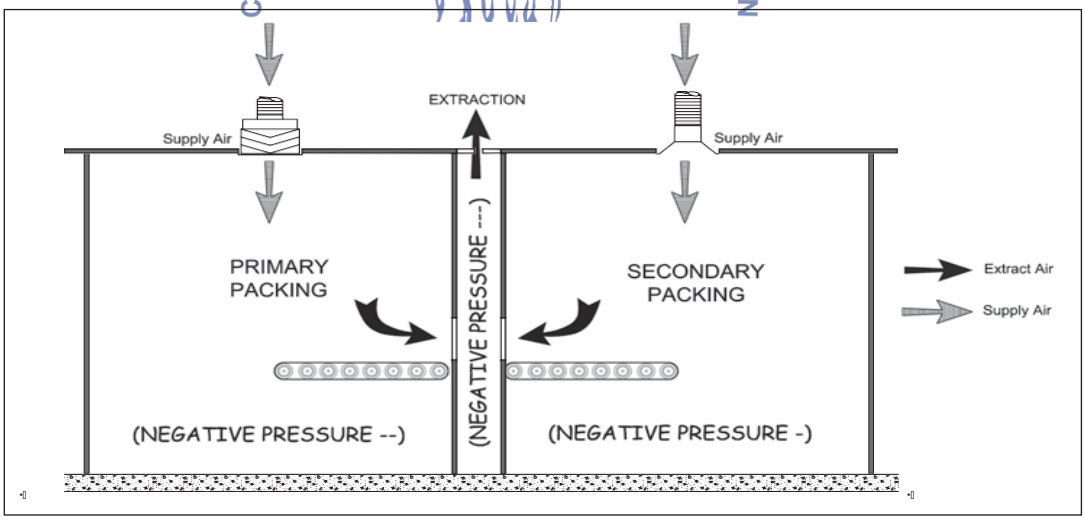
(xi) airlocks, pass-through hatches, etc., shall have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, airlock or pass-through hatch bordering on an external or non-good manufacturing practices area shall be at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility;

(xii) if the facility provides insufficient containment, and operators'

garments are contaminated with dust, the operators leaving the containment area shall pass through a decontamination system e.g., air showers or a mist shower system, to assist with removing or controlling dust particles on their garments. Operators shall follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering shall be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities shall be in place.

7.3. If required, appropriate measures shall be taken to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area.

Note.- This could be overcome by having a pass-through chamber over the "mouse hole" which is maintained at a negative pressure to both primary and secondary packing. This typical arrangement is illustrated in Figure below. This principle can be applied to other situations where containment from two sides is required. The typical airflow pattern for contaminant shall be as specified in the figure below–



7.4. Where possible, HEPA filters in the supply air system shall be terminally mounted to provide protection against back-flow cross-contamination in the event of failure in the supply airflow.

7.5. In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection.

7.6. There shall be a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications. These shall be available for inspection.

7.7. There shall be an indication of pressure gradients that are monitored by means of digital or analogue pressure indicators.

7.8. Consideration shall be given to providing an emergency power supply, e.g., diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

7.9. The principles of airflow direction, air filtration standards, temperature, humidity and related parameters shall be ensured and the filtration shall be consistent with the zone concepts and product protection required.

8. Air-Handling Units (AHU):-

8.1. The decision to use return air or re-circulated air shall be made on the basis of a risk assessment.

8.2. Where a full fresh-air or single-pass system is used, an energy recovery wheel could be considered. In such cases, there shall not be any potential for air leakage between the supply air and exhaust air as it passes through the wheel. The relative pressures between supply and exhaust air systems shall be such that the exhaust-air system operates at a lower pressure than the supply system. (Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)

8.3. Risk management principles shall be applied to address the potential of cross-contamination where energy wheels are used.

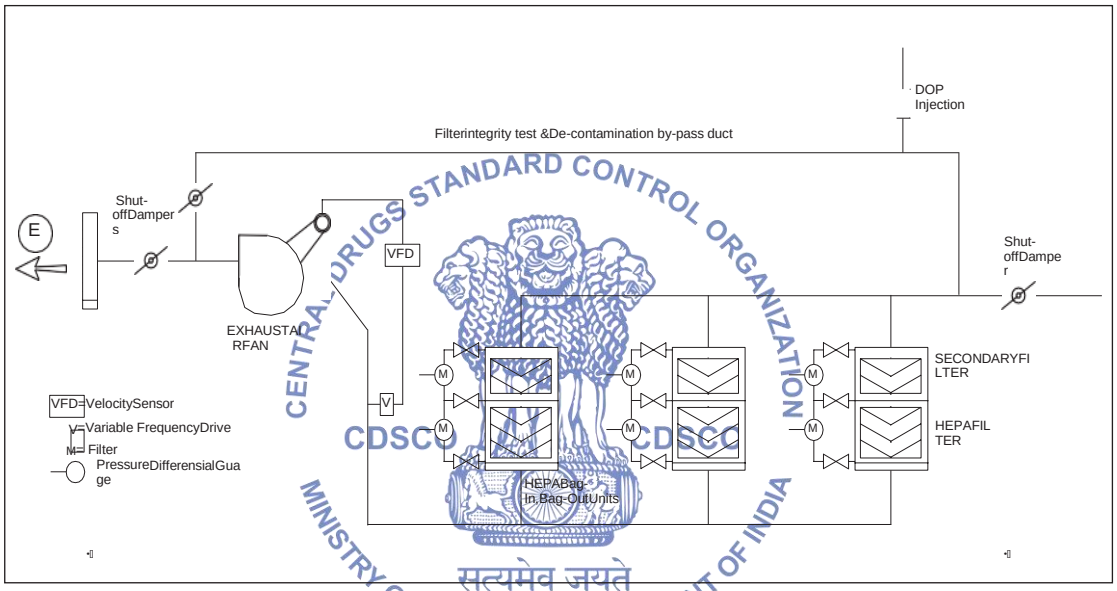
8.4. If return air is to be re-circulated it shall pass through a safe change filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU; however, the safe change filter shall be a dedicated unit. With this arrangement the return air passes through two sets of HEPA filters in series, i.e., the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.

8.5. The starting and stopping of the supply and exhaust air fans and associated system ventilation fans shall be synchronised such that the premises retain their design pressure and flow relationships during start-

up and shut-down. Processing shall stop when the fans are not running. This fan interlock sequence shall also apply if any fan shall fail, to ensure that there is no airflow reversal in the system.

9. Safe change filter housings:-

9.1. Safe change or bag-in-bag-out filter housings shall be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed. The Safe change filter bypass arrangement shall be as specified in the figure below–



9.2. The final filters on the safe change unit shall be HEPA filters with at least an H13 classification according to European norms filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters shall also be removable through the bag-in-bag-out method.

9.3. For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series shall be considered to provide additional protection the first filter fail.

9.4. All filter banks shall be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges shall be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing shall be provided with stopcocks, for safe removal or calibration of gauges.

9.5. Monitoring of filters shall be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

9.6. Computer based data monitoring systems may be installed to monitor filter condition.

9.7. Filter pressure gauges shall be marked with the clean filter resistance and the change-out filter resistance.

9.8. Installed filter leakage tests shall be performed in accordance with ISO standards. Injection ports (upstream) and access ports (downstream) shall, therefore, be provided for this purpose.

9.9. The exhaust air fan on a safe change filter system shall be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests and for this reason a bypass damper system shall be provided, as illustrated in figure at paragraph 9.1, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively, an independent booster fan system can be used, with appropriate shut-off dampers.

9.10. The bypass arrangement as shown in figure at paragraph 9.1also permits decontamination of the filters by means of circulation of a sanitising agent.

9.11. All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, shall be passed through safe change filter housings before being exhausted to the atmosphere.

9.12. All exhaust points outside the building shall be located as far as possible from air entry points and exit points shall be at a high level to minimise the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions shall be taken into account when positioning exhaust and supply points.

9.13. Where excessively dust-laden air is handled, a dust collector or bag

house shall be considered with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, PPE and breathing air systems shall then be provided to protect the operators during removal of dust from the collector bins.

9.14. Portable vacuum cleaners and portable dust collectors shall be fitted with H13 HEPA filters. These types of units shall be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel shall be provided with suitable PPE.

9.15. Records of the safe disposal of all contaminated filters and dust shall be kept.

10. Personnel decontamination systems:-

10.1. If required, a means of preventing contaminants from leaving the facility on the garments of personnel shall be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.

10.2. An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g., from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g., at low level) shall draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note.- When air showers are used these shall be correctly designed to effectively extract dust. Air filtration of the supply air and return or exhaust air shall comply with the same filtration standards as used in the manufacturing facility. Normally the fan shall be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

10.3. Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.

10.4. Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operators' garments or causing contaminants to adhere to the garments so that they are not easily liberated.

10.5. Personnel shall change into clean garments after having taken a shower.

11. Effluent treatment:-

11.1. Liquid and solid waste effluent shall be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.

11.2. All effluent shall be disposed of in a safe manner and the means of disposal shall be documented. Where external contractors are used for effluent disposal they shall have certification authorising them to handle and treat hazardous products.

12. Maintenance:- The efficient and safe operation of a facility handling hazardous materials is reliant on regular maintenance being carried out, to ensure that all parameters remain within specified tolerances.

13. Qualification and validation:-

System qualification and validation shall be carried out.

PART IV

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF BIOLOGICAL PRODUCTS

Note.—Good Manufacturing Practices for pharmaceutical products: main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Biological products. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Principles and general considerations:-

1.1. Biological products can be defined according to their source material and method of manufacture. The source materials and methods employed in the manufacture of biological products for human use therefore represent critical factors in shaping their appropriate regulatory control. Biological products are derived from cells, tissues or microorganisms and reflect the inherent variability characteristic of living materials. The active substances in biological products are often too complex to be fully characterised by utilising physicochemical testing methods alone and may show a marked heterogeneity from one preparation or batch or both. Consequently, special considerations are needed when manufacturing biological products in order to maintain

consistency in product quality.

1.2. The guidance provided in this Part applies to the manufacture, control and testing of biological products for human use from starting materials and preparations (including seed lots, cell banks and intermediates) to the finished product.

1.3. Manufacturing procedures within the scope of this Schedule includes-

(a) growth of strains of microorganisms and eukaryotic cells;

(b) extraction of substances from biological tissues, including human, animal and plant tissues, and fungi;

(c) recombinant DNA (rDNA) techniques;

(d) hybridoma techniques; and

(e) propagation of microorganisms in embryos or animals.

1.4. Medicinal products of biological origin manufactured by these procedures include allergens, antigens, vaccines, certain hormones, cytokines, monoclonal antibodies (mAbs), enzymes, animal immune sera, products of fermentation (including products derived from rDNA), biological diagnostic reagents for in-vivo use and Advanced Therapy Medicinal Products (ATMPs) used for example in gene therapy and cell therapy.

1.5. The manufacture, control and administration of biological active substances and finished products require certain specific considerations and precautions arising from the nature of these products and their processes. Unlike conventional pharmaceutical products which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and finished products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. As these biological processes may display inherent variability, the range and nature of by-products may also be variable. As a result, QRM principles are particularly important for this class of materials and shall be used to develop the control strategy across all stages of manufacture so as to minimise variability and reduce the opportunity for contamination and cross-contamination.

1.6. Materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of target cells and microorganisms. Therefore, extraneous microbial contaminants have the opportunity to grow. Furthermore, many biological products have

limited ability to withstand certain purification techniques, particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations in minimising such contamination events. Manufacturing shall be consistent with other specifications set out in the product summary files, marketing authorisation or clinical trial approvals [for example, number of generations (expressed as doublings or passages) between the seed lot or cell bank and the finished product].

1.7. Many biological materials (such as live-attenuated bacteria and viruses) cannot be terminally sterilised by heat, gas or radiation. In addition, some products, such as certain live and adjuvant vaccines [for example, Bacilli Calmette Guerin (BCG) or Cholera], may not be sterilised by filtration processes. For these axenic products, processing shall be conducted aseptically to minimise the introduction of contaminants from the point where a potential contamination cannot be removed from the manufacturing process. The validation of specific and critical manufacturing steps such as virus removal or inactivation shall be carried out. Robust environmental controls and monitoring and, wherever feasible, *in situ* cleaning and sterilisation systems, together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.

1.8. Control usually involves biological analytical techniques, which typically have a greater variability than physicochemical determinations. The combination of variability in starting materials and the potential for subtle changes during the manufacturing process of biological products also requires an emphasis on production consistency. This is of particular concern because of the need to link consistency to original clinical trials documenting the product's safety and efficacy. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

1.9. Because of the risks inherent in producing and manipulating pathogenic and transmissible microorganisms during the production and testing of biological materials, GMP shall prioritise the safety of the recipient to whom the biological product is administered, the safety of personnel

during operation and the protection of the environment.

1.10 Biosafety considerations shall follow the guidelines issued by the Central Government in this regard. In the context of manufacturing pathogenic biological products of Biosafety Risk Group 3 and 4, close collaboration between such institutions is especially required to assure that both product contamination and environmental contamination levels are controlled within the acceptable limits.

2. Pharmaceutical quality system and quality risk management:-

2.1. Biological products, like any pharmaceutical product, shall be manufactured in accordance with the requirements of a pharmaceutical quality system (product quality system) based on a life-cycle approach, good manufacturing practices for pharmaceutical products. Main principles- This approach facilitates innovation and continual improvement and also strengthens the link between pharmaceutical development and manufacturing activities.

2.2. QRM principles shall be used to develop the control strategy across all manufacturing and control stages including materials sourcing and storage, personnel and materials flow, manufacture and packaging, quality control, quality assurance, storage and distribution activities, as described in this Part. Due to the inherent variability of biological processes and starting materials, ongoing trend analysis and periodic review are particularly important elements of product quality system. Thus, special attention shall be paid to starting material controls, change control, trend analysis and deviation management in order to ensure production consistency. Monitoring systems shall be designed so as to provide early detection of any unwanted or unanticipated factors that may affect the quality, safety and efficacy of the product. The effectiveness of the control strategy in monitoring, reducing and managing such risks shall be regularly reviewed and the systems updated as required taking into account scientific and technical progress.

3. Personnel:-

3.1. Personnel responsible for production and control shall have an adequate background in relevant scientific disciplines such as microbiology, biology, biometry, chemistry, medicine, pharmacy,

pharmacology, virology, immunology, biotechnology and veterinary medicine, together with sufficient practical experience to enable them to perform their duties.

3.2. The health status of personnel shall be taken into consideration as part of ensuring product safety. Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) shall be vaccinated with appropriate specific vaccines and have regular health checks. Any changes in the health status of personnel which could adversely affect the quality of the product shall preclude their working in the production area, and appropriate records kept. The scope and frequency of health monitoring shall be commensurate with the risk to the product and personnel.

3.3. Training in cleaning and disinfection procedures, hygiene and microbiology shall emphasise the risk of microbial and adventitious contamination and the nature of the target microorganisms and growth media routinely used.

3.4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control, maintenance and cleaning staff) shall be defined on the basis of quality risk management principles. In general, all personnel including those not routinely involved in the production operation (such as management, engineering staff and validation staff or auditors) shall not pass from areas with exposure to live microorganisms, genetically modified microorganisms, animal tissue, toxins, venoms or animals, to areas where other products (inactivated or sterile) or different organisms are handled. If such passage is unavoidable during a working day, then contamination control measures (for example, clearly defined decontamination measures such as a complete change of appropriate clothing and shoes and showering, if applicable) shall be followed by all personnel visiting any such production area unless otherwise justified on the basis of QRM.

3.5. Because the risks are difficult to manage, personnel working in an animal facility shall be restricted from entering production areas where potential risks of cross-contamination exist.

3.6. Staff assigned to the production of Bacille Calmette-Guerin (BCG) products shall not work with other infectious agents. In particular, they shall not work with virulent strains of Mycobacterium tuberculosis, nor

shall they be exposed to a known risk of tuberculosis infection. Additionally, they shall be carefully monitored with regular health checks that screen for tuberculosis infection.

3.7. If personnel working in BCG manufacturing and in animal quarters, need to be reassigned to other manufacturing units, they shall not be allowed into such units until they pass their health check.

4. Starting materials:-

4.1. The source, origin and suitability of active substances, starting materials (for example, cryo-protectants and feeder cells), buffers and media (for example, reagents, growth media, serum, enzymes, cytokines, growth factors and amino acids) and other components of the finished product shall be clearly defined and controlled according to the principles set out in Part I of this Schedule.

4.2. Manufacturers shall retain information describing the source and quality of the biological materials used for at least one year after the expiry date of the finished products and according to regulations concerning biological products. It has been found that documents retained for longer periods may provide useful information related to Adverse Events Following Immunisation (AEFI) and other investigations.

4.3. All starting material suppliers (i.e., manufacturers) shall be initially qualified on the basis of documented criteria and a risk-based approach. Regular assessment of their status shall also be carried out. Particular attention shall be given to the identification and monitoring of any variability that may affect biological processes. When starting materials are sourced from brokers who could increase the risk of contamination by performing repackaging operations under GMP they shall be carefully qualified; an audit may form part of such qualification, as needed.

4.4. An identity test or equivalent, shall be performed on each batch of received starting materials prior to release. The number of containers sampled shall be justified on the basis of QRM principles and in agreement with all applicable guidelines. The identification of all starting materials shall be in compliance with the requirements appropriate to the stage of manufacture. The level of testing shall be commensurate with the qualification level of the supplier and the

nature of the materials used. In the case of starting material used to manufacture active substances, the number of samples taken shall be based on statistically recognised criteria and QRM principles. However, for starting materials and intermediates used in the formulation of finished product, each container shall be sampled for identity testing in accordance with the main principles of GMP for pharmaceutical products unless reduced testing has been validated.

4.5. The sampling process shall not adversely affect the quality of the product. Incoming starting materials shall be sampled under appropriate conditions in order to prevent contamination and cross-contamination.

4.6. Where justified (such as the special case of sterile starting materials) it may be acceptable to reduce the risk of contamination by not performing sampling at the time of receipt but to perform the testing later, on the samples taken at the time of use. In such cases, release of the finished product is conditional upon satisfactory results of these tests.

4.7. Where, the necessary tests for approving starting materials take a significantly long time, it may be permissible by exception to process starting materials before the test results are available. The use of these materials shall be clearly justified in a documented manner, and the risks shall be understood and assessed under the principles of QRM. In such cases, release of the finished product is conditional upon satisfactory results from the tests. It must be ensured that this is not standard practice and occurs only with justification of the risk taken.

4.8. The risk of contamination of starting materials during their passage along the supply chain shall be assessed, with particular emphasis on adventitious agents such as those causing Transmissible spongiform encephalopathies (TSEs). Other materials that come into direct contact with manufacturing equipment or with potential product contact surfaces (such as filter media, growth media during aseptic process simulations and lubricants) shall also be controlled. A quality risk assessment shall be performed to evaluate the potential for adventitious agents in biological starting materials.

4.9. Where required, the sterilisation of starting materials shall be carried out by heat, whenever possible. Where necessary, other appropriate validated methods may also be used for this purpose (such as

irradiation and filtration).

4.10. The controls required for ensuring the quality of sterile starting materials and of the aseptic manufacturing process shall be based on the principles and guidance contained in Part II of this Schedule.

4.11. The transport of critical materials, reference materials, active substances, human tissues and cells to the manufacturing site shall be controlled as part of a written quality agreement between the responsible parties, if they are different commercial entities. Manufacturing sites shall have documentary evidence of adherence to the specified storage and transport conditions, including cold chain requirements, if required. The required traceability starting at tissue establishments through the recipients, and including the traceability of materials in contact with the cells or tissues shall be ensured, maintained and documented.

5. Seed lots and cell banks:-

5.1. The recommendations set out in GMP for API shall be followed taking into consideration specific guidance for API manufactured by cell culture or fermentation.

5.2. Where human or animal cells are used as feeder cells in the manufacturing process, appropriate controls over their sourcing, testing, transport and storage shall be in place.

5.3. In order to prevent the unwanted drift of genetic properties which might result from repeated subcultures or multiple generations, the production of biological products obtained by microbial culture, cell culture or propagation in embryos and animals shall be based on a system of master and working seed lots or cell banks or both; which is the beginning of the manufacturing process of certain biological products (for example, vaccines).

5.4. The number of generations (expressed as passages or doublings) between the seed lot or cell bank and the finished product, defined as maximum, shall be consistent with the marketing authorisation dossier and shall not be exceeded.

5.5. Cell-based medicinal products are often generated from a cell stock obtained from a limited number of passages. In contrast with the two-tier system of Master Cell Banks (MCBs) and Working Cell Banks (WCBs), the number of production runs from a cell stock is limited by the number

of aliquots obtained after expansion and does not cover the entire life-cycle of the product. Cell stock changes shall be covered by a validation protocol and communicated to the National Regulatory Authority (NRA), as applicable.

5.6. Establishment and handling of the MCBs and WCBs shall be performed under conditions which are demonstrably appropriate. These shall include an appropriately controlled environment to protect the seed lot and the cell bank, and the personnel handling them. During the establishment of the seed lot and cell bank, no other living or infectious material (such as viruses, cell lines or microbial strains) shall be handled simultaneously in the same area or by the same persons.

5.7. Quarantine and release procedures for master and working cell banks or seed lots shall be followed, including adequate characterisation and testing for contaminants. Initially, full characterisation testing of the MCB shall be done, including genetic identification. A new MCB (from a previous initial clone, MCB or WCB) shall be subjected to the same established testing as the original MCB, unless otherwise justified. Thereafter, the viability, purity and other stability indicating attributes of seed lots and cell banks shall be checked regularly according to justified criteria. Evidence of the stability and recovery of the seed lots and banks shall be documented and records shall be kept in a manner that permits trend evaluation.

5.8. Each storage container shall be adequately sealed, clearly labelled and kept at an appropriate temperature. A stock inventory shall be kept. The storage temperature shall be recorded continuously and, where applicable, the liquid nitrogen level shall be monitored. Any deviation from the set limits, and any corrective and preventive action taken, shall be recorded. Temperature deviations shall be detected as early as possible (for example, through the use of an alarm system for temperature and nitrogen levels).

5.9. Seed lots and cell banks shall be stored and used in such a way so as to minimise the risks of contamination or alteration (for example, stored in qualified ultra-low temperature freezers or liquid nitrogen storage containers). Control measures for the storage of different seeds or cells or both in the same area or equipment shall prevent mix-up and shall take into account the infectious nature of the materials in order to prevent cross-contamination.

5.10. Master Seed Lots (MSLs), MCBs, and preferably also Working Seed Lots (WSLs) and WCBs, shall be stored in two or more controlled separate sites in order to minimise the risk of total loss due to natural disaster, equipment malfunction or human error. A contingency plan shall be in place.

5.11. The storage and handling conditions for the cell or seed banks shall be defined. Access shall be controlled and restricted to authorised personnel and appropriate access records maintained. Records of location, identity and inventory of individual containers shall also be kept. Once containers are removed from the seed lot or cell bank management system, they shall not be returned to the stock.

6. Premises and equipment:-

6.1. In general, preparations containing live microorganisms or live viruses shall not be manufactured and containers shall not be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms and viruses, then the use of multi-product facilities may be justifiable. In such cases, measures such as campaign production, closed systems or disposable systems or both shall be considered and shall be based on QRM principles

6.2. Documented QRM shall be carried out for every additional product in a biological manufacturing multi-product facility, which may include a potency and toxicological evaluation based on cross-contamination risks. Other factors to be taken into account include facility or equipment design and use, personnel and material flows, microbiological controls, physicochemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from product evaluation. The outcome of the QRM process shall be the basis for determining the necessity for premises and equipment to be dedicated to a particular product or product family, and the extent to which this shall be the case. This may include dedicating specific product contact parts.

6.3. Inactivated vaccines, antisera and other biological products including those made by rDNA techniques, toxoids and bacterial extracts may,

following inactivation, be manufactured on the same premises provided that adequate decontamination and cleaning measures are implemented on the basis of QRM.

6.4. Cleaning and sanitisation shall take into account the fact that processes often include the handling of growth media and other growth-promoting agents. Validation studies shall be carried out to ensure the effectiveness of cleaning, sanitisation and disinfection, including elimination of residues of used agents. Environmental and personnel safety precautions shall be taken during the cleaning and sanitisation processes. The use of cleaning and sanitising agents shall not pose any major risk to the performance of equipment. The use of closed systems to improve asepsis and containment shall be considered where practicable. Where open systems are utilised during processing (for example, during addition of growth supplements, media, buffers and gases, and during sampling and aseptic manipulations during the handling of live cells such as in cell-therapy products) control measures shall be put in place to prevent contamination, mix-up and cross-contamination. Logical and unidirectional flows of personnel, materials and processes, and the use of clean-in-place and sterilise-in-place systems, shall be considered wherever possible. Where sterile single-use systems such as bags and connectors are utilised, they shall be qualified with respect to suitability, extractables, leachables and integrity.

6.5. Because of the variability of biological products, and of the corresponding manufacturing processes, approved starting materials that have to be measured or weighed for the production process (such as growth media, solutions and buffers) may be kept in small stocks in the production area for a specified period of time according to defined criteria for the duration of manufacture of the batch or of the campaign. Appropriate storage conditions and controls shall be maintained during such temporary storage. These materials shall not be returned to the general stock. Materials used to formulate buffers, growth media and so on shall be weighed and made into a solution in a contained area using local protection (such as a classified weighing booth) and outside the aseptic processing areas in order to minimise particulate contamination of the later.

6.6. In manufacturing facilities, the mix-up of entry and exit of personnel

shall be avoided through the use of separate changing rooms or through procedural controls where Biosafety Risk Group 3 or 4 organisms are handled.

7. Containment:-

7.1. Airborne dissemination of live microorganisms and viruses used for the production process, including those from personnel, shall be avoided.

7.2. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Drainage systems shall be designed in such a way that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Specific and validated decontamination systems shall be considered for effluents when infectious or potentially infectious materials are used for production. Regulations issued by the Central Government in this regard shall be complied with in order to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

7.3. Dedicated production areas shall be used for the handling of live cells capable of persistence in the manufacturing environment, for pathogenic organisms of Biosafety Risk Group 3 or 4 or for spore-forming organisms until the inactivation process is accomplished and verified. For Bacillus anthracis, Clostridium tetani and Clostridium botulinum strictly dedicated facilities shall be utilised for each individual product. Up to date information on these and other high-risk or "special" agents shall be sought from major information resources. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product shall be processed at any one time.

7.3.1. Use of any pathogenic organism above Biosafety Risk Group 3 may be allowed according to the biohazard classification of the organism, the risk assessment of the biological product and its emergency demand.

7.4. Production of BCG related product shall take place in a dedicated area and by means of dedicated equipment and utilities (such as HVAC systems) in order to minimise the hazard of cross-contamination.

7.5. Specific containment requirements apply to poliomyelitis vaccine to

minimise poliovirus facility associated risk and for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses. The measures and procedures necessary for containment (i.e., for protecting the environment and ensuring the safety of the operator) shall not conflict with those for ensuring product quality.

7.6. Air-handling systems shall be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas as required. The need for dedicated air handling units or single pass systems shall be based on QRM principles, taking into account the biohazard classification and containment requirements of the relevant organism, and process and equipment risks. In the case of Biosafety Risk Group 3 organisms, air shall not be recirculated to any other area in the facility and shall be exhausted through HEPA filters that are regularly checked for performance. A dedicated non-recirculating ventilation system and HEPA filtering of exhaust air are required when handling Biosafety Risk Group 4 organisms.

7.7. Primary containment equipment shall be designed and initially qualified for integrity in order to ensure that the escape of biological agents or material into the immediate working area and outside environment is prevented. Thereafter, in line with relevant guidelines and quality risk management principles, periodical tests shall be performed to ensure that the equipment is in proper working condition.

7.8. Activities associated with the handling of live biological agents (such as centrifugation and blending of products which can lead to aerosol formation) shall be contained in such a way so as to prevent contamination of other products or the egress of live agents into the working or outside environment or both. The viability of such organisms and their biohazard classification shall be taken into consideration as part of the management of such risks. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures shall be available for each organism or groups of related organisms. Where different strains of a single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative

strain, unless the strains vary significantly in their resistance to the decontaminating agents used.

7.9. Areas where Biosafety Risk Group 3 or 4 organisms are handled shall always have a negative air pressure relative to the environment. This will ensure the containment of the organism in unlikely events such as failure of the door interlock. Air-lock doors shall be interlocked to prevent them from being opened simultaneously. Differential pressure alarms shall be present wherever required and shall be validated and monitored.

7.10. Air vent filters shall be hydrophobic and subject to integrity testing at intervals determined by a QRM approach.

7.11. Where the filtration of exhaust air is necessary, the safe changing of filters shall be ensured or bag-in-bag-out housings shall be employed. Once removed, filters shall be decontaminated and properly destroyed. In addition to HEPA filtration other inactivation technologies such as heat inactivation and steam scavenging may be considered for exhaust air to ensure effective inactivation of pathogenic organisms of Biosafety Risk Group 3 or 4.

8. Clean rooms:-

8.1. In order to address the specific manufacturing processes involved in the production of biological products, and particularly vaccines, the environmental monitoring of clean rooms in vaccine manufacturing facilities; points to consider for manufacturers of human vaccines guidance document may be used to develop the environmental classification requirements for biological manufacturing processes. As part of the control strategy, the degree of environmental control of particulate and microbial contamination of the production premises shall be adapted to the intermediate or finished product and also to the production step, taking into account the potential level of contamination of the starting materials and the risks to the finished product.

8.2. The environmental monitoring programme shall be supplemented with methods to detect the presence of the specific microorganisms used for production (for example, recombinant yeast and toxin or polysaccharide producing bacteria). The environmental monitoring programme may also include detection of the produced organisms and

adventitious agents of production organisms, especially when campaign manufacture is applied on the basis of QRM principles.

9. Production:-

9.1. Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention shall be paid to the control strategy for ensuring that effective steps are in place for preventing or minimising the occurrence of unwanted bioburden, endotoxins, viruses of animal and human origin and associated metabolites.

9.2. The QRM process shall be the basis for implementing the technical and organisational measures required to control the risks of contamination and cross-contamination. These could include, though are not limited to-

(i) carrying out processing and filling in segregated areas;

(ii) containing material transfer by means of an airlock and appropriate type of pass box with validated transfer procedures, clothing change and effective washing and decontamination of equipment;

(iii) recirculation of only treated (HEPA filtered) air;

(iv) acquiring knowledge of the key characteristics (for example, pathogenicity, detectability, persistence and susceptibility to inactivation) of all cells, organisms and any adventitious agents within the same facility;

(v) when considering the acceptability of concurrent work in cases where production is characterised by multiple small batches from different starting materials (for example, cell-based products) taking into account factors such as the health status of donors and the risk of total loss of a product from or for specific patients during development of the cross-contamination control strategy;

(vi) preventing the risk of live organisms and spores entering non-related areas or equipment by addressing all potential routes of cross-contamination (for example, through the HVAC system) through the use of single use components and closed systems;

(vii) conducting environmental monitoring specific to the microorganism being manufactured in adjacent areas while paying attention to cross-contamination risks arising from the use of certain monitoring equipment (used for airborne particle

monitoring) in areas handling live or spore-forming organisms or both; and

(viii) using campaign-based production.

9.3. When applicable, the inoculum preparation area shall be designed so as to effectively control the risk of contamination, and shall be equipped with a biosafety hood for primary containment.

9.4. If possible, growth media shall be sterilisedin situ by heat or in-line microbial-retentive filters. Additionally, in-line microbial-retentive filters shall be used for the routine addition of gases, media, acids, alkalis and so on to fermenters or bioreactors.

9.5. Data from continuous monitoring of certain production processes (fermentation) shall form part of the batch record. Where continuous culture is used, special consideration shall be given to parameters such as temperature, pH, pO2, CO2 and the rate of feed or carbon source with respect to growth of cells.

9.6. In cases where a viral inactivation or removal process is performed, measures shall be taken (for example, in relation to facility layout, unidirectional flow and equipment) to avoid the risk of recontamination of treated products by non-treated products.

9.7. A wide variety of equipment and components (for example, resins, matrices and cassettes) are used for purification purposes. QRM principles shall be applied to devise the control strategy regarding such equipment and associated components when used in campaign manufacture and in multi-product facilities. The reuse of components at different stages of processing of one product is discouraged but, if performed, shall be validated. Acceptance criteria, operating conditions, regeneration methods, lifespan and sanitisation or sterilisation methods, cleaning process, and hold time between the use of reused components shall be defined and validated. The reuse of components for different products is not acceptable.

9.8. Where adverse donor (human or animal) health information becomes available after procurement or processing or both, and this information relates to product quality, then appropriate measures shall be taken including product recall, if applicable.

9.9. Antibiotics may be used during the early stages of production to help prevent inadvertent microbial contamination or to reduce the bioburden of living tissues and cells. In this case, the use of antibiotics

shall be well justified, and they shall be cleared from the manufacturing process at the stage specified in the marketing authorisation. Acceptable residual levels shall be defined and validated. Penicillin and other beta lactam antibiotics shall not be used at any stage of the process.

9.10. A procedure shall be in place to address equipment or accessories failure or both (air vent filter failure) which shall include a product impact review. If such failures are discovered following batch release, the Licensing Authority shall be notified and the need for a batch recall shall be considered.

10. Campaign production:-

10.1. The decision to use a facility or filling line for campaign manufacture shall be justified in a documented manner and shall be based on a systematic risk approach for each product (or strain) taking into account the containment requirements and the risk of cross-contamination to the next product. Campaign changeover procedures, including sensitive techniques used for the determination of residues, shall be validated and proper cleaning acceptance criteria shall be defined on a toxicology basis of product residues from the last campaign, as applicable. Equipment assigned to continued production or to campaign production of successive batches of the same intermediate product shall be cleaned at appropriate validated intervals to prevent build-up and carryover of contaminants (product degradants or objectionable levels of microorganisms).

10.2. For downstream operations of certain products (for example, pertussis or diphtheria vaccines) campaign production may be acceptable if well justified. For finishing operations (formulation and filling) the need for dedicated facilities or the use of campaigns in the same facility will depend on the specific characteristics of the biological product, on the characteristics of the other products (including any non-biological products), on the filling technologies used (single use closed systems). Labelling and packaging operations can be carried out in a multiproduct facility.

10.3. Campaign changeover involves intensive decontamination or sterilisation (if required) and cleaning of the equipment and manufacturing area. Decontamination or sterilisation (if required) and

cleaning shall include all equipment and accessories used during production, as well as the facility itself. The following recommendations shall be considered, namely:-

(i) waste shall be removed from the manufacturing area or sent to the bio-waste system in a safe manner;

(ii) materials shall be transferred by a validated procedure; and

(iii) the Quality Unit shall confirm area clearance by inspection, and review the campaign changeover data (including monitoring results) prior to releasing the area for the next product.

10.4. When required, the corresponding diluent for the product can be filled in the same facility in line with the defined campaign production strategy for finished product.

10.5. When campaign-based manufacturing is considered, the facility layout and the design of the premises and equipment shall permit effective cleaning and decontamination or sterilisation (if required) based on QRM principles and validated procedures following the production campaign. In addition, consideration may need to be given at the design stage of facility layout to the possible need for fumigation.

11.Labelling:-

11.1. The information provided on the inner label (also called the container label) and on the outer label (on the packaging) shall be readable and legible and the content approved by the Licensing Authority.

11.2. Minimal key information shall be printed on the inner label and additional information shall be provided on the outer label (for example, carton) or product leaflet or both.

11.3. The suitability of labels for low and ultra-low storage temperatures shall be verified, if applicable. The label shall remain properly attached to the container under different storage conditions during the shelf-life of the product. The label and its adhesive shall have no adverse effect on the quality of the product caused by leaching, migration or other means.

12.Validation:-

12.1. Biological processes, handling of live materials and using campaign-based production, if applicable, are the major aspects of biological product manufacturing which require process and cleaning validation.

The validation of such processes given the typical variability of biological products, the possible use of harmful and toxic materials and the need for inactivation processes plays an important role in demonstrating production consistency and in proving that the critical process parameters and product attributes are controlled.

12.2. A QRM approach shall be used to determine the scope and extent of validation.

12.3. All critical biological processes (including inoculation, multiplication, fermentation, cell disruption, inactivation, purification, virus removal, removal of toxic and harmful additives, filtration, formulation and aseptic filling) are subject, as applicable, to process validation. Manufacturing control parameters to be validated may include specific addition sequences, mixing speeds, time and temperature controls, limits of light exposure and containment.

12.4. After initial process validation studies have been finalised and routine production has begun, critical processes shall be subject to monitoring and trending with the objective of assuring consistency and detecting any unexpected variability. The monitoring strategy shall be defined, taking into consideration factors such as the inherent variability, complexity of quality attributes and heterogeneity of biological products. A system or systems for detecting unplanned departures from the process as designed shall be in place to ensure that the process remains in a state of control. Collection and evaluation of information and data on the performance of the process will allow for detection of undesired process variability and will determine whether action shall be taken to prevent, anticipate or correct problems so that the process remains under control.

12.5. Cleaning validation shall be performed in order to confirm the effectiveness of cleaning procedures designed to remove biological substances, growth media, process reagents, cleaning agents, inactivation agents and so on. Careful consideration shall be given to cleaning validation when campaign-based production is practiced.

12.6. Critical processes for inactivation or elimination of potentially harmful microorganisms of Biosafety Risk Group 2 or above, including genetically modified ones, are subject to validation.

12.7. Process revalidation may be triggered by a process change as part of the change control system. In addition, because of the variability of

processes, products and methods, process revalidation may be conducted at pre-determined regular intervals according to risk considerations. A detailed review of all changes, trends and deviations occurring within a defined time period for example, one year, based on the regular Product Quality Review (PQR) may indicate a need for process revalidation.

12.8. The integrity and specified hold times of containers used to store intermediate products shall be validated unless such intermediate products are freshly prepared and used immediately.

13.Quality Control:-

13.1. As part of quality control sampling and testing procedures for biological materials and products, special consideration shall be given to the nature of the materials being sampled (for example, the need to avoid contamination, ensure biocontainment or cold chain requirements) in order to ensure that the testing carried out is representative.

13.2. Samples for post-release use typically fall into one of two categories reference samples or retention samples for the purposes of analytical testing and identification respectively. For finished products the reference and retention samples will in many instances be presented identically as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

13.2.1. Reference samples of biological starting materials shall be retained under the recommended storage conditions for at least one year beyond the expiry date of the corresponding finished product. Reference samples of other starting materials (other than solvents, gases and water) as well as intermediates for which critical parameters cannot be tested in the final product shall be retained for at least two years after the release of the product if their stability allows for this storage period. Certain starting materials such as components of growth media need not necessarily be retained.

13.2.2. Retention samples of a finished product shall be stored in their final packaging at the recommended storage conditions for at least one year after the expiry date.

13.3. For cell-based products, microbiological tests (for example, sterility

tests or purity checks) shall be conducted on cultures of cells or cell banks free of antibiotics and other inhibitory substances in order to provide evidence of the absence of bacterial and fungal contamination, and to be able to detect fastidious organisms where appropriate. Where antibiotics are used, they shall be removed by filtration at the time of testing.

13.4. The traceability, proper use and storage of reference standards shall be ensured, defined and recorded. The stability of reference standards shall be monitored, and their performance trended. The National or World Health Organisation (WHO) Recommendations for the preparation, characterisation and establishment of biological reference standards shall be followed.

13.5. All stability studies including real time or real condition stability, accelerated stability and stress testing shall be carried out. Trend analysis of the test results from the stability monitoring programme shall assure the early detection of any process or assay drift and this information shall be part of the PQR of biological products.

13.6. For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative or validated techniques are available, the frequency of testing may take into account a risk-based approach. The principle of bracketing and matrix designs may be applied if scientifically justified in the stability protocol.

13.7. All analytical methods used in the quality control and in-process control of biological products shall be well characterised, validated and documented to a satisfactory standard in order to yield reliable results. The fundamental parameters of this validation include linearity, accuracy, precision, selectivity, specificity, sensitivity and reproducibility.

13.8. For test methods described in relevant pharmacopoeial monographs, qualification of the laboratory test equipment and personnel shall be performed. In addition, repeat precision and comparability precision shall be shown in the case of animal tests. Repeatability and reproducibility shall also be demonstrated by reviewing retrospective test data. In addition to the common parameters typically used for validating assays (accuracy and precision) additional measurements (for example, of the performance of references, critical reagents or

cell lines or both) shall be considered during the validation of bioassays based on the biological nature of the assay and reagents used.

14.Documentation (batch processing records):-

14.1. In general, the processing records of regular production batches shall provide a complete account of the manufacturing activities of each batch of biological product showing that it has been produced, tested and dispensed into containers in accordance with the approved procedures. In the case of vaccines, a batch processing record and a summary protocol shall be prepared for each batch for the purpose of lot release by the Licensing Authority. The information included in the summary protocol for independent lot release of vaccines by regulatory authorities. The summary protocol and all associated records shall be of a type approved by the Licensing Authority.

14.2. Manufacturing batch records shall be retained for at least one year after the expiry date of the batch of the biological product and shall be readily retrievable for inspection by the Licensing Authority. It has been found that documents retained for longer periods may provide useful information related to AEFI and other investigations.

14.3. Starting materials may require additional documentation on source, origin, supply chain, method of manufacture and controls applied in order to ensure an appropriate level of control, including the microbiological quality, if applicable.

14.4. Some product types may require a specific definition of what materials constitute a batch particularly somatic cells in the context of ATMPs. For autologous and donor matched situations, the manufactured product shall be viewed as a batch.

15.Use of animals:-

15.1. A wide range of animals is used for the manufacture or quality control of biological products. Special considerations are required when animal facilities are present at a manufacturing site.

15.2. The presence of live animals in the production area shall be avoided unless otherwise justified. Embryonated eggs are allowed in the production area, if applicable. If the extraction of tissues or organs from animals is required then particular care shall be taken to prevent

contamination of the production area (for example, appropriate disinfection procedures shall be undertaken).

15.3. Areas used for performing tests involving animals or microorganisms shall be well separated from premises used for the manufacturing of products and shall have completely separate ventilation systems and separate staff. The separation of different animal species before and during testing shall be considered, as the necessary animal acclimatisation process, as part of the test requirements.

15.4. In addition to monitoring compliance with TSE regulations and other adventitious agents that are of concern (including those causing zoonotic diseases and diseases in source animals) shall also be monitored and recorded in line with specialist advice on establishing such programmes. Instances of ill health occurring in the source or donor animals shall be investigated with respect to their suitability and the suitability of in-contact animals, for continued use (for example, in manufacture, as sources of starting materials and for quality control and safety testing). Decisions shall be documented.

15.5. A look-back procedure shall be in place in relation to the decision making process used to evaluate the continued suitability of the biological active substance or finished product in which animal sourced starting materials have been used or incorporated. This decision making process may include the retesting of reference samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source or donor animals shall be documented and shall be taken into account when considering the removal of those animals from the programme for defined periods.

15.6. Particular care shall be taken to prevent and monitor infections in source or donor animals. Measures taken shall cover sourcing, facilities, husbandry, biosafety procedures, testing regimes, control of bedding and feed materials, one hundred percent fresh air supply, appropriate design of the HVAC system, water supply and appropriate temperature and humidity conditions for the species being handled. This is of special relevance to Specific Pathogen-Free (SPF) animals where pharmacopoeial monograph requirements shall be met. Housing and health monitoring shall also be defined for other

categories of animals (for example, healthy flocks or herds).

15.7. For products manufactured from transgenic animals, traceability shall be maintained in the creation of such animals from the source animals.

15.8. For different animal species and lines, key criteria shall be defined, monitored and recorded. This may include the age, sex, weight and health status of the animals.

15.9. Animals, biological agents and tests carried out shall be appropriately identified to prevent any risk of mix-up and to control all identified hazards.

15.10. The facility layout shall ensure a unidirectional and segregated flow of healthy animals, inoculated animals and waste decontamination areas. Personnel and visitors shall also follow a defined flow in order to avoid cross-contamination.

16.Complaints:-

16.1. The person responsible for handling complaints and deciding on the measures to be taken to deal with them shall have appropriate training or experience in the specific features of the quality control of biological products.

16.2. There are basically two types of complaints, product quality complaints and adverse reactions or events.

16.3. The first type of complaint may be caused by problems such as faulty manufacture, product defects or deterioration as well as, particular to biological products, adulteration of the biological products. These complaints shall be recorded in detail and the causes thoroughly investigated (e.g., by comparison with the reference samples kept from the same batch). There shall also be written procedures to describe the action to be taken.

16.4. To address the second type of complaint, reports of any adverse reaction or event shall be entered in a separate register in accordance with requirements. An investigation shall be conducted to find out whether the adverse reaction or event is due to a quality problem and whether such reactions or events have already been reported in the literature or whether it is a new observation. In either case, complaint records shall be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed

products. The safety monitoring of biological products shall be carried out through pharmacovigilance systems dealing with specific issues relating to adverse reactions and adverse events following treatment with biological products.

16.5. The licensing authority shall be kept informed of any complaints leading to a recall or restriction on supply and the records shall be available for inspection.

17. Product recalls:- Recall and Rapid Alert System for Drugs (including Biological and Vaccine) shall be in place for the product recall.

PART V

SPECIFIC REQUIREMENTS FOR RADIOPHARMACEUTICAL PRODUCTS

Note.- Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of Radiopharmaceutical Products. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Principles:- Radiopharmaceuticals shall be manufactured in accordance with the basic principles of GMP. The matters covered under this Part shall therefore be considered as supplementary to the general requirements for GMP and relate specifically to the production and control of radiopharmaceuticals. Many radiopharmaceuticals are released and administered to patients shortly after their production because of their short half-lives, so that quality control may sometimes be retrospective. In view of the same, strict adherence to GMP is mandatory.

2. Personnel:-

2.1. The manufacturing establishment, whether a hospital radiopharmacy, centralised radio-pharmacy, nuclear centre or institution, industrial manufacturer or Positron Emission Tomography (PET) Centre and its personnel shall be under the control of a person who has a proven record of academic achievement together with a demonstrated level of practical expertise and experience in radio-pharmacy and radiation hygiene. Supporting academic and technical personnel shall have the necessary

post graduate or technical training and experience appropriate to their functions.

2.2. Personnel required to work in radioactive, clean and aseptic areas shall be selected with care, to ensure that they can be relied on to observe the appropriate codes of practice and are not subject to any disease or condition that can compromise the integrity of the product. Health checks on personnel shall be requested before employment and periodically thereafter. Any changes in personal health status (e.g., in haematology) may require the temporary exclusion of the person from further radiation exposure.

2.3. Only the minimum number of personnel required shall be present in clean and aseptic areas when work is in progress. Access to these areas shall be restricted during the preparation of radiopharmaceuticals, kits or sterile set-ups. Inspection and control procedures shall be conducted from outside these areas as far as possible.

2.4. During the working day, personnel may pass between radioactive and non-radioactive areas only if the safety rules of radiation control (health physics control) are followed.

2.5. The release of a batch may be approved only by an authorised person or a person with academic qualifications officially registered as a suitably qualified person, and with appropriate experience in the manufacture of radiopharmaceuticals.

2.6. To ensure the safe manufacture of radiopharmaceuticals, personnel shall be trained in GMP, the safe handling of radioactive materials and radiation safety procedures. They shall also be required to take periodic courses and receive training to keep abreast of the latest developments in their fields.

2.7. Training records shall be maintained and periodic assessments of the effectiveness of training programmes shall be made.

2.8. All personnel engaged in production, maintenance and testing shall follow the relevant guidelines for handling radioactive products and be monitored for possible contamination or irradiation exposure or both.

3. Premises and equipment:-

3.1. As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials must be

specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility. Interior surfaces (walls, floors and ceilings) shall be smooth, impervious and free from cracks; they shall not shed matter and shall permit easy cleaning and decontamination. Drains shall be avoided wherever possible and, unless essential, shall be excluded from aseptic areas.

3.2. Specific disposal systems shall be mandatory for radioactive effluents. These systems shall be effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility.

3.3. Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material and be regularly sanitised. Adequate precautions shall be taken to avoid contamination of the drainage system with radioactive effluents.

3.4. Lighting, heating, ventilation and, if necessary, air-conditioning shall be designed to maintain a satisfactory temperature and relative humidity to ensure the comfort of personnel working in protective clothing. Buildings shall be in a good state of repair. The condition of the buildings shall be reviewed regularly and repairs carried out when and where necessary. Special care shall be exercised to ensure that building repair or maintenance operations do not compromise the products. Premises shall provide sufficient space for the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms shall be clean, sanitary and free from radioactive contamination.

3.5. Ventilation of radiopharmaceutical production facilities shall meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Suitable pressure and airflow patterns shall be maintained by appropriate isolation or enveloping methods. Air handling systems for both radioactive and non-radioactive areas shall be fitted with alarms so that the working personnel in the laboratory are warned of any failure of these systems.

3.6. Dedicated facilities and equipment shall be used for the manufacture of any radiopharmaceutical product derived from human blood or plasma. Autoclaves used in production areas for radio- pharmaceuticals may be placed behind a lead shield to minimise the radiation exposure of the operators. Such autoclaves shall be checked for contamination

immediately after use to minimise the possibility of cross-contamination by radioactivity of the products in the next autoclave cycles.

3.7. All containers of radiopharmaceutical substances, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross-contamination shall be prevented by the adoption of some or all of the following measures, namely:-

(i) processing and filling in segregated areas;

(ii) avoiding the manufacture of different products at the same time, unless they are effectively segregated;

(iii) containing material transfer by means of airlocks, air extraction, changing clothes and careful washing and decontamination of equipment;

(iv) protecting against the risks of contamination caused by recirculation of untreated air or by accidental re-entry of extracted air;

(v) using "closed systems" of manufacture;

(vi) taking care to prevent aerosol formation; and

(vii) using sterilised containers.

3.8. Positive pressure areas shall be used to process sterile products. In general, any radioactivity shall be handled within specifically designed areas maintained under negative pressures. The production of sterile radioactive products shall therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met.

3.9. Separate air-handling units shall be used for radioactive and non-radioactive areas. Air from operations involving radioactivity shall be exhausted through appropriate filters that are regularly checked for performance.

3.10. Pipework, valves and vent filters shall be properly designed to facilitate validated cleaning and decontamination.

4. Production:-

4.1. SOPs must be available for all operating procedures and shall be regularly reviewed and kept up to date for all manufacturing operations. All entries on batch records shall be initiated by the operator and independently checked by another operator or supervisor.

4.2. Specifications for starting materials shall include details of their source, origin and (where applicable) method of manufacture and of the controls

used to ensure their suitability for use. Release of a finished product shall be conditional on satisfactory results being obtained in the tests on starting materials.

4.3. Careful consideration shall be given to the validation of sterilisation methods.

4.4. A wide variety of equipment is used in the preparation of radiopharmaceuticals. Equipment for chromatography shall, in general, be dedicated to the preparation and purification of one or several products labelled with the same radionuclide to avoid radioactive cross-contamination. The life span of columns shall be defined. Great care shall be taken in cleaning, sterilising and operating freeze-drying equipment used for the preparation of kits.

4.5. A list of critical equipment shall be drawn up, including any equipment such as a balance, pyrogen oven, dose calibrator, sterilising filter, etc., where an error in the reading or function could potentially cause harm to the patient being given the final product. These devices shall be calibrated or tested at regular intervals and shall be checked daily or before production is started. The results of these tests shall be included in the daily production records.

4.6. Specific equipment for radioactive measurements may be required as well as radioactive reference standards. For the measurement of very short half-lives, national central laboratories shall be contacted to calibrate the apparatus. Where this is not possible, alternative approaches, such as documented procedures, may be used.

4.7. In the case of labelling kits, freeze drying shall be carried out as an aseptic procedure. If an inert gas such as nitrogen is used to fill vials, it must be filtered to remove possible microbial contamination.

4.8. The dispensing, packaging and transportation of radiopharmaceuticals shall comply with the relevant provisions of the Atomic Energy Act 1962 and the rules made thereunder.

5. Labelling:-

5.1. All products shall be clearly identified by labels, which must remain permanently attached to the containers under all storage conditions. An area of the container shall be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling, the label shall appear on its package.

5.2. The labels of radiopharmaceuticals shall comply with the requirements specified in rule 96.

5.3. The label on the container shall show-

(a) the name of the drug product or the product identification code or both;

(b) the name of the radionuclide;

(c) the name of the manufacturer or the company and the person responsible for placing the drug on the market;

(d) the radioactivity per unit dose-

(i) for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in the container;

(ii) for solid preparations, such as freeze dried preparations, the total radioactivity at a stated date and, if necessary, hour;

(iii) for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour, and the number of capsules in the container; and

(iv) where relevant, the international symbol for radioactivity.

5.4. The label on the package shall state-

(a) the qualitative and quantitative composition;

(b) the radioactive isotopes and the amount of radioactivity at the time of dispatch;

(c) the route of administration;

(d) the expiry date;

(e) any special storage conditions; and

(f) mandatory information related to transport regulations for radioactive materials.

5.5. The leaflet in the package shall contain the specific product information and indications for use. This information is especially important for preparation kits (cold kits), and shall include-

(a) the name of the product and a description of its use;

(b) the contents of the kit;

(c) the identification and quality requirements concerning the radio labelling materials that can be used to prepare the radiopharmaceutical, namely-

(i) the directions for preparing the radiopharmaceutical, including the range of activity and the volume, together with a statement

of the storage requirements for the prepared radiopharmaceutical;

(ii) a statement of the shelf-life of the prepared radio pharmaceutical;

(iii) the indications and contraindications (pregnancy, children, drug reactions, etc.) in respect of the prepared radiopharmaceutical;

(iv) warnings and precautions in respect of the components and the prepared radiopharmaceutical, including radiation safety aspects;

(v) where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical, including the route of elimination and the effective half-life;

(vi) the radiation dose that a patient will receive from the prepared radiopharmaceutical;

(vii) the precautions to be taken by users and patients during the preparation and administration of the product and the special precautions for the disposal of the container and any unconsumed portions;

(viii) a statement of the recommended use of the prepared radio-pharmaceutical and the recommended dosage;

(ix) a statement of the route of administration of the prepared radiopharmaceutical; and

(x) if appropriate, for particular kits (i.e., those subject to variability beyond the recommended limits), the methods and specifications needed to check radiochemical purity.

6. Production and distribution records:-

6.1. The processing records of regular production batches must provide a complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the written procedures.

6.2. Separate records for the receipt, storage, use and disposal of radioactive materials shall be maintained in accordance with the relevant provisions of the Atomic Energy Act 1962 and the rules made thereunder.

6.3. Distribution records shall be kept. Since the return of radioactive products is not practical, the purpose of recall procedures for such

products is to prevent their use rather than an actual return.

7. Quality assurance and quality control:-

7.1. Radiopharmaceuticals are nearly always used before all quality control testing (e.g., tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential.

7.2. Quality assurance or quality control or both shall have the following principal responsibilities, namely-

(a) the preparation of detailed instructions for each test and analysis;

(b) ensuring the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination;

(c) ensuring that environmental monitoring and equipment and process validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;

(d) the release or rejection of starting materials and intermediate products;

(e) the release or rejection of packaging and labelling materials;

(f) the release or rejection of each batch of finished preparation;

(g) the evaluation of the adequacy of the conditions under which the starting materials, intermediate products and finished radiopharmaceutical preparations are stored;

(h) the evaluation of the quality and stability of the finished products and, when necessary, of the starting materials and intermediate products;

(i) the establishment of expiry dates on the basis of the validity period related to specified storage conditions;

(j) the establishment and revision of the control procedures and specifications;

(k) assuming the responsibility for retaining samples of radiopharmaceutical products; and

(l) assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceutical products.

7.3. Whenever the size of the establishment permits, quality assurance and quality control duties shall be organised in separate groups. Quality assurance shall also include the monitoring and validation of the production process.

7.4. A manufacturer's quality control laboratory shall be separated from the production area. The control laboratory shall be designed, equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, the preparation of records and the performance of the necessary tests.

7.5. The performance of all qualitative and quantitative tests mentioned in the specifications for the starting materials may be replaced by a system of certificates issued by the supplier of these materials, provided that-

(a) there is a history of reliable production;

(b) the producer or supplier is regularly audited; and

(c) at least one specific identity test is conducted by the manufacturer of the finished radiopharmaceutical.

7.6. Samples of the intermediate and final products shall be retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control. These samples shall be kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g., for radiopharmaceuticals with a short half-life.

7.7. Sampling procedures may be adapted for the purposes of sampling, the type of controls being applied, and the nature of the material being sampled (e.g., a small batch size or its radioactive content or both). The procedure shall be described in a written protocol.

PART VI

SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

This Part shall apply to phytopharmaceutical drugs as defined under clause (eb) of rule 2,in addition to other relevant Parts based on the dosage form.

Note.—Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of Phytopharmaceuticals. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General:-

1.1. Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible

manufacturing techniques and procedures, phytopharmaceuticals are prepared from materials of plant origin, which are often obtained from varied geographical or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of phytopharmaceuticals are often substantially different from those employed for conventional pharmaceutical products.

1.2. Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of Phytopharmaceuticals. For this reason, application of GMPs in the manufacture of Phytopharmaceuticals is an essential tool to assure their quality.

2. **Quality assurance in the manufacture of Phytopharmaceuticals:-** In addition to the use of modern analytical techniques (especially High Performance Thin-Layer Chromatography (HPTLC), Gas Chromatography (GC), High Performance Liquid Chromatography (HPLC), Capillary Electrophoresis (CE), Mass Spectrometry (MS) and Atomic Absorption (AA) to characterise phytopharmaceuticals, quality assurance also requires the control of starting materials, storage and processing. For this reason, an appropriate quality assurance system shall be applied in the manufacture of phytopharmaceuticals.

3. **Good manufacturing practice for Phytopharmaceuticals:-** The general principles of GMP are set out in the Part I. Cultivation and collection of medicinal plants, as the starting materials for phytopharmaceuticals are not covered under this Schedule. The first critical step of their production where the application of GMP starts shall be clearly designated. This is of particular importance for those products which consist solely of comminuted or powdered plant materials.

4. **Sanitation and hygiene:-**

4.1. Because of their origin, plant materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, phytopharmaceuticals that may be especially prone to microbiological contamination are produced. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene during manufacture is necessary.

4.2. Water supply to the manufacturing unit shall be monitored and if necessary treated appropriately to ensure consistency of quality.

4.3. Waste from the manufacturing unit shall be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste bins shall be available, emptied and cleaned as needed, on daily basis.

5. Qualification and validation:-

5.1. Qualification of critical equipment, process validation and change control are particularly important in the production of Phytopharmaceuticals with unknown therapeutically active constituents. In this case, the reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches.

5.2. The written procedure shall specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (e.g., retrospective, prospective or concurrent) and the number of process runs.

5.3. A formal change control system shall be established to evaluate the potential effects of any changes on the quality of the Phytopharmaceuticals, particularly content of the active ingredients. Scientific judgement shall be used to determine which additional testing and validation studies are appropriate to justify a change in a validated process.

6. Complaints:-

6.1. The person responsible for handling complaints and deciding on the measures to be taken to deal with them shall have appropriate training or experience in the specific features of the quality control of Phytopharmaceuticals.

6.2. There are basically two types of complaints, product quality complaints and adverse reactions or events.

6.3. The first type of complaint may be caused by problems such as faulty manufacture, product defects or deterioration, particular to Phytopharmaceuticals, adulteration of the plant material. These complaints shall be recorded in detail and the causes thoroughly investigated (e.g., by comparison with the reference samples kept from the same batch). There shall also be written procedures to describe the action to be taken.

6.4. To address the second type of complaint, reports of any adverse reaction or event shall be entered in a separate register. An investigation shall be conducted to find out whether the adverse reaction or event is due to quality problem and whether such reactions or events have already been reported in the literature or whether it is a new observation. In either case, complaint records shall be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products.

6.5. The licensing authority shall be kept informed of any complaints leading to a recall or restriction on supply and the records shall be made available for inspection.

7. Product recalls:-In case of quality failures or serious adverse events of life threatening situations, the products shall be recalled in prompt and effective manner up to the retailers' level. There shall be a SOP for storage of recalled Phytopharmaceuticals in a secure segregated area.

8. Contract production and analysis:-

8.1. The contract partner shall have adequate premises and equipment for the production of Phytopharmaceuticals according to GMP. Validated methods shall be applied for cleaning the equipment and premises carefully before using them to produce different products. In the case of raw materials used for producing food, it is realistic to require manufacturing departments to be separated from those where the plant raw material will be cut or powdered for use in the preparation of drugs.

8.2. Technical aspects of the contract shall be drawn up by the competent persons suitably knowledgeable on the specific characteristics of

Phytopharmaceuticals, including their production and quality control testing.

9. Self-inspection:-At least one member of the self-inspection team shall possess a thorough knowledge of Phytopharmaceuticals.

10. Personnel:-

10.1. The release of phytopharmaceuticals shall be authorised by a person who has been trained in the specific features of the processing and quality control of plant materials, plant preparations and finished phytopharmaceutical products.

10.2. Personnel dealing with the production and quality control of Phytopharmaceuticals shall have adequate qualifications and training in the specific issues relevant to Phytopharmaceuticals.

11. Training:-

11.1. The personnel shall have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of Phytopharmaceuticals).

11.2. Training records shall be maintained and periodic assessments of the effectiveness of training programmes shall be made.

12. Personal hygiene:-

12.1. Personnel entrusted with the handling of plant materials, plant preparations and finished plant products shall be required to have a high degree of personal hygiene and to have received adequate training in maintaining appropriate standards of hygiene. The personnel shall not work, if they have infectious diseases or skin diseases. Written procedures listing the basic hygiene requirements shall be made available.

12.2. Personnel must be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing. They shall wear suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture.

13.Premises:-

13.1. As a general principle, premises shall be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to good manufacturing practices for pharmaceutical products as given in Part I.

13.2. Because of their potential for degradation and infestation with certain pests as well as their sensitivity to microbiological contamination, production and particularly storage of plant materials and plant preparations shall assume special importance.

13.3. **Storage areas-**

13.3.1. Storage areas shall be well organised and tidy. Special attention shall be paid to cleanliness and good maintenance. Any accidental spillage shall be cleaned up immediately using methods that minimise the risk of cross- contamination of other materials and shall be reported.

13.3.2. The set-up of storage areas depends on the type of materials stored. The areas shall be well labelled and materials stored in such a way so as to avoid any risk of cross-contamination. An area shall be identified for the quarantine of all incoming plant materials.

13.3.3. Storage areas shall be laid out to permit effective and orderly segregation of the various categories of materials stored and to allow rotation of stock. Different plant materials shall be stored in separate areas.

13.3.4. To protect the stored material and reduce the risk of pest attacks, the duration of storage of any plant material in unpacked form shall be kept to a minimum.

13.3.5. Incoming fresh plant materials shall be processed, unless specified otherwise, as soon as possible. If appropriate, they shall be stored between 2 °C and 8 °C, whereas frozen materials shall be stored below –18 °C.

13.3.6. Where materials are stored in bulk, to reduce the risk of mould formation or fermentation, it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas shall also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures shall be taken to limit

the spread of animals and microorganisms brought in with the plant material and to prevent cross-contamination.

13.3.7. Plant materials, even when stored in fibre drums, bags or boxes, shall be stored off the floor and suitably spaced to permit cleaning and inspection.

13.3.8. The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; appropriate steps shall be taken to ensure that these conditions are provided, maintained, monitored and recorded.

13.3.9. Plant materials, including raw plant materials, shall be kept in a dry area protected from moisture and processed following the principle of "first in, first out" (FIFO).

13.4. **Production areas-**

13.4.1. Production areas shall comply with the general requirements of good manufacturing practices for pharmaceutical products: main principles (see Part I). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. Moreover, the special nature of the production of Phytopharmaceuticals requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism shall be employed to prevent accumulation of fumes and vapours.

13.4.2. To facilitate cleaning and to avoid cross-contamination, adequate precautions shall be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g., by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

14.Equipment:-

14.1. Processing of plant materials may generate dust or material which is susceptible to pest-infestation or microbiological contamination and cross- contamination. Effective cleaning of the equipment is therefore particularly important.

14.2. Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment shall be dried immediately after cleaning to

prevent the growth of microorganisms. Cleaning with compressed air and brushes shall be done with care and avoided if possible, as these methods increase the risk of product contamination.

14.3. Non-wooden equipment shall be used unless tradition demands wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.), this shall be dedicated, unless otherwise justified. When such equipment is used, it is advisable that it does not come into direct contact with chemicals or contaminated material. If the use of wooden equipment is unavoidable, special consideration must be given to its cleaning as wooden materials may retain odours, be easily discoloured and are easily contaminated.

15. Materials:-

15.1. All incoming plant materials shall be quarantined and stored under appropriate conditions that take into account the degradability of plant materials and plant preparations.

15.2. Only permitted substances shall be used for fumigation and allowable limits for their residues together with specifications for the apparatus used shall be set.

16. Reference samples and standards:- The reference standard for a phytopharmaceuticals may be a botanical sample of the plant material; a sample of the plant preparation, e.g., Extract; or a chemically defined substance, e.g., a known active constituent, a marker substance or a known impurity. The reference standard shall be of a quality appropriate to its purpose. If the phytopharmaceuticals is not described in a recognised pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the medicinal plant (e.g., if the whole medicinal plant is a tree) shall be available. All reference standards shall be stored under appropriate conditions to prevent degradation. Their expiry or revalidation date or both shall be determined and indicated.

17. Documentation:- The general principles for documentation are set out in Part I.

18. Specifications:-

18.1. The specifications for starting materials, for plant preparations and finished phytopharmaceuticals are primarily intended to define the quality rather than to establish full characterisation, and shall focus on those characteristics found to be useful in ensuring safety and efficacy. Consistent quality for Phytopharmaceuticals (finished products) can only be assured, if the starting plant materials are defined in a rigorous and detailed manner. In some cases more detailed information may be needed on aspects of collection or agricultural production. For instance, the selection of seeds, conditions of cultivation and harvesting are important aspects in producing a reproducible quality of Phytopharmaceuticals. Their characterisation (which also includes a detailed evaluation of the botanical and phytochemical aspects of the medicinal plant, manufacture of the Phytopharmaceutical preparation and the finished Phytopharmaceutical product) is therefore essential to allow the establishment of specifications which are both comprehensive and relevant. The specifications for plant materials shall as far as possible include, as a minimum, the following information-

18.1.1. **Plant materials**:-

18.1.1.1. The family and botanical name of the plant used according to the binomial system (genus, species, variety and the authority, i.e., the reference to the originator of the classification, e.g., Linnaeus).

18.1.1.2. Details of the source of the plant, such as country or region (also collected from the wild and, where applicable, method of cultivation, dates and conditions of harvesting (e.g., whether there was extreme weather), collection procedures, collection area, and brand, quantity and date of pesticide application, as per the WHO Guidelines on good agricultural and collection practices.

18.1.1.3. Whether the whole plant or only a part is used. In the latter case, which part of the plant is used and its state, e.g., whole or reduced. For dried plant material, the drying system shall be specified, if applicable.

18.1.1.4. A description of the plant material based on visual

(macroscopic) or microscopic examination or both.

18.1.2. Suitable identity tests including, where appropriate, identification tests (such as Thin Layer Chromatography (TLC) or other chromatographic fingerprint) for known active ingredients or markers. A reference sample shall be available for identification purposes.

18.1.3. Details of the assay, where appropriate, of active constituents or markers.

18.1.4. Limit tests such as dry residue of liquids, ash value (total ash and ash insoluble in hydrochloric acid), water-soluble extractives, moisture or water content and loss on drying (taking into account the presence of essential oils if any).

18.1.5. Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination in plant materials or plant preparations used in the manufacture of Phytopharmaceuticals.

18.1.6. Tests for toxic metals and for likely contaminants, foreign materials and adulterants.

18.1.7. Tests for fungal, microbiological contamination, fumigant residues (if applicable), mycotoxins (aflatoxins), pest-infestations, radioactivity and their acceptable limits.

18.1.8. Other appropriate tests (e.g., particle size, swelling index and residual solvents in Phytopharmaceutical preparations and biological fingerprints such as induced fluorescent markers).

18.1.9. Specifications for starting materials (and also of primary or printed packaging materials) shall include, if applicable, reference to a pharmacopoeial monograph.

18.1.10. If the plant material for processing does not comply with its quality specifications, the norms that apply for its rejection and to storage and disposal of the rejected plant material, shall be included.

18.1.11. Qualitative and quantitative information on the active ingredients or constituents with known therapeutic activity in plant materials and plant preparations shall be given as described in paragraph 23.5 (Packaging materials and labelling) of this Part.

19.Finished phytopharmaceuticals:-

19.1. Tests for microbiological contamination and tests for other toxicants.

19.2. Uniformity of weight (e.g., for tablets, single-dose powders, suppositories, capsules and powder in sachets), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (tablets or capsules), if applicable.

19.3. Physical appearance such as colour, odour, form, shape, size and texture.

19.4. Loss on drying or water content.

19.5. Identity tests, qualitative determination of relevant substances of the plants (e.g., fingerprint chromatograms).

19.6. Quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available.

19.7. Limit tests for residual solvents.

19.8. Other specifications as per the general monograph under the Indian Pharmacopeia for the applicable dosage forms.

19.9. The control tests and specifications for the finished phytopharmaceutical product shall be such as to allow the qualitative and quantitative determination of the main active constituents. If the therapeutic activity of constituents is known, these constituents shall be indicated in the documentation. If such substances are not known (e.g., because they are part of a complex mixture), the constituents useful for assessing the quality shall be identified as markers. In both cases, the assay (i.e., quantitative determination) specifications shall be defined. When the therapeutic activity of the constituents cannot be determined quantitatively, specifications shall be based on the determination of markers.

19.10. If either the final product or the phytopharmaceutical preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the mixture of several active ingredients may be determined. The need for such a procedure shall be justified.

19.11. The concept of different acceptance criteria for release versus shelf-life specifications applies to finished phytopharmaceutical drugs only and not to plant materials and plant preparations. Adequate retest

periods shall be established for the latter. Example, where this may be applicable include assay and impurity (degradation product) levels.

20. Plant preparations:-The specifications of plant preparations consist, depending on the preparation in question, of the relevant items of the specifications for plant materials or for finished phytopharmaceutical products as specified in the preceding paragraph.

21. Processing instructions:-

21.1. The processing instructions shall describe the different operations to be performed on the plant material, such as drying, crushing, milling and sifting. They shall also include the time and, if applicable, temperatures required in the drying process and the methods to be used to control fragment or particle size. Instructions on removing foreign matter and other unwanted materials shall also be given.

21.2. The drying conditions chosen shall be appropriate to the type of plant material processed. This depends on both the character of the active ingredients (e.g., essential oils) and the type of plant part collected (e.g., root, leaf or flower). Drying by direct exposure to sunlight, if not specifically contraindicated, is possible, but drying on the ground shall be avoided. If the plant shall be processed fresh, without drying, the reasons and criteria determining the use of fresh material shall be stated.

21.3. For the production of processed extracts, the instructions shall specify details of any vehicle or solvent that may be used, the duration and temperature needed for extraction, and any concentration stages and methods that may be required.

21.4. The permissible environmental conditions e.g., temperature, humidity and standard of cleanliness, shall be stated.

21.5. Any treatment, such as fumigation, used to reduce fungal or microbiological contamination or other infestation, together with methods of determining the extent of such contamination and potential residues, shall be documented. Instructions on the conduct of such procedures shall be available and shall include details of the process, tests and allowable limits for residues together with specifications for apparatus used.

21.6. Steps in the processes of blending and adjustment to reach defined

contents of pharmacologically active constituents shall be clearly documented.

21.7. The rules that apply to the disposal of spent plant material after processing shall also be elaborated.

22. Good practices in production:-

22.1. To ensure not only the quality, but also the safety and efficacy of complex products of biological origin such as Phytopharmaceuticals, it is essential that the steps in their production are clearly defined.

22.2. Selection of the first production step covered in this Part,-

22.2.1. For medicinal plants which are either cultivated or collected from the wild, and which may be used in crude form or subjected to simple processing techniques (cutting or comminuting) the first critical step of their production, i.e., where the application of these guidelines starts, shall be clearly designated. The rationale for this designation shall be stated and documented. Guidance is provided below. However, for processes such as extraction, fermentation and purification, this rationale shall be established on a case to case basis-

(a) collection or cultivation or harvesting of medicinal plants shall follow other relevant guidance;

(b) generally, post harvest processing including primary cutting is (or shall be) covered by Good Agricultural Practices guidelines (GAP). If further comminuting is carried out in the manufacturing processing, it shall be covered by GMP. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of plant materials, application of the parameters under this Part may be extended to encompass these steps;

(c) when the active ingredient, consists exclusively of comminuted or powdered herbs, application of parameters under this Part starts at the physical processing following primary cutting and comminuting, and includes packaging;

(d) when phytopharmaceutical extracts are used, the principles of parameters under this Part shall apply to any production step following postharvest processing; and

(e) in the case of finished plant products manufactured by

fermentation, application of GMP shall cover any production step following primary cutting and comminuting. Particular attention shall be given to the introduction of cells from a cell bank into the fermentation process.

22.3. **General considerations**-

22.3.1. Materials shall be handled in a fashion that is not detrimental to the product. On arrival at the processing facility, the plant material shall be promptly unloaded and unpacked. During this operation, the plant material shall not come into direct contact with the soil. Moreover, it shall not be exposed directly to the sun (except in cases where this is a specific requirement, e.g., sun-drying) and it shall be protected from rain and microbiological contamination.

22.3.2. Attention shall be paid to "classification" of clean area requirements taking into account the possible high degree of initial microbial contamination of plant materials. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to processing of plant materials. Specific and detailed requirements shall be developed to cover microbial contamination of equipment, air, surfaces and personnel, and also for rest rooms, utilities, ancillary and supporting systems (e.g., water and compressed air).

22.3.3. Care shall be taken to choose cleaning methods appropriate to the characteristics of the plant materials being processed. Washing dried plant materials with water is generally inappropriate. When it is necessary to clean them, an air duster or air shower shall be employed. In cases when immersion of plant materials in water or other appropriate agents (such as disinfectants) for cleaning is unavoidable (e.g., to eliminate suspected coliform bacteria), it shall be kept to a minimum.

22.3.4. The presence of plant materials from different species and varieties, or different plant parts shall be controlled during the entire production process to avoid contamination, unless it is assured that these materials are equivalent.

22.3.5. If time limits are specified in the master production instructions, these limits shall not be exceeded, to ensure the

quality of intermediates and finished products. The less is known about the constituents responsible for the therapeutic activity, the more strictly this rule shall be obeyed. Such time limits, however, may be inappropriate when processing to achieve a target value (e.g., drying to a predetermined specification) because completion of processing steps is determined by in-process sampling and testing.

22.4. **Mixing of batches and blending-**

22.4.1. Phytopharmaceutical drugs with constituents of known therapeutic activity are often standardised (i.e., adjusted to a defined content of such constituents). The methods used to achieve such standardisation shall be documented. If another substance is added for these purposes, it is necessary to specify, as a range, the quantity that may be added. Blending different batches of a specific plant material (e.g., before extraction) or by mixing different lots of similar plant preparations may also be acceptable. Records shall be maintained to ensure traceability. The blending process shall be adequately controlled and documented and the blended batch shall be tested for conformity with established specifications where appropriate.

22.4.2. Batches shall be mixed only if it can be guaranteed that the mixture will be homogeneous. Such processes shall be well documented.

22.4.3. Out-of-specification batches of phytopharmaceutical drugs shall not be blended with other batches for the purpose of meeting specifications, except for standardization of the content of constituents with known pharmaceutical therapeutic effect. Every batch incorporated into the blend shall have been manufactured using an established process and shall have been individually tested and found to meet with the appropriate specifications prior to blending.

22.4.4. Where particular physical attributes of the material are critical, blending operations shall be validated to show uniformity of the combined batch. Validation shall include testing of critical attributes (e.g., particle size distribution, bulk density and tap density) that may be affected by the

blending process.

22.4.5. The expiry date of the blended batch shall be chosen according to the date of manufacture of the oldest batch in the blend.

23. Good practices in quality control:-

23.1. General-

23.1.1. The personnel of quality control units shall have the necessary expertise in Phytopharmaceuticals to enable them to carry out identification tests and recognise adulteration, the presence of fungal growth or infestations and lack of uniformity in a consignment of plant materials.

23.1.2. The quality control of the plant material, plant preparations and finished plant products shall establish their quality, but does not imply the control of every single constituent.

23.2. **Sampling-** Plant materials are an aggregate of individual plants or different parts of the same plant and thus, have an element of heterogeneity, sampling shall be carried out with special care by personnel with the necessary expertise.

23.3. **Testing-**

23.3.1. The identity and quality of plant material, plant preparations and of finished phytopharmaceutical products shall be tested.

23.3.2. Plant material, plant preparations (including extracts) and finished products can be categorised as follows-

(a) the active constituents are identified, and may be quantified as such;

(b) the main group of components which contribute to the activity (i.e., the constituents with known therapeutic activity) are known and can be quantified as a total (e.g., essential oils) or calculated using a representative substance belonging to the group (e.g., flavonoids);

(c) the former is not identified or not quantifiable or both, but marker substances are; and

(d) others, where quantification (i.e., specification for a certain quantity of a constituent) is not applicable or feasible.

23.3.3. Identification methods may be based on-

(i) physical and if applicable, macroscopic (organoleptic) and

microscopic tests;

(ii) chromatographic procedures [TLC, HPLC, HPTLC or Gas Liquid Chromatography (GLC)], spectrometric techniques [ultraviolet-visible (UV-VIS), IR, Nuclear Magnetic Resonance (NMR), MS]; and

(iii) chemical reactions.

23.3.4. The identification test methods shall be specific for the plant material, preparation or finished product and ideally shall be capable of discriminating between the required plant material and potential substitutes or adulterants that are likely to occur. The identification methods used for group (a) and group(b) shall be capable of detecting the said active ingredients and at least the main ingredients shall be stated on the label. For group (c), the analytical procedure shall be based on characteristic constituents, if any.

23.3.5. Reference samples of plant materials shall be made available for use in comparative tests e.g., visual and microscopic examination and chromatography.

23.3.6. Quantitative determination of known active components for members of group(a) and group(b) and of markers for members of group (c) is necessary.

23.3.7. The development and execution of quality control methods for plant materials, preparations and the finished products shall be in line with paragraph 18 (Specifications) of this Part. Tests and quality requirements that are characteristic of the given analyte shall be selected.

23.3.8. Particularly for plant materials in group (d) and for finished products containing such materials, characteristic chromatograms (fingerprint chromatograms) may be applicable. Using these methods may ensure that the main constituents can be easily followed throughout the production process. Caution is necessary, however, for every delivery of plant materials and every batch of plant preparations (including extracts) will have slightly different chromatograms or fingerprints resulting from differences in chemical compositions caused by intrinsic or extrinsic factors.

23.4. **Stability studies-**

23.4.1. If the expiry date for a plant material or phytopharmaceutical preparation is given, some stability data to support the proposed shelf-life under the specified storage conditions shall be available. Stability data are always required to support the shelf-life proposed for the finished products (guidance document reference)

23.4.2. Finished phytopharmaceutical products may contain several plant materials or plant preparations, and it is often not feasible to determine the stability of each active ingredient. Moreover, because the plant material, in its entirety, is regarded as the active ingredient, a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Chromatography allows tracing of changes which may occur during storage of a complex mixture of biologically active substances contained in plant materials. It shall be shown, as far as possible, e.g., by comparisons of appropriate characteristics or fingerprint chromatograms that the identified active ingredient (if any) and other substances present in the plant material or finished product are likewise stable and that their content as a proportion of the whole remains within the defined limits.

23.4.3. The fingerprint methods used for the stability studies shall be as similar as possible to those used for quality control purposes.

23.4.4. For identified active ingredients, constituents with known therapeutic activity and markers, widely used general methods of assay and physical and sensory or other appropriate tests may be applied.

23.4.5. To determine the shelf-life of finished products, strong emphasis shall also be placed on other tests in paragraph 18 (Specifications), i.e., moisture content, microbial contamination and general dosage form control tests.

23.4.6. The stability of preservatives and stabilisers shall be monitored. When these are not used, alternative tests shall be done to ensure that the product is self-preserving over its shelf-life.

23.4.7. Samples used for stability studies shall be stored in the containers intended for marketing.

23.4.8. Normally the first three commercial production batches shall be

included in the stability monitoring programme to confirm the expiry date. However, where data from previous studies, including pilot batches, show that the product is expected to remain stable for at least two years, fewer than three batches can be used. The testing frequency depends on the characteristics of the phytopharmaceutical medicinal products and shall be determined on a case-to-case basis.

23.4.9. 23.4.9 The protocol for on-going stability studies shall be documented. This would normally involve one batch per year being included in a stability monitoring programme.

23.5. **Packaging materials and labeling-**

23.5.1. All packaging materials, such as bottles and other materials shall be stored properly. Controls on the issue and use of these packaging materials shall be adequate to ensure that incorrect labels and cartons are not used.

23.5.2. All containers and closures shall be thoroughly cleaned and dried before being used to pack the products.

23.5.3. 23.5.3 There shall be adequate information on the label (or the package insert) to inform the users of the composition of the product (in addition to the brand name, if any), indications or actions, directions for use, cautions and adverse reactions if any, and the expiry date.

23.5.4. Finished plant products may contain several plant materials or plant preparations. Unless otherwise fully justified, the full quantitative composition of the phytopharmaceutical ingredients shall be stated on the product label. If this is not possible, at least the main ingredients shall be stated on the label while the full qualitative composition could appear on the package insert.

23.5.5. The qualitative and quantitative particulars of the active ingredients in plant materials and plant preparations shall be expressed in the following manner, namely-

23.5.5.1. For plant materials and plant preparations consisting of comminuted or powdered plant materials-

(a) the quantity of the plant material must be stated or, if constituents with known therapeutic activity are unidentified, the quantity of the plant material or

phytopharmaceutical preparation shall be stated; or

(b) the quantity of the plant material or phytopharmaceutical preparation shall be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity.

23.5.5.2. For plant preparations produced by steps, which exceed commination, the nature and concentration of the solvent and the physical state of the extract shall be given. Furthermore, the following shall be indicated-

(a) the equivalent quantity or the ratio of a phytopharmaceutical material to phytopharmaceutical preparation must be stated, if therapeutic activity of the constituents is unknown (this does not apply to fatty or essential oils); or

(b) if the therapeutic activity of the constituents is known, the quantity of the phytopharmaceutical preparation may be given as a range, corresponding to a defined quantity of the constituents with known therapeutic activity.

23.5.6. The composition of any solvent or solvent mixture used and the physical state of the extract shall be identified.

23.5.7. If any other substance is added during the manufacture of the phytopharmaceutical preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substances shall be described as such or as “other ingredients” and the genuine extract as the “active ingredient”. However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content or for any other purpose, the final mixture shall be regarded as the genuine extract and listed as the “active ingredient” in the unit formula.

PART VII

SPECIFIC REQUIREMENTS FOR THE MANUFACTURE OF INVESTIGATIONAL PHARMACEUTICAL PRODUCTS FOR CLINICAL TRIALS IN HUMANS

Note.—Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of Investigational Pharmaceutical Products for Clinical Trials in Humans. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General considerations:-

1.1. This Part supplements the general principle of GMP as specified in Part I and the guidelines on Good Clinical Practices (GCP) for clinical trials on pharmaceutical products in India. The application of the principles of GMP to the preparation of investigational products to be used in Phase I or Phase II or Phase III of the clinical studies is necessary.

1.1.1. To assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials.

1.1.2. To assure consistency between the investigational product and the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product.

1.1.3. To protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilisation, contamination and cross-contamination, mix-ups, wrong labelling, etc.) or from starting materials and components of inadequate quality.

1.1.4. To document all changes in the manufacturing process.

1.2. In this context, the selection of an appropriate dosage for clinical trials is important. While it is accepted that in early trials (Phase I or Phase II), the dosage form may be very different from the anticipated final formulation (e.g., a capsule instead of a tablet), in the pivotal Phase III studies, it shall be similar to the projected commercial presentation; otherwise these trials will not necessarily prove that the marketed product is both efficacious and safe.

1.3. If there are significant differences between the clinical and commercial

dosage forms, data shall be submitted to the Licensing Authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials. Final manufacturing methods must be revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.

1.4. This document specifically addresses those practices that may be different for investigational products, which are usually not manufactured in accordance with a set routine and which may possibly be incompletely characterised during the initial stages of clinical development.

2. Quality assurance:-

2.1. Quality assurance of pharmaceutical products has been defined and discussed in detail in Part I.

2.2. The quality of dosage forms in Phase III clinical studies shall be characterised and assured at the same level as for routinely manufactured products. The quality assurance system, designed, established and verified by the manufacturer, shall be described in writing, taking into account the GMP principles to the extent that they are applicable to the operations in question. This system shall also cover the interface between the manufacture and the trial site (e.g., shipment, storage, occasional additional labelling).

3. Validation:-

3.1. Some of the production processes for investigational products that have not received marketing authorisation may not be validated to the extent necessary for a routine production operation. The product specifications and manufacturing instructions may vary during development. The increased complexity in the manufacturing operations requires a highly effective quality assurance system.

3.2. For sterile products, there shall be no reduction in the degree of validation of sterilising equipment required. Validation of aseptic processes presents special problems when the batch size is small, since the number of units filled may not be adequate for a validation exercise. Filling and sealing, which is often done by hand, can compromise the maintenance of sterility. Greater attention shall therefore be given to environmental monitoring.

4. **Complaints:-** The conclusions of any investigation carried out in response to a complaint shall be discussed between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, to determine the cause and to take any necessary corrective action.

5. **Recalls:-** Recall procedures shall be understood by the sponsor, investigator and monitor in addition to the persons responsible for recalls as described in the guide on GMP.

6. **Personnel:-** Although it is likely that the number of staff involved will be small, people shall be separately designated as responsible for production and quality control. All production operations shall be carried out under the control of a clearly identified responsible person. Personnel concerned with development, involved in production and quality control, need to be instructed in the principles of GMP.

7. **Premises and equipment:-**
   7.1. During the manufacture of investigational products, different products may be handled in the same premises and at the same time and this reinforces the need to eliminate all risks of contamination, including cross-contamination. Special attention shall be paid to line clearance in order to avoid mix-ups. Validated cleaning procedures shall be followed to prevent cross-contamination.
   7.2. For the production of particular products, campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account shall be taken of the solubility of the product and excipients in various cleaning agents.

8. **Materials:-**
   8.1. **Starting materials-**
      8.1.1. The consistency of production may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties shall therefore be defined,

documented in their specifications, and controlled. Existing compendial Standards, shall be taken into consideration. Specifications for active ingredients shall be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active ingredients shall be periodically reassessed.

8.1.2. Detailed information on the quality of active and non-active ingredients, as well as of packaging materials, shall be available so as to make it possible to recognise and as necessary, allow for any variation in production.

8.1.3. Chemical and biological reference standards for analytical purposes.

8.1.4. Reference standards from reputable sources shall be used, if available; otherwise the reference substances for the active ingredients shall be prepared, tested and released as reference materials by the producer of the investigational pharmaceutical product or by the producer of the active ingredient used in the manufacture of that product.

8.1.5. Detailed information on reference products for clinical trials shall be in accordance with the New Drugs and Clinical Trial Rules, 2019.

8.1.6. In studies in which an investigational product is compared with a marketed product, steps shall be taken to ensure the integrity and quality of the reference products (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made in the product, data shall be available (e.g., on stability, comparative dissolution) that demonstrate that these changes do not influence the original quality characteristics of the product.

9. Documentation:-

9.1. Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), master formulae and processing and packaging instructions may be changed frequently as a result of new experience in the development of an investigational product. Each new version shall take into account the latest data and include a reference to the previous version so that traceability is

ensured. Rationale for changes shall be stated and recorded.

9.2. Batch processing and packaging records shall be retained for at least two years after the termination or discontinuance of the clinical trial, or after the approval of the investigational product.

9.3. The sponsor may request the processing or packaging of a certain number of units or their shipping. It may only be given by the sponsor to the manufacturer of an investigational product. It shall be in writing (though it may be transmitted by electronic means), precise enough to avoid any ambiguity and formally authorised, and refer to the approved product specification file.

9.4. **Product specification files-**

9.4.1. A product specification file or files shall contain the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and shipping. It shall indicate who has been designated or trained as the authorised person responsible for the release of batches. It shall be continuously updated while at the same time ensuring appropriate traceability to the previous versions.

9.5. **Specifications-**

9.5.1. In developing specifications, special attention shall be paid to characteristics which affect the efficacy and safety of pharmaceutical products, namely-

(a) the accuracy of the therapeutic or unitary dose, homogeneity, content uniformity;

(b) the release of active ingredients from the dosage form: dissolution time, etc.; and

(c) the estimated stability, if necessary, under accelerated conditions, the preliminary storage conditions and the shelf-life of the product.

9.5.2. In addition, the package size shall be suitable for the requirements of the trial.

9.5.3. Specifications may be subject to change as the development of the product progresses. Changes shall, however, be made in accordance with a written procedure and clearly recorded. Specifications shall be based on all available scientific data, current state-of-the-art technology and the regulatory and pharmacopoeial requirements.

9.6. **Master formulae and processing instructions-**

9.6.1. These may be changed in the light of experience, but allowance must be made for any possible repercussions on stability and above all on bioequivalence between batches of finished products. Changes shall be made in accordance with a written procedure and clearly recorded.

9.6.2. It may sometimes not be necessary to produce master formulae and processing instructions, but for every manufacturing operation or supply there shall be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

9.7. **Packaging instructions**- The number of units to be packaged shall be specified before the start of the packaging operations. Account shall be taken of the number of units necessary for carrying out quality controls and of the number of samples from each batch used in the clinical trial to be kept as a reference for further rechecking and control. Reconciliation shall be carried out at the end of the packaging and labelling process.

9.8. **Labelling instructions-**

9.8.1. The information presented on labels shall include-

(a) the name of the sponsor;
(b) a statement "for clinical research use only";
(c) a trial reference number;
(d) a batch number;
(e) the patient identification number;
(f) the storage conditions; and
(g) the expiry date (month or year) or a retest date.

9.8.2. Additional information may be displayed in accordance with the order (e.g., dosing instructions, treatment period and standard warnings). When necessary for blinding purposes, the batch number may be provided separately. A copy of each type of label shall be kept in the batch packaging record.

9.9. **Processing and packaging batch records-** Processing and packaging batch records shall be kept in sufficient detail for the sequence of operations to be accurately traced. They shall contain any relevant remarks which increase existing knowledge of the product, allow improvements in the manufacturing operations and justify the

procedures used.

9.10. **Coding (or randomisation) systems-**

9.10.1. Procedures shall be established for the generation, distribution, handling and retention of any randomisation code used in packaging' investigational products.

9.10.2. A coding system shall be introduced to permit the proper identification of "blinded" products. The code, together with the randomisation list, must permit proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation. The coding system must permit determination without delay in an emergency situation of the identity of the actual treatment product received by individual subjects.

10.Production:-

10.1. Products intended for use in clinical trials (late Phase II and Phase III studies) shall as far as possible be manufactured at a licensed facility, namely-

(a) a pilot plant, primarily designed and used for process development;

(b) a small-scale facility (sometimes called a "pharmacy") separate both from the company's pilot plant and from routine production;

(c) a larger-scale production line assembled to manufacture materials in larger batches, e.g., for late Phase III trials and first commercial batches; and

(d) the normal production line used for licensed commercial batches, and sometimes for the production of investigational pharmaceutical products if the number, e.g., of ordered ampoules, tablets or other dosage forms, is large enough;

10.1.1. The relation between the batch size for investigational pharmaceutical products manufactured in a pilot plant or small-scale facility to the planned full-size batches may vary widely depending on the pilot plant or "pharmacy" batch size demanded and the capacity available in full-size production.

10.1.2. The present guidelines are applicable to licensed facilities of the first and second types. It is easier to assure compliance with GMP in facilities of the second type, since processes are kept constant in the course of production and are not normally

changed for the purpose of process development. Facilities of the remaining types shall be subject to all GMP rules for pharmaceutical products.

10.1.3. Administratively, the manufacturer has yet another possibility, namely to contract out the preparation of investigational products. Technically, however, the licensed facility will be of one of the above-mentioned types. The contract must then clearly state, *inter alia*, the use of the pharmaceutical products in clinical trials. Close cooperation between the contracting parties is essential.

10.2. **Manufacturing operations-**

10.2.1. Validated procedures may not always be available during the development phase, which makes it difficult to know in advance what critical parameters and in-process controls would help to control these parameters. Provisional production parameters and in-process controls may then usually be deduced from experience with analogous products. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continuously to the experience gained in production.

10.2.2. For sterile investigational products, assurance of sterility shall be not less than for licensed products. Cleaning procedures shall be appropriately validated and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

10.3. **Packaging and labeling-**

10.3.1. The packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) when "blinded" labels are used than for licensed products. Supervisory procedures such as label reconciliation, line clearance, etc., and the independent checks by quality control staff shall accordingly be intensified.

10.3.2. The packaging must ensure that the investigational product remains in good condition during transport and storage at intermediate destinations. Any opening of or tampering with the outer packaging during transport shall be readily discernible.

10.4. **Blinding operations-** In the preparation of "blinded" products, in-process control shall include a check on the similarity in appearance and any other required characteristics of the different products being compared.

11. Quality control:-

11.1. As processes may not be standardised or fully validated, end-product testing is more important in ensuring that each batch meets its specification. The test or analysis of materials and investigational products shall be in compliance to Schedule L1.

11.2. Product release is often carried out in two stages, before and after final packaging-

11.2.1. Bulk product assessment- This shall cover all relevant factors, including production conditions, the results of in-process testing, a review of manufacturing documentation and compliance with the product specification file and the order.

11.2.2. Finished product assessment- This shall cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the product specification file and the order.

11.3. When necessary, quality control shall also be used to verify the similarity in appearance and other physical characteristics, odour and taste of "blinded" investigational products.

11.4. Samples of each batch of product shall be retained in the primary container used for the study or in a suitable bulk container for at least two years after the termination or completion of the relevant clinical trial. If the sample is not stored in the pack used for the study, stability data shall be available to justify the shelf-life in the pack used. Properly stored reatained sample e.g., API or drug substance, in-process material, phase-I investigational drug) that can be subsequently analysed for comparison can provide important links in reproducing comparable products.

12. Shipping, returns, and destruction:-

12.1. The shipping, return and destruction of unused products shall be carried out in accordance with the written procedures laid down in the

protocol. All unused products sent outside the manufacturing plant shall, as far as possible, either be returned to the manufacturer or destroyed in accordance with clearly defined instructions.

12.2. **Shipping-**

12.2.1. Investigational products shall be shipped in accordance with the shipping orders given by the sponsor.

12.2.2. A shipment is sent to an investigator only after the following two-step release procedure:- (i) the release of the product after quality control ("technical green light"); and (ii) the authorisation to use the product, given by the sponsor ("regulatory green light"). Both releases shall be recorded.

12.2.3. The sponsor shall ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol.

12.2.4. A detailed inventory of the shipments made by the manufacturer shall be maintained and shall make particular mention of the addressee's identification.

12.3. **Returns-**

12.3.1. Investigational products shall be returned under agreed conditions defined by the sponsor, specified in written procedures and approved by authorised staff members.

12.3.2. Returned investigational products shall be clearly identified and stored in a dedicated area. Inventory records of returned medicinal products shall be kept. The responsibilities of the investigator and the sponsor are dealt with in greater detail in the guidelines on GCP.

12.4. **Destruction-**

12.4.1. The sponsor is responsible for the destruction of unused investigational products, which shall therefore not be destroyed by the manufacturer without prior authorisation by the sponsor. Destruction operations shall be carried out in accordance with the environmental safety requirements.

12.4.2. Destruction operations shall be recorded in such a manner that all operations are documented. The records shall be kept by the sponsor.

12.4.3. If requested to destroy products, the manufacturer shall deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents shall permit the batches involved to

be clearly identified.

PART VIII

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ORAL SOLID DOSAGE FORMS (TABLETS AND CAPSULES)

Note.—Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of oral Solid Dosage Forms (Tablets and capsules). In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General:-

1.1. The processing of dry materials and products creates problems of dust control and cross-contamination. Special attention is, therefore, needed in the design, maintenance and use of premises and equipment in order to overcome these problems. Wherever required, enclosed dust control manufacturing systems shall be employed**.**

1.2. Suitable environmental conditions for the products handled shall be maintained by installation of air conditioning, wherever necessary. Effective air extraction systems, with discharge points situated to avoid contamination of other products and processes shall be provided. Filters shall be installed to retain dust and to protect the factory and local environment.

1.3. Special care shall be taken to protect against subsequent contamination of the product by particles of metal or wood. The use of metal detector is recommended. Wooden equipment shall be avoided. Screens, sieves, punches and dies shall be examined for wear and tear or for breakage before and after each use.

1.4. All ingredients for a dry product shall be sifted before use unless the quality of the input material can be assured. Such sifting shall normally be carried out at dedicated areas.

1.5. Where the facilities are designed to provide special environmental conditions of pressure differentials between rooms, these conditions shall be regularly monitored and any deviation shall be brought to the immediate attention of the Production and Quality assurance departments.

1.6. Care shall be taken to guard against any material lodging and remaining undetected in any processing or packaging equipment. Particular care shall be taken to ensure that any vacuum, compressed air or air-extraction nozzles are kept clean and that there is no evidence of lubricants leaking into the product from any part of the equipment.

1.7. Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct Oral Solid Dosage (OSD) manufacturing site, measures shall be taken to ensure that dust cannot move from one cubicle to another.

1.8. Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade shall be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.

1.9. The corridor shall be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

1.10. Highly potent products shall be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.

1.11. The pressure cascade for each facility shall be individually assessed according to the product handled and level of protection required.

1.12. Building structure shall be given special attention to accommodate the pressure cascade design.

1.13. Ceilings and walls, close fitting doors and sealed light fittings shall be in place, to limit ingress or egress of air.

1.14. The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas shall be such that there is no risk of overlap in the acceptable operating range, e.g., 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in the failure of the pressure cascade, where the first room is at the maximum pressure limit and the second room is at its minimum pressure limit.

1.15. Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used to segregate areas.

1.16. The effect of room pressure tolerances shall be calculated and taken into consideration.

1.17. The pressure control and monitoring devices used shall be calibrated and qualified. Compliance with specifications shall be regularly verified and

the results recorded. Pressure control devices shall be linked to an alarm system set according to the levels determined by a risk analysis.

1.18. Manual control systems, where used, shall be set up during commissioning, with set point marked, and shall not change unless other system conditions change.

1.19. Airlocks can be important components in setting up and maintaining pressure cascade systems and also to limit cross-contamination.

1.20. Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:-

(a) Cascade airlock: higher pressure on one side of the airlock and lower pressure on the other;

(b) Sink airlock: lower pressure inside the airlock and higher pressure on both outer sides; and

(c) Bubble airlock: higher pressure inside the airlock and lower pressure on both outer sides.

1.21. Doors shall open to the high pressure side, so that room pressure assists in holding the door closed and in addition self-closers shall be provided. If the doors open to the low pressure side, the door closer springs shall be sufficient to hold the door closed and prevent the pressure differential from pushing the door open. There shall be a method to indicate if both doors to airlocks are open at the same time, or alternatively these shall be interlocked. The determination of which doors shall be interlocked shall be the subject of a risk assessment study.

1.22. Central dust extraction systems shall be interlocked with the appropriate air-handling systems, to ensure that they operate simultaneously.

1.23. Room pressure differential between adjacent cubicles, which are linked by common dust extraction ducting, shall be avoided.

1.24. Air shall not flow through the dust extraction ducting or return air ducting from the room with the higher pressure to the room with the lower pressure (this would normally occur only if extract or return systems were inoperative). Systems shall be designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure.

1.25. Adequate room pressure differential indication shall be provided so that each critical room pressure can be traced back to ambient pressure (by summation of the room pressure differentials), in order to determine the room actual absolute pressure. Room pressure indication gauges shall have a range and graduation scale which enables the reading to accuracy,

as appropriate; normal operating range, alert and action limits shall be defined and displayed at the point of indication. A colour coding gauge may be helpful. Room pressure indication may be either analogue or digital, and may be represented as either pressure differentials or absolute pressures. Whichever system is used any out-of-specification condition shall be easily identifiable.

1.26. Material Pass-Through-Hatches (PTH) or Pass Boxes (PB) can also be used for separating two different zones. PTHs fall into two categories, namely a dynamic PTH or a passive PTH. Dynamic PTHs have an air supply to or extraction from them, and can then be used as bubble, sink or cascade PTHs.

1.27. Where appropriate, temperature and relative humidity shall be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator where necessary.

1.28. Maximum and minimum room temperatures and relative humidity shall be appropriate. Alert and action limits on temperatures and humidity shall be set, as appropriate.

1.29. The operating band or tolerance between the acceptable minimum and maximum temperatures shall not be made too close. Tight control tolerances may be difficult to achieve and can also add unnecessary installation and running costs.

1.30. Cubicles or suites, in which products requiring low relative humidity are processed, shall have well sealed walls and ceilings and shall also be separated from adjacent areas with higher relative humidity by means of suitable airlocks.

1.31. Precautions shall be taken to prevent moisture migration that increases the load on the HVAC system.

1.32. Humidity control shall be achieved by removing moisture from the air, or adding moisture to the air, as relevant.

1.33. Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.

1.34. Duct material in the vicinity of the humidifier shall not add contaminants to air that will not be removed by filtration further downstream.

1.35. Air filters shall not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth.

1.36. Cold surfaces shall be insulated to prevent condensation within the clean

area or on air-handling components.

1.37. When specifying relative humidity, the associated temperature shall also be specified.

1.38. Chemical driers using silica gel or lithium chloride are acceptable, provided that they do not become sources of contamination.

1.39. Wherever possible, dust or vapour contamination shall be removed at source. Point-of-use extraction, i.e., as close as possible to the point where the dust is generated, shall be employed. Spot ventilation or capture hoods may be used as appropriate.

1.40. Point-of-use extraction shall be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.

1.41. Dust extraction ducting shall be designed with sufficient transfer velocity to ensure that dust is carried away and does not settle in the ducting. Periodic checks shall be performed to ensure that there is no build-up of the dust in the ducting.

1.42. The required transfer velocity shall be determined on the density of the dust (the denser the dust, the higher the transfer velocity shall be, e.g., 15–20 m/s).

1.43. Airflow direction shall be carefully chosen to ensure that the operator does not contaminate the product and also so that the operator is not put at risk by the product.

1.44. Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow shall be used to assist in removing dust and vapours from the room.

1.45. Typically, in a room operating with turbulent airflow, the air shall be introduced from ceiling diffusers, located at the door entry side of the room and extracted from the rear of the room at low level to help give a flushing effect in the room. Correct flushing of the rooms may be verified by airflow visualisation smoke tests.

1.46. When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, shall be used.

1.47. Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and shall be provided with adequate filtration to prevent contamination of the

ambient air.

1.48. Where the powders are not highly potent, final filters on a dust exhaust system shall be fine dust filters with a filter classification of 5µ.

1.49. Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they shall usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow.

1.50. Mechanical-shaker dust collectors shall not be used for applications where continuous airflow is required, in order to avoid unacceptable fluctuations in room pressures, except in the case where room pressures are automatically controlled.

1.51. When wet scrubbers are used, the dust-slurry shall be removed by a suitable means, e.g., a drainage system or waste removal contractor.

1.52. The quality of the exhaust air shall be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

1.53. Where necessary, additional filtration may be provided downstream of the dust collector.

1.54. The systems for fume, dust and effluent control shall be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross-contamination, e.g., an exhaust-air discharge point located close to the HVAC system fresh air inlet.

1.55. Fumes shall be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).

1.56. Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.

1.57. Deep-bed scrubbers shall be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers shall be specific to the effluent being treated.

1.58. The type and quantity of the vapours to be removed shall be known to enable the appropriate filter media, as well as the volume of media required to be determined.

1.59. There shall be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

1.60. Depending on the airborne contaminants in the return air system it may be acceptable to use re-circulated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus,

prevent cross-contamination.

1.61. HEPA filters may not be required where the air handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.

1.62. Re-circulation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.

1.63. HEPA filters may be located in the air handling unit or placed terminally. Where HEPA filters are terminally mounted they shall preferably not be connected to the ducting by means of flexible ducting. Due to the high air pressure required for the terminal filter; this connection shall preferably be a rigid duct connection. Where flexible ducting is used, it shall be as short as possible and properly fixed to withstand duct pressure.

1.64. Air containing dust from highly toxic processes or solvents or flammable vapours shall never be re-circulated to the HVAC system.

1.65. Adequate airlocks, such as personnel airlocks (PAL), material airlocks (MAL), change rooms and passages shall be provided to protect passage between different cleanliness conditions. These shall have supply and extract air systems as appropriate.

1.66. Areas such as airlocks, change rooms and passages, shall be designed so that the required pressure cascades can be achieved.

1.67. Detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials shall be prepared and maintained.

1.68. Where possible, personnel and materials shall not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone; (if moving from a lower cleanliness zone to a higher cleanliness zone, changing or decontamination procedures shall be followed).

1.69. The final stage of the changing room shall, in the “at rest” state, be the same good manufacturing practices classification grade as the area into which it leads.

2. Sifting, mixing and granulation:-

2.1. Unless operated as a closed system, mixing, sifting and blending equipment shall be fitted with dust extractors or in a dedicated area for

each operation.

2.2. Residues from sieving operations shall be examined periodically for evidence of the presence of unwanted materials.

2.3. Critical operating parameters like time and temperature for each mixing, blending and drying operation shall be specified in a Master Formula, monitored during processing, and recorded in the batch records.

2.4. Filter bags fitted to fluid-bed-drier shall not be used for different products, without being washed in between use. With certain highly potent or sensitising products, bags specific to one product only shall be used. Air entering the drier shall be filtered. Steps shall be taken to prevent contamination of the site and local environment by dust in the air leaving the drier due to close positioning of the air-inlets and exhaust.

2.5. Granulation and coating solutions shall be made, stored and used in a manner which minimises the risk of contamination or microbial growth.

3. Compression (Tablets):-

3.1. Each tablet compressing machine shall be provided with effective dust control facilities to avoid cross contamination. Unless the same product is being made on each machine or unless the compression machine itself provides its own enclosed air controlled environment, the machine shall be installed in separate cubicles.

3.2. Suitable physical, procedural and labelling arrangements shall be made to prevent mix up of materials, granules and tablets on compression machinery.

3.3. Accurate and calibrated weighing equipment shall be readily available and used for in-process monitoring of tablet weight variation. Procedures used shall be capable of detecting out of limits tablets.

3.4. At the commencement of each compression run and in case of multiple compression points in a compression machine, sufficient individual tablets shall be examined at fixed intervals to ensure that a tablet from each compression station or from each compression point has been inspected for suitable Pharmacopoeial parameters like “appearance”, “weight variation”, “disintegration”, “hardness”, “friability” and “thickness”. The results shall be recorded as part of the batch documentation.

3.5. Tablets shall be de-dusted, preferably by automatic device and shall be monitored for the presence of foreign materials besides any other

defects.

3.6. Tablets shall be collected into clean, labelled containers.

3.7. Rejected or discarded tablets shall be isolated in identified containers and their quantity recorded in the Batch Manufacturing Record.

3.8. In-process control shall be employed to ensure that the products remain within specification. During compression, samples of tablets shall be taken at regular intervals of not greater than thirty minutes to ensure that they are being produced in compliance with specified in-process specification. The tablets shall also be periodically checked for additional parameters such as “appearance”, “weight variation”, “disintegration”, “hardness”, “friability” and “thickness” and contamination by lubricating oil.

4. Coating (Tablets):-

4.1. Air supplied to coating pans for drying purposes shall be filtered air and of suitable quality. The area shall be provided with suitable exhaust system and environmental control (temperature and humidity) measures.

4.2. Coating solutions and suspensions shall be made afresh and used in a manner which shall minimise the risk of microbial growth. Their preparation and use shall be documented and recorded.

5. Filling of Hard Gelatin Capsule:- Empty capsules shells shall be regarded as “drug component” and treated accordingly. They shall be stored under conditions which shall ensure their safety from the effects of excessive heat and moisture

6. Printing (Tablets and Capsules):-

6.1. Special care shall be taken to avoid product mix-up during any printing of tablets and capsules. Where different products or different batches of the same product, are printed simultaneously, the operations shall adequately be segregated. Edible grade colours and suitable printing ink shall be used for such printing.

6.2. After printing, tablets and capsules shall be approved by Quality Control before release for packaging or sale.

7. Packaging (Strip and Blister):-

7.1. Care shall be taken when using automatic tablet and capsule counting,

strip and blister packaging equipment to ensure that all "rogue" tablets, capsules or foils from packaging operation are removed before a new packaging operation is commenced. There shall be an independent recorded check of the equipment before a new batch of tablets or capsules is handled.

7.2. Uncoated tablets shall be packed on equipment designed to minimise the risk of cross-contamination. Such packaging shall be carried out in an isolated area when potent tablets or Beta lactum containing tablets are being packed.

7.3. The strips coming out of the machine shall be inspected for defects such as misprint, cuts on the foil, missing tablets and improper sealing.

7.4. Integrity of individual packaging strips and blisters shall be subjected to vacuum test periodically to ensure leak proofness of each pocket strip and blister and records maintained.

PART IX

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ORAL LIQUIDS (SYRUPS, ELIXIRS, EMULSIONS AND SUSPENSIONS)

Note.- Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Syrups, Elixirs, Emulsions and Suspensions. In addition to these requirements, the following specific requirements shall also be followed, namely:-

1. Principle:- Syrups, Elixirs, Emulsions and Suspensions may be susceptible to microbial and other contamination during manufacture. Therefore, special measures must be taken to prevent any contamination.

2. Building and Equipment:-

2.1. The premises and equipment shall be designed, constructed and maintained to suit the manufacturing of Oral Liquids. The layout and design of the manufacturing area shall strive to minimise the risk of cross-contamination and mix-ups.

2.2. The use of closed systems of processing and transfer is recommended in order to protect the product from contamination. Production areas where the products or open clean containers are exposed shall normally be effectively ventilated with filtered air.

2.3. Manufacturing area shall have entry through double door air-lock facility. It shall be made fly proof by use of 'fly catcher' or 'air curtain'.

2.4. Drainage shall be of adequate size and have adequate traps, without open channels and the design shall be such as to prevent back flow. Drains shall be shallow to facilitate cleaning and disinfecting.

2.5. The production area shall be cleaned and sanitised at the end of every production process.

2.6. Tanks, containers, pipe work and pumps shall be designed and installed so that they can be easily cleaned and sanitised. Equipment design shall be to prevent accumulation of residual microbial growth or cross-contamination.

2.7. Stainless Steel or any other appropriate material shall be used for parts of equipments coming in direct contact with the products. The use of glass apparatus shall be minimum.

2.8. Arrangements for cleaning of containers, closures and droppers shall be made with the help of suitable machines or devices equipped with high pressure air, water and steam jets.

2.9. The quality of materials received in bulk tankers shall be checked before they are transferred to bulk storage tanks.

2.10. Care shall be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.

2.11. The furniture used shall be smooth, washable and made of stainless steel or any other appropriate material which is scratch proof, washable and smooth.

3. Purified Water:-

3.1. The chemical and microbiological quality of purified water used shall be specified and monitored routinely. The microbiological evaluation shall include testing for absence of pathogens and shall not exceed 100 cfu per ml.

3.2. There shall be a written procedure for operation and maintenance of the purified water system. Care shall be taken to avoid the risk of microbial proliferation with appropriate methods like recirculation, use of Ultra Violet (UV) treatment, treatment with heat and sanitising agent. After any chemical sanitisation of the water system, a flushing shall be done to ensure that the sanitising agent has been effectively

removed.

4. Manufacturing:-

4.1. Manufacturing personnel shall wear wherever required non fibre shedding clothing to prevent contamination of the product.

4.2. Materials likely to shed fibre like gunny bags, or wooden pallets shall not be carried into the area where products or cleaned containers are exposed.

4.3. Care shall be taken to maintain the homogeneity of emulsion by use of appropriate emulsifier and suspensions by use of appropriate stirrer during filling. Mixing and filling processes shall be specified and monitored. Special care shall be taken at the beginning of the filling process after stoppage due to any interruption and at the end of the process to ensure that the product is uniformly homogenous during the filling process.

4.4. The primary packaging area shall have an air supply which is filtered through level-3 filters [Production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable]. The temperature of the area shall not exceed 30 degrees centigrade.

4.5. When the bulk product is not immediately packed, the maximum period of storage and storage conditions shall be specified in the Master Formula. The maximum period of storage time of a product in the bulk stage shall be validated.

PART X

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF TOPICAL PRODUCTS i.e., EXTERNAL PREPARATIONS (CREAMS, OINTMENTS, PASTES, MULSIONS, LOTIONS, SOLUTIONS, DUSTING POWDERS AND IDENTICAL PRODUCTS)

Note.- Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Topical Products i.e., External Preparations (Creams, Ointments, Pastes, Emulsions, Lotions, Solutions, Dusting powders and

identical products used for external applications). In addition to these requirements, the following specific requirements shall also be followed, namely:—

(1) The entrance to the area where topical products are manufactured shall be through a suitable airlock. Outside the airlock, insectocutors shall be installed.
(2) The air to this manufacturing area shall be filtered through suitable filters and shall be air-conditioned. The HVAC system shall be in place.
(3) The area shall be fitted with an exhaust system of suitable capacity to effectively remove vapours, fumes, smoke or floating dust particles.
(4) The equipment used shall be designed and maintained to prevent the product from being accidentally contaminated with any foreign matter or lubricant.
(5) Suitable cleaning equipment and material shall be used in the process of cleaning or drying the process equipment or accessories used.
(6) Water used in compounding shall be Purified Water IP.
(7) Powders, whenever used, shall be suitably sieved before use.
(8) Heating vehicles and a base like petroleum jelly shall be done in a separate mixing area in suitable stainless steel vessels, using steam, gas, electricity, solar energy, etc.
(9) A separate packing section may be provided for primary packaging of the products.

For production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable).

PART XI

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF METERED–DOSE– INHALERS (MDI)

Note.– The Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Metered-Dose-Inhalers (MDI). In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. **Principle:-** Manufacture of pressurised aerosol products for inhalation with metering valves requires some special provisions arising from the particular nature of this pharmaceutical form. It shall occur under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and in the case of suspensions, of uniformity is also of particular importance. There are presently two common manufacturing and filling methods as follows:–
   (a) Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is filled into the container, the valve is crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.
   (b) One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure or at a low temperature or both. The suspension is then filled directly into the container in one shot.

2. **General:-** Manufacture of Metered-Dose-Inhalers shall be done under conditions which shall ensure minimum microbial and particulate contamination. Assurance of the quality of components and the bulk product is very important. Where medicaments are in suspended state, uniformity of suspension shall be established. Manufacture and filling shall be carried out as far as possible in a closed system.

3. **Building and civil works:-**
   3.1. The building shall be located on a solid foundation to reduce risk of cracking walls and floor due to the movement of equipment and machinery.
   3.2. All building surfaces shall be impervious, smooth and non-shedding. Flooring shall be continuous and provided with a cover between the floor and the wall as well as between the wall and the ceiling. Ceiling shall be solid, continuous and proceeded a cone with the walls. Light fittings and air-grills shall be flush with the ceiling. All service lines requiring maintenance shall be erected in such a manner that these are accessible from outside the production area.
   3.3. The manufacturing area shall be segregated into change rooms for

personnel, container preparation area, bulk preparation and filling area, quarantine area and spray testing and packing areas.

3.4. Secondary change rooms shall be provided for operators to change from factory clothing to special departmental clothing before entering the manufacturing and filling area.

3.5. Separate area shall be provided for de-cartooning of components before they are air washed.

3.6. The propellants used for manufacture shall be delivered to the manufacturing area distribution system by filtering them through 2µ filters. The bulk containers of propellants shall be stored, suitably identified, away from the manufacturing facilities.

4. Environmental conditions:-

4.1. Where products or clean components are exposed, the area shall be supplied with filtered air of Grade C and personnel shall be entered through airlocks.

4.2. The requirements of temperature and humidity in the manufacturing area shall be decided depending on the type of product and propellants handled in the facility. Other support areas shall have comfort levels of temperature and humidity.

4.3. There shall be a difference in room pressure between the manufacturing area and the support areas and the differential pressure shall be not less than 15 Pascals, (0.06 inches or 1.5 mm water gauge).

4.4. There shall be a written schedule for the monitoring of environmental conditions. Temperature and humidity shall be monitored daily.

4.5. The HVAC system shall be in place.

5. Garments:-

5.1. Personnel in the manufacturing and filling section shall wear suitable single piece garment made out of non-shedding, tight weave material. Personnel in support areas shall wear clean factory uniforms.

5.2. Gloves made of suitable material having no interaction with the propellants shall be used by the operators in the manufacturing and filling areas. Preferably, disposable gloves shall be used.

5.3. Suitable department specific PPE like footwear and safety glasses shall be used, wherever hazard exists.

6. Sanitation:-

6.1. There shall be written procedures for the sanitation of the MDI manufacturing facility. Special care shall be taken to handle residues and rinses of propellants.

6.2. Use of water for cleaning shall be restricted and controlled. Routinely used disinfectants are suitable for sanitising the different areas. Records of sanitation shall be maintained.

7. Equipment:-

7.1. Manufacturing equipment shall be of closed system. The vessels and supply lines shall be of stainless steel.

7.2. Suitable check weights, spray testing machines and labelling machines shall be provided in the department.

7.3. All the equipment shall be suitably calibrated and their performance validated on receipt and thereafter periodically.

8. Manufacture:-

8.1. Metering valves for aerosols are a more complex engineering article than most pharmaceutical components. Specifications, sampling and testing shall be appropriate for this situation. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

8.2. All propellants (e.g., liquid or gaseous propellants) shall be filtered to remove particles greater than 0.2µ. An additional filtration where possible immediately before filling is desirable.

8.3. There shall be an approved Master Formula Records for the manufacture of metered dose inhalers.

8.4. The primary packing material shall be appropriately cleaned by compressed air suitably filtered through 0.2µ filter. The humidity of the compressed air shall be controlled as applicable.

8.5. The valves shall be carefully handled and after de-cartooning, these shall be kept in clean, closed containers in the filling room.

8.6. Containers and valves shall be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g., lubricants) or undue microbiological contaminants. After cleaning valves shall be kept in clean, closed containers and precautions taken not to introduce contamination during subsequent handling, e.g., taking samples.

Containers shall be provided to the filling line in a clean condition or cleaned on line immediately before filling.

8.7. For suspensions, the bulk shall be kept stirred continuously. Precautions shall be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

8.8. In-process controls shall include periodical checking of weight of bulk formulation filled in the containers. In a two-shot-filling process (liquid filling followed by gaseous filling), it shall be ensured that one hundred per cent check on weight is carried out.

8.9. Controls after filling shall ensure the absence of undue leakage. Any leakage test shall be performed in a way which avoids microbial contamination or residual moisture.

8.10. Filled containers shall be quarantined for a suitable period established by the manufacturer to detect leaking containers prior to testing, labelling and packing.

9. Documentation:- In addition to the routine good manufacturing practices documentation, manufacturing records shall show the following additional information:–

(1) temperature and humidity in the manufacturing area;
(2) periodic filled weights of the formulation;
(3) records of rejections during on line check weighing; and
(4) records of rejection during spray testing.

PART XII

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENTS

Note.— Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of API. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Introduction:-

1.1. **General-** This document is intended to provide guidance regarding GMP for the manufacturing of APIs under an appropriate system for managing quality. It is also intended to help and ensure that APIs meet the requirements for quality and purity that they purport or are

represented to possess. In this Part "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls.

1.2. **Scope-**

1.2.1. This Part applies to the manufacture of APIs for use in Finished Pharmaceutical Products (FPPs). It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilisation and aseptic processing of sterile APIs are not covered by this Part, but shall be performed in accordance with GMP guidelines for sterile products.

1.2.2. This Part covers APIs that are manufactured by chemical synthesis, extraction, cell culture or fermentation by recovery from natural sources or by any combination of these processes.

1.2.3. Specific guidance for APIs manufactured by cell culture or fermentation is described in paragraph 17 of this Part.

1.2.4. This Part excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it includes APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this Part. In addition, this Part does not apply to medical gases, bulk-packaged FPPs, and manufacturing and control aspects specific to radiopharmaceuticals.

1.2.5. Paragraph 18 contains guidance that only applies to the manufacture of APIs used in the production of FPPs specifically for clinical trials (investigational medicinal products).

1.2.6. An "API starting material" is a raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in house.

1.2.7. API starting materials normally have defined chemical properties and structure. The company shall designate and document the

rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API starting materials" are entered into the process. For other processes (e.g. fermentation, extraction or purification) this rationale shall be established on a case-to-case basis.

1.2.8. Table specified in paragraph 1.2.9. provides guidance on the point at which the API starting material is normally introduced into the process. From this point on, appropriate GMP as defined in this Part shall be applied to these intermediate or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it shall be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

1.2.9. The guidance in this Part would normally be applied to the steps shown in grey in Table below. It does not imply that all steps shown shall be completed. The stringency of GMP in API manufacturing shall increase as the process proceeds from early API steps to final steps, purification and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g., milling and micronising), shall be conducted at least to the standards of this Part.

TABLE

APPLICATION OF THIS GUIDE TO API MANUFACTURING

Type of manufacturing	Application of this guide to steps (shown in grey) used in this type of manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediates	Isolation and purification	Physical processing and packaging
API derived from animal sources	Collection of organ, fluid or tissue	Cutting, mixing or initial processing	Introduction of the API starting	Isolation and purification	Physical processing and packaging

			material into process		
API extracted from plant sources	Collection of plants	Cutting and initial extraction	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
phytopharmaceutical extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants or cultivation and harvesting	Cutting or comminuting			Physical processing and packaging
Biotechnology: fermentation or cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture or fermentation	Isolation and purification	Physical processing and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging

1.2.10. This Part shall not apply to steps prior to the introduction of the defined "API starting material".

2. Quality management:-

2.1. Principles-

2.1.1. Quality shall be the responsibility of all persons involved in the

manufacturing.

2.1.2. Each manufacturer shall establish, document and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.1.3. The system for managing quality shall encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities shall be defined and documented.

2.1.4. There shall be a quality units that is independent of production and that fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organisation.

2.1.5. The persons authorised to release intermediates and APIs shall be specified.

2.1.6. All quality related activities shall be recorded at the time they are performed.

2.1.7. Any deviation from established procedures shall be documented and explained. Critical deviations shall be investigated and the investigation and its conclusions shall be documented.

2.1.8. No materials shall be released or used before the satisfactory completion of evaluation by the quality units unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in paragraph 10.2 of this Part or the use of raw materials or intermediates pending completion of evaluation).

2.1.9. Procedures shall exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality related complaints, recalls and regulatory actions).

2.2. **Responsibilities of the quality units-**

2.2.1. The quality units shall be involved in all quality-related matters.

2.2.2. The quality units shall review and approve all appropriate quality related documents.

2.2.3. The main responsibilities of the independent quality units shall

not be delegated. These responsibilities shall be described in writing and shall include but not necessarily be limited to:—

(i) releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;

(ii) establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;

(iii) reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;

(iv) making sure that critical deviations are investigated and resolved;

(v) approving all specifications and master production instructions;

(vi) approving all procedures impacting the quality of intermediates or APIs;

(vii) making sure that internal audits (self-inspections) are performed;

(viii) approving intermediate and API contract manufacturers;

(ix) approving changes that potentially impact quality of intermediates or APIs;

(x) reviewing and approving validation protocols and reports;

(xi) making sure that quality related complaints are investigated and resolved;

(xii) making sure that effective systems are used for maintaining and calibrating critical equipment;

(xiii) making sure that materials are appropriately tested and the results are reported;

(xiv) making sure that there are stability data to support retest or expiry dates and storage conditions on APIs or intermediates where appropriate; and

(xv) performing product quality reviews as defined in paragraph 2.5.

2.3. **Responsibility for production activities-** The responsibility for production activities shall be described in writing and shall include but not necessarily be limited to:-

(i) preparing, reviewing, approving and distributing the instructions for

the production of intermediates or APIs according to written procedures;

(ii) producing APIs and, when appropriate, intermediates according to pre-approved instructions;

(iii) reviewing all production batch records and ensuring that these are completed and signed;

(iv) making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;

(v) making sure that production facilities are clean and when appropriate disinfected;

(vi) making sure that the necessary calibrations are performed and records are kept;

(vii) making sure that the premises and equipment are maintained and records are kept;

(viii) making sure that validation protocols and reports are reviewed and approved;

(ix) evaluating proposed changes in product, process or equipment; and

(x) making sure that new and when appropriate, modified facilities and equipment are qualified.

2.4. **Internal audits (self-inspection)-**

2.4.1. In order to verify compliance with the principles of GMP for APIs, regular internal audits shall be performed in accordance with an approved schedule.

2.4.2. Audit findings and corrective actions shall be documented and brought to the attention of the responsible management of the firm. Agreed corrective actions shall be completed in a timely and effective manner.

2.5. **Product quality review-**

2.5.1. Regular quality reviews of APIs shall be conducted with the objective of verifying the consistency of the process. Such reviews shall normally be conducted and documented annually and shall include at least a review of:—

(i) critical in-process control and critical API test results;

(ii) all batches that failed to meet established specifications;

(iii) all critical deviations or non-conformances and related investigations;

(iv) any changes carried out to the processes or analytical methods;
(v) results of the stability monitoring programme;
(vi) quality-related returns, complaints and recalls; and
(vii) adequacy of corrective actions.

2.5.2. The results of this review shall be evaluated and an assessment made of whether corrective action or any revalidation shall be undertaken. Reasons for such corrective action shall be documented. Agreed corrective actions shall be completed in a timely and effective manner.

3. Personnel-

3.1. Personnel qualifications-

3.1.1. There shall be an adequate number of personnel qualified by appropriate education, training or experience to perform and supervise the manufacture of intermediates and APIs.

3.1.2. The responsibilities of all personnel engaged in the manufacture of intermediates and APIs shall be specified in writing.

3.1.3. Training shall be regularly conducted by qualified individuals and shall cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employees' functions. Records of training shall be maintained. Training shall be periodically assessed.

3.2. Personnel hygiene-

3.2.1. Personnel shall practice good sanitation and health habits.

3.2.2. Personnel shall wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing shall be changed when appropriate. Additional protective apparel, such as head, face, hand and arm coverings shall be worn when necessary to protect intermediates and APIs from contamination.

3.2.3. Personnel shall avoid direct contact with intermediates or APIs.

3.2.4. 3.2.4 Smoking, eating, drinking, chewing and the storage of food shall be restricted to certain designated areas separate from the manufacturing areas.

3.2.5. Personnel with an infectious disease or who have open lesions on the exposed surface of the body shall not engage in activities

that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions shall be excluded from activities where their health condition could adversely affect the quality of the APIs, until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardise the safety or quality of the APIs.

3.3. **Consultants-**

3.3.1. Consultants advising on the manufacture and control of intermediates or APIs shall have sufficient education, training and experience or any combination thereof to advise on the subject for which they are retained.

3.3.2. Records shall be maintained stating the name, address, qualifications and type of service provided by these consultants.

4. Buildings and facilities-

4.1. **Design and construction-**

4.1.1. Buildings and facilities used in the manufacture of intermediates and APIs shall be located, designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities shall also be designed to minimise potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities shall also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.1.2. Buildings and facilities shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.1.3. Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.1.4. The flow of materials and personnel through the building or facilities shall be designed to prevent mix-ups or contamination.

4.1.5. There shall be defined areas or other control systems for the following activities:-

(i) receipt, identification, sampling and quarantine of incoming

materials, pending release or rejection;

(ii) quarantine before release or rejection of intermediates and APIs;

(iii) sampling of intermediates and APIs;

(iv) holding rejected materials before further disposition (e.g., return, reprocessing or destruction);

(v) storage of released materials;

(vi) production operations;

(vii) packaging and labelling operations; and

(viii) laboratory operations.

4.1.6. Adequate, clean washing and toilet facilities shall be provided for personnel. These washing facilities shall be equipped with hot and cold water as appropriate, soap or detergent, air driers or single use towels. The washing and toilet facilities shall be separate from, but easily accessible to the manufacturing areas. Adequate facilities for showering or changing clothes shall be provided, when appropriate.

4.1.7. Laboratory areas and operations shall normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements and the laboratory and its operations do not adversely affect the production process or intermediates or APIs.

4.2. **Utilities-**

4.2.1. All utilities that could impact on product quality (e.g., steam, gases, compressed air and heating, ventilation and air conditioning) shall be qualified and appropriately monitored and action shall be taken when limits are exceeded. Drawings for these utility systems shall be available.

4.2.2. Adequate ventilation, air filtration and exhaust systems shall be provided, where appropriate. These systems shall be designed and constructed to minimise risks of contamination and cross-contamination and shall include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity and temperature as appropriate to the stage of manufacture. Particular attention shall be given to the areas where APIs are

exposed to the environment.

4.2.3. If air is recirculated to production areas, appropriate measures shall be taken to control risks of contamination and cross-contamination.

4.2.4. Permanently installed pipework shall be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems or alternative means. Pipework shall be located to avoid risks of contamination of the intermediates or APIs.

4.2.5. Drains shall be of adequate size and shall be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3. **Water-**

4.3.1. Water used in the manufacture of APIs shall be demonstrated to be suitable for its intended use.

4.3.2. Unless otherwise justified, process water shall, at a minimum, meet World Health Organisation guidelines for drinking (potable) water quality.

4.3.3. If drinking (potable) water is insufficient to assure API quality, and tighter chemical or microbiological water quality specifications are called for, appropriate specifications for physical and chemical attributes, total microbial counts, objectionable organisms or endotoxins shall be established.

4.3.4. Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process shall be validated and monitored with appropriate action limits.

4.3.5. Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile FPP, water used in the final isolation and purification steps shall be monitored and controlled for total microbial counts, objectionable organisms and endotoxins.

4.4. **Containment-**

4.4.1. Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, shall be employed in the production of highly sensitising materials, such as penicillins or cytotoxic drugs or sex hormones or anabolic or androgenic steroids.

4.4.2. Appropriate measures shall be established and implemented to prevent cross-contamination, e.g., from personnel or materials, moving from one dedicated area to another.

4.4.3. Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials shall not be conducted using the buildings and equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials shall be separate from APIs.

4.5. **Lighting-** Adequate lighting shall be provided in all areas to facilitate cleaning, maintenance and proper operations.

4.6. **Sewage and refuse-** Sewage, refuse and other wastes (e.g., solids, liquids, or gaseous by- products from manufacturing) in and from buildings and the immediate surrounding area shall be disposed of in a safe, timely and sanitary manner. Containers and pipes for waste material shall be clearly identified.

4.7. **Sanitation and maintenance:—**

4.7.1. Buildings used in the manufacture of intermediates and APIs shall be properly maintained and repaired and kept in a clean condition.

4.7.2. Written procedures shall be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities.

4.7.3. When necessary, written procedures shall also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitising agents to prevent the contamination of equipment, raw materials, packaging or labelling materials, intermediates and APIs.

5. Process equipment:-

5.1. **Design and construction-**

5.1.1. Equipment used in the manufacture of intermediates and APIs shall be of appropriate design and adequate size and suitably located for its intended use, cleaning, sanitisation (where appropriate) and maintenance.

5.1.2. Equipment shall be constructed so that surfaces that contact raw materials, intermediates or APIs do not alter the quality of the

intermediates and APIs beyond the official or other established specifications.

5.1.3. Production equipment shall only be used within its qualified operating range.

5.1.4. Major equipment (e.g., reactors and storage containers) and permanently installed processing lines used during the production of an intermediate or API shall be appropriately identified.

5.1.5. Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants shall not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this shall be evaluated to ensure that there are no detrimental effects upon the fitness for the purpose of the material. Wherever possible, food-grade lubricants and oils shall be used.

5.1.6. Closed or contained equipment shall be used whenever appropriate. Where open equipment is used or equipment is opened, appropriate precautions shall be taken to minimise the risk of contamination.

5.1.7. A set of current drawings shall be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2. **Equipment maintenance and cleaning-**

5.2.1. Schedules and procedures (including assignment of responsibility) shall be established for the preventive maintenance of equipment.

5.2.2. Written procedures shall be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures shall contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures shall include:-

(i) assignment of responsibility for cleaning of equipment;

(ii) cleaning schedules including where appropriate, sanitising schedules;

(iii) a complete description of the methods and materials including dilution of cleaning agents used to clean equipment;

(iv) when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;

(v) instructions for the removal or obliteration of previous batch identification;

(vi) instructions for the protection of clean equipment from contamination prior to use;

(vii) inspection of equipment for cleanliness immediately before use, if practical; and

(viii) establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.2.3. Equipment and utensils shall be cleaned, stored and, where appropriate, sanitised or sterilised to prevent contamination or carryover of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.2.4. Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, this equipment shall be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of microorganisms).

5.2.5. Non-dedicated equipment shall be cleaned between production of different materials to prevent cross-contamination.

5.2.6. Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents shall be defined and justified.

5.2.7. Equipment shall be identified as to its contents and its cleanliness status by appropriate means.

5.3. **Calibration-**

5.3.1. Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs shall be calibrated according to written procedures and an established schedule.

5.3.2. Equipment calibrations shall be performed using standards traceable to certified standards, if these exist.

5.3.3. Records of these calibrations shall be maintained.

5.3.4. The current calibration status of critical equipment shall be known and verifiable.

5.3.5. Instruments that do not meet calibration criteria shall not be used.

5.3.6. Deviations from approved standards of calibration on critical instruments shall be investigated to determine if these could have had an impact on the quality of the intermediates or APIs manufactured using this equipment since the last successful calibration.

5.4. **Computerised systems-**

5.4.1. GMP-related computerised systems shall be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.

5.4.2. Appropriate installation qualification and operational qualification shall demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.4.3. Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at the time of installation, a retrospective validation could be conducted, if appropriate documentation is available.

5.4.4. Computerised systems shall have sufficient controls to prevent unauthorised access or changes to data. There shall be controls to prevent omissions in data (e.g., the system being turned off and data not captured). There shall be a record of any data change made, the previous entry, the person who made the change and when the change was made.

5.4.5. Written procedures shall be available for the operation and maintenance of computerised systems.

5.4.6. Where critical data are being entered manually, there shall be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.

5.4.7. Incidents related to computerised systems that could affect the quality of intermediates or APIs or the reliability of records or test results shall be recorded and investigated.

5.4.8. Changes to the computerised system shall be made according to a change procedure and shall be formally authorised,

documented and tested. Records shall be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records shall demonstrate that the system is maintained in a validated state.

5.4.9. A back-up system shall be provided so that there is no permanent loss of records due to system breakdown or failure. Means of ensuring data protection shall be established for all computerised systems.

5.4.10. Data may be recorded by a second means in addition to the computer system.

6. Documentation and records:-

6.1. Documentation system and specifications-

6.1.1. All documents related to the manufacture of intermediates or APIs shall be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.1.2. The issuance, revision, superseding and withdrawal of all documents shall be controlled with maintenance of revision histories.

6.1.3. A procedure shall be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records and distribution records). The retention periods for these documents shall be specified.

6.1.4. All production, control and distribution records shall be retained for at least one year after the expiry date of the batch. For APIs with retest dates, records shall be retained for at least three years after the batch is completely distributed.

6.1.5. Entries in records shall be made indelibly in spaces provided for such entries, directly after performing the activities and shall identify the person making the entry. Corrections to entries shall be dated and signed ensuring that the original entry remains readable.

6.1.6. During the retention period, originals or copies of records shall

be readily available at the establishment where the activities described in these records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.1.7. Specifications, instructions, procedures and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy shall be readily available.

6.1.8. Specifications shall be established and documented for raw materials, intermediates where necessary, APIs and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria shall be established and documented for in-process controls.

6.1.9. If electronic signatures are used on documents they shall be authenticated and secure.

6.2. **Equipment cleaning and use record-**

6.2.1. Records of major equipment use, cleaning, sanitisation and sterilisation and maintenance shall show the date, time (if appropriate), product and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

6.2.2. If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance and use can be part of the batch record or maintained separately.

6.3. **Records of raw materials, intermediates, API labelling and packaging materials-**

6.3.1. Records of raw materials, intermediates, API labelling and packaging materials shall be maintained including:-

(i) the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control numbers, if known, or other identification number; the number allocated on receipt; and the date of receipt;

(ii) the results of any test or examination performed and the conclusions derived from this;

(iii) records tracing the use of materials;

(iv) documentation of the examination and review of API labelling and packaging material for conformity with established specifications; and

(v) the final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

6.3.2. Master (approved) labels shall be maintained for comparison to issued labels.

6.4. **Master production instructions (master production and control records):-**

6.4.1. To ensure uniformity from batch to batch, master production instructions for each intermediate and API shall be prepared, dated and signed by one person and independently checked, dated and signed by a person in the quality units.

6.4.2. Master production instructions shall include:-

(i) the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;

(ii) a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;

(iii) an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production shall be included. Variations to quantities shall be included where they are justified;

(iv) the production location and major production equipment to be used;

(v) detailed production instructions, including the-

(a) sequences to be followed;
(b) ranges of process parameters to be used;
(c) sampling instructions and in-process controls with their acceptance criteria, where appropriate;
(d) time limits for completion of individual processing steps and the total process, where appropriate; and
(e) expected yield ranges at appropriate phases of processing or time;

(vi) where appropriate, special notations and precautions to be followed, or cross-references; and

(vii) the instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5. **Batch production records (batch production and control records)-**

6.5.1. Batch production records shall be prepared for each intermediate and API and shall include complete information relating to the production and control of each batch. The batch production record shall be checked before issuance to assure that it is the correct version and is a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document shall include a reference to the current master production instruction being used.

6.5.2. These records shall be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code, together with the date and time can serve as the unique identifier until the final number is allocated.

6.5.3. Documentation of completion of each significant step in the batch production records (batch production and control records) shall include-

(i) dates and, when appropriate, times;

(ii) identity of major equipment (e.g., reactors, driers and mills) used;

(iii) specific identification of each batch, including weights, measures and batch numbers of raw materials, intermediates

or any reprocessed materials used during manufacturing;

(iv) actual results recorded for critical process parameters;

(v) any sampling performed;

(vi) signatures of the persons performing and directly supervising or checking each critical step in the operation;

(vii) in-process and laboratory test results;

(viii) actual yield at appropriate phases or times;

(ix) description of packaging and label for intermediate or API;

(x) representative label of API or intermediate, if made commercially available;

(xi) any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation, if stored separately; and

(xii) results of release testing.

6.5.4. Written procedures shall be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation shall extend to other batches that may have been associated with the specific failure or deviation.

6.6. **Laboratory control records-**

6.6.1. Laboratory control records shall include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows-

(i) a description of samples received for testing, including the name of the material or its source, batch number or other distinctive code, the date on which the sample was taken and where appropriate, the quantity and date the sample was received for testing;

(ii) a statement of reference to each test method used;

(iii) a statement of the weight or measure of sample used for each test as described by the method;

(iv) data on or cross reference to the preparation and testing of reference standards, reagents and standard solutions;

(v) a complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory

instrumentation, properly identified to show the specific material and batch tested;

(vi) a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors and equivalency factors;

(vii) a statement of the test results and how they compare with established acceptance criteria;

(viii) the signature of the person who performed each test and the dates the tests were performed; and

(ix) the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.

6.6.2. Complete records shall also be maintained for-

(i) any modifications to an established analytical method;

(ii) periodic calibration of laboratory instruments, apparatus, gauges and recording devices;

(iii) all stability testing performed on APIs; and

(iv) out of specification (OOS) investigations.

6.7. **Batch production record review-**

6.7.1. Written procedures shall be established and followed for the review and approval of batch production and laboratory control records including packaging and labelling to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.7.2. Batch production and laboratory control records of critical process steps shall be reviewed and approved by the quality units before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality units.

6.7.3. All deviation, investigation and OOS reports shall be reviewed as part of the batch record review before the batch is released.

6.7.4. The quality units can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. Materials management:-

7.1. General controls-

7.1.1. There shall be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials.

7.1.2. Manufacturers of intermediates or APIs or both shall have a system for evaluating the suppliers of critical materials.

7.1.3. Materials shall be purchased against an agreed specification, from a supplier or suppliers approved by the quality units.

7.1.4. If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer shall be known to the intermediate or API manufacturer or both.

7.1.5. Changing the source of supply of critical raw materials shall be done according to paragraph 13 of this Part.

7.2. Receipt and quarantine-

7.2.1. Upon receipt and before acceptance, each container or grouping of containers of materials shall be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), damage to containers, broken seals and evidence of tampering or contamination. Materials shall be held under quarantine until they have been sampled, examined or tested as appropriate, and then released for use.

7.2.2. Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they shall be identified as correct, tested, if appropriate and released. Procedures shall be available to prevent discharging incoming materials wrongly into the existing stock.

7.2.3. If bulk deliveries are made in non-dedicated tankers, there shall be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following-

(i) certificate of cleaning;

(ii) testing for trace impurities; and

(iii) audit of the supplier.

7.2.4. Large storage containers and their attendant manifolds, filling and discharge lines shall be appropriately identified.

7.2.5. Each container or grouping of containers (batches) of materials shall be assigned and identified with a distinctive code, batch or receipt number. This number shall be used in recording the disposition of each batch. A system shall be in place to identify the status of each batch.

7.3. **Sampling and testing of incoming production materials-**

7.3.1. At least one test to verify the identity of each batch of material shall be conducted, with the exception of the materials described below in paragraph 7.3.2. A supplier's certificate of analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.3.2. Supplier approval shall include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analysis shall be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis shall be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis shall be checked at regular intervals.

7.3.3. Processing aids, hazardous or highly toxic raw materials, other special materials or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels and recording of batch numbers shall help in establishing the identity of these materials. The lack of on-site testing for these materials shall be justified and documented.

7.3.4. Samples shall be representative of the batch of material from which they are taken. Sampling methods shall specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The decision on the number of containers to sample and the sample size shall be based upon a sampling plan that takes into consideration the criticality of the material, variability of the material, past quality history of the supplier and the

quantity needed for analysis.

7.3.5. Sampling shall be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.3.6. Containers from which samples are withdrawn shall be opened carefully and subsequently reclosed. They shall be marked to indicate that a sample has been taken.

7.4. **Storage-**

7.4.1. Materials shall be handled and stored in such a manner as to prevent degradation, contamination and cross-contamination.

7.4.2. Materials stored in fibre drums, bags or boxes shall be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.4.3. Materials shall be stored under conditions and for a period that will have no adverse effect on their quality and shall normally be controlled so that the oldest stock is used first.

7.4.4. Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.4.5. Rejected materials shall be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

7.5. **Re-evaluation-** Materials shall be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. Production and in-process controls:-

8.1. **Production operations-**

8.1.1. Raw materials for manufacturing of intermediates and APIs shall be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices shall be of suitable accuracy for the intended use.

8.1.2. If a material is sub-divided for later use in production operations, the container receiving the material shall be suitable and shall be identified that the following information is available-

(i) material name or item code;

(ii) receiving or control number;

(iii) weight or measure of material in the new container; and
(iv) re-evaluation or retest date, if appropriate.

8.1.3. Critical weighing, measuring or sub-dividing operations shall be witnessed or subjected to an equivalent control. Prior to use, production personnel shall verify that the materials are those specified in the batch record for the intended intermediate or API.

8.1.4. Other critical activities shall be witnessed or subjected to an equivalent control.

8.1.5. Actual yields shall be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges shall be established based on previous laboratory, pilot scale or manufacturing data. Deviations in yield associated with critical process steps shall be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.1.6. Any deviation shall be documented and explained. Any critical deviation shall be investigated.

8.1.7. The processing status of major units of equipment shall be indicated either on the individual units of equipment or by appropriate documentation, computer control systems or alternative means.

8.1.8. Materials to be reprocessed or reworked shall be appropriately controlled to prevent unauthorised use.

8.2. **Time limits-**

8.2.1. If time limits are specified in the master production instructions (see paragraph 6.4.2), these time limits shall be met to ensure the quality of intermediates and APIs. Deviations shall be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation or drying to a predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.2.2. Intermediates held for further processing shall be stored under appropriate conditions to ensure their suitability for use.

8.3. **In-process sampling and control-**

8.3.1. Written procedures shall be established to monitor the progress

and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria shall be defined based on the information gained during the development stage or historical data.

8.3.2. The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

8.3.3. Critical in-process controls (and critical process monitoring), including the control points and methods, shall be stated in writing and approved by the quality units.

8.3.4. In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality units' approval if the adjustments are made within pre-established limits approved by the quality units. All tests and results shall be fully documented as part of the batch record.

8.3.5. Written procedures shall describe the sampling methods for in-process materials, intermediates and APIs. Sampling plans and procedures shall be based on scientifically sound sampling practices.

8.3.6. In-process sampling shall be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures shall be established to ensure the integrity of samples after collection.

8.3.7. OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring or adjusting the process.

8.4. **Blending batches of intermediates or APIs-**

8.4.1. For the purpose of this Schedule, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g. collecting several

centrifuge loads from a single crystallisation batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.4.2. OOS batches shall not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend shall have been manufactured using an established process and shall have been individually tested and found to meet appropriate specifications prior to blending.

8.4.3. Acceptable blending operations include but are not limited to-

(i) blending of small batches to increase batch size;

(I) blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.4.4. Blending processes shall be adequately controlled and documented and the blended batch shall be tested for conformance to established specifications, where appropriate.

8.4.5. The batch record of the blending process shall allow traceability back to the individual batches that make up the blend.

8.4.6. Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations shall be validated to show homogeneity of the combined batch. Validation shall include testing of critical attributes (e.g., particle size distribution, bulk density and tap density) that may be affected by the blending process.

8.4.7. If the blending could adversely affect stability, stability testing of the final blended batches shall be performed.

8.4.8. The expiry or retest date of the blended batch shall be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5. **Contamination control-**

8.5.1. Residual materials can be carried over into successive batches of the same intermediate or API, if there is adequate control. Examples include residue adhering to the wall of a microniser, residual layer of damp crystals remaining in a centrifuge bowl after discharge and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the

next step in the process. Such carryover shall not result in the carry-over of degradants or microbial contamination that may adversely alter the established impurity profile of the API.

8.5.2. Production operations shall be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.5.3. Precautions to avoid contamination shall be taken when APIs are handled after purification.

9. Packaging and identification labelling of APIs and intermediates:-

9.1. General-

9.1.1. There shall be written procedures describing the receipt, identification, quarantine, sampling, examination, testing and release and handling of packaging and labelling materials.

9.1.2. Packaging and labelling materials shall conform to the established specifications. Those that do not comply with the specifications shall be rejected to prevent their use in operations for which they are unsuitable.

9.1.3. Records shall be maintained for each shipment of labels and packaging materials showing receipt, examination or testing and whether they are accepted or rejected.

9.2. Packaging materials-

9.2.1. Containers shall provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.2.2. Containers shall be clean and where indicated by the nature of the intermediate or API, sanitised to ensure that they are suitable for their intended use. These containers shall not be reactive, additive or absorptive to ensure that they do not alter the quality of the intermediate or API beyond the specified limits.

9.2.3. If containers are reused, they shall be cleaned in accordance with documented procedures and all previous labels shall be removed or defaced.

9.3. Label issuance and control-

9.3.1. Access to the label storage areas shall be limited to authorised personnel.

9.3.2. Procedures shall be used to reconcile the quantities of labels issued, used and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies shall be investigated and the investigation shall be approved by the quality units.

9.3.3. All excess labels bearing batch numbers or other batch-related printing shall be destroyed. Returned labels shall be retained and stored in a manner that prevents mix-ups and provides proper identification.

9.3.4. Obsolete and out dated labels shall be destroyed.

9.3.5. Printing devices used to print labels for packaging operations shall be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.3.6. Printed labels issued for a batch shall be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination shall be documented.

9.3.7. A printed label representative of those used shall be included in the batch production record.

9.4. **Packaging and labelling operations-**

9.4.1. There shall be documented procedures designed to ensure that the correct packaging materials and labels are used.

9.4.2. Labelling operations shall be designed to prevent mix-ups. They shall be physically or spatially separated from operations involving other intermediates or APIs.

9.4.3. Labels used on containers of intermediates or APIs shall indicate the name or identifying code, the batch number of the product and the storage conditions, when such information is critical to assure the quality of the intermediate or API.

9.4.4. If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents and special transport conditions and any special legal requirements shall also be included on the label. For intermediates or APIs with an expiry date, this date shall be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date shall be

indicated on the label and certificate of analysis.

9.4.5. Packaging and labelling facilities shall be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination shall be documented in the batch production records, the facility log or other documentation system.

9.4.6. Packaged and labelled intermediates or APIs shall be examined to ensure that containers and packages in the batch have the correct label. This examination shall be part of the packaging operation. Results of these examinations shall be recorded in the batch production or control records.

9.4.7. Intermediate or API containers that are transported outside the manufacturer's control shall be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10.Storage and distribution:-

10.1. **Warehousing procedures-**

10.1.1. Facilities shall be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records shall be maintained of these conditions, if they are critical for the maintenance of material characteristics.

10.1.2. Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned or recalled materials, separate storage areas shall be assigned for their temporary storage until the decision as to their future use has been taken.

10.2. **Distribution procedures-**

10.2.1. APIs and intermediates shall only be released for distribution to third parties after they have been released by the quality units. APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorised by the quality units and if appropriate controls and documentation are in place.

10.2.2. APIs and intermediates shall be transported in a manner that does not adversely affect their quality.

10.2.3. Special transport or storage conditions for an API or intermediate shall be stated on the label.

10.2.4. The manufacturer shall ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.2.5. A system shall be in place by which the distribution of each batch of intermediate or API or both can be readily determined to permit its recall.

11.Laboratory controls:-

11.1. General controls-

11.1.1. The independent quality units shall have at its disposal adequate laboratory facilities.

11.1.2. There shall be documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Laboratory records shall be maintained in accordance with paragraph 6.6.

11.1.3. All specifications, sampling plans and test procedures shall be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, labels and packaging materials conform to established standards of quality and purity. Specifications and test procedures shall be consistent with those included in the registration or filing. There can be specifications in addition to those in the registration or filing. Specifications, sampling plans and test procedures, including changes to them, shall be drafted by the appropriate organisational unit and reviewed and approved by the quality units.

11.1.4. Appropriate specifications shall be established for APIs in accordance with accepted standards and be consistent with the manufacturing process. The specifications shall include a control of the impurities (e.g., organic impurities, inorganic impurities and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms shall be established and met. If the API has a specification for endotoxins, appropriate action limits shall be established and met.

11.1.5. Laboratory controls shall be followed and documented at the time of performance. Any departure from the procedures described in paragraph 11.1.4 shall be documented and explained.

11.1.6. Any OOS result obtained shall be investigated and documented according to the procedure. This procedure shall require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions and conclusions. Any resampling or retesting after OOS results shall be performed according to the documented procedure.

11.1.7. Reagents and standard solutions shall be prepared and labelled following written procedures. "Use by" dates shall be applied as appropriate for analytical reagents or standard solutions.

11.1.8. Primary reference standards shall be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard shall be documented. Records shall be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

11.1.9. Where a primary reference standard is not available from an officially recognised source, an "in-house primary standard" shall be established. Appropriate testing shall be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing shall be maintained.

11.1.10. Secondary reference standards shall be appropriately prepared, identified, tested, approved and stored. The suitability of each batch of secondary reference standard shall be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard shall be periodically requalified in accordance with a written protocol.

11.2. **Testing of intermediates and APIs-**

11.2.1. For each batch of intermediate and API, appropriate laboratory tests shall be conducted to determine conformance to the specifications.

11.2.2. An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process shall normally be established for each API. The impurity profile shall include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed and classification of each identified impurity (e.g., inorganic, organic or solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs of phytopharmaceutical or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B (1).

11.2.3. The impurity profile shall be compared at appropriate intervals with the impurity profile in the regulatory submission or compared with historical data in order to detect changes to the API resulting from modifications to raw materials, equipment operating parameters or the production process.

11.2.4. Appropriate microbiological tests shall be conducted on each batch of intermediate and API where microbial quality is specified.

11.3. **Certificates of analysis-**

11.3.1. Authentic certificates of analysis shall be issued for each batch of intermediate or API on request.

11.3.2. Information on the name of the intermediate or API, including where appropriate its grade, the batch number and the date of release, shall be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date shall be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date shall be indicated on the label and certificate of analysis.

11.3.3. The certificate shall list each test performed in accordance with compendial or customer requirements, including the acceptance limits and the numerical results obtained (if test results are numerical).

11.3.4. Certificates shall be dated and signed by authorised personnel from the quality units and shall show the name, address and telephone number of the original manufacturer. Where the

analysis has been carried out by a repacker or reprocessor, the certificate of analysis shall show the name, address and telephone number of the repacker or reprocessor and a reference to the name of the original manufacturer.

11.3.5. If new certificates are issued by or on behalf of repackers or reprocessors, agents or brokers, these certificates shall show the name, address and telephone number of the laboratory that performed the analysis. They shall also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which shall be attached.

11.4. **Stability monitoring of APIs-**

11.4.1. A documented, on-going testing programme shall be designed to monitor the stability characteristics of APIs and the results shall be used to confirm appropriate storage conditions and retest or expiry dates.

11.4.2. The test procedures used in stability testing shall be validated and be stability-indicating.

11.4.3. Stability samples shall be stored in containers that simulate the market container. For example, if the API is marketed in bags within fibre drums, stability samples can be packaged in bags of the same material and in smaller drums of similar or identical material composition to the drums in which the API is marketed.

11.4.4. Normally the first three commercial production batches shall be placed on the stability monitoring programme to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

11.4.5. Thereafter at least one batch per year of API manufactured (unless none is produced that year) shall be added to the stability monitoring programme and tested at least annually to confirm the stability.

11.4.6. For APIs with short shelf-lives, testing shall be done more frequently. For example, for those biotechnological or biological and other APIs with shelf-lives of one year or less, stability samples shall be obtained and shall be tested monthly for the first three months, and at three-monthly intervals after

that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., nine-month testing) can be considered.

11.5. **Expiry and retest dating-**

11.5.1. When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information shall be available (e.g., published data and test results).

11.5.2. An API expiry or retest date shall be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.5.3. Preliminary API expiry or retest dates can be based on pilot-scale batches if-

(i) the pilot batches employ a method of manufacture and a procedure that simulates the final process to be used on a commercial manufacturing scale; and

(ii) the quality of the API represents the material to be made on a commercial scale.

11.5.4. A representative sample shall be taken for the purpose of performing a retest.

11.6. **Reserve or retention samples-**

11.6.1. The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing.

11.6.2. Appropriately identified reserve samples of each batch of API shall be retained for one year after the expiry date assigned by the manufacturer to the batch, or for three years after distribution of the batch, whichever is longer. For APIs with retest dates, similar reserve samples shall be retained for three years after the batch has been completely distributed by the manufacturer.

11.6.3. The reserve sample shall be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities shall be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial

monograph, two full specification analyses.

12. Validation:-

12.1. **Validation policy-**

12.1.1. The company's overall policy, intentions and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems and personnel responsible for design, review, approval and documentation of each validation phase, shall be documented.

12.1.2. The critical parameters and attributes shall normally be identified during the development stage or from historical data and the ranges necessary for the reproducible operation shall be defined. This shall include-

(i) defining the API in terms of its critical product attributes;

(ii) identifying process parameters that could affect the critical quality attributes of the API; and

(iii) determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.1.3. Validation shall extend to those operations determined to be critical to the quality and purity of the API.

12.2. **Validation documentation-**

12.2.1. A written validation protocol shall be established that specifies how validation of a particular process will be conducted. The protocol shall be reviewed and approved by the quality units and other designated units.

12.2.2. The validation protocol shall specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

12.2.3. A validation report that cross-references the validation protocol shall be prepared, summarising the results obtained, commenting on any deviations observed and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.2.4. Any variations from the validation protocol shall be

documented with appropriate justification.

12.3. **Qualification-**

12.3.1. Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems shall be completed. Qualification is usually carried out by conducting the following activities, individually or combined:-

(i) Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment or systems is suitable for the intended purpose;

(ii) Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and user requirements;

(iii) Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges;

(iv) Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4. **Approaches to process validation-**

12.4.1. Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.4.2. There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These three approaches and their applicability are outlined in the following paragraph.

12.4.3. Prospective validation shall normally be performed for all API processes referred to in paragraph 12.1.3. Prospective validation performed on an API process shall be completed before the commercial distribution of the FPP manufactured from that API.

12.4.4. Concurrent validation can be conducted when data from replicate production runs are unavailable because only a

limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in FPPs for commercial distribution based on thorough monitoring and testing of the API batches.

12.4.5. An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities or the production process. This validation approach may be used where-

(a) critical quality attributes and critical process parameters have been identified;

(b) appropriate in-process acceptance criteria and controls have been established;

(c) there have not been significant process or product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and

(d) impurity profiles have been established for the existing API.

12.4.6. Batches selected for retrospective validation shall be representative of all batches made during the review period, including any batches that failed to meet specifications, and shall be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5. **Process validation programme-**

12.5.1. The number of process runs for validation shall depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches shall be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). Generally, for retrospective validation, data from ten to thirty consecutive batches shall be examined to assess process consistency, but fewer batches can be examined, if justified.

12.5.2. Critical process parameters shall be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimise energy consumption or equipment use, need not be included in the process validation.

12.5.3. Process validation shall confirm that the impurity profile for each API is within the limits specified. The impurity profile shall be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6. **Periodic review of validated systems-** Systems and processes shall be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7. **Cleaning validation-**

12.7.1. Cleaning procedures shall normally be validated. In general, cleaning validation shall be directed to those situations or process steps where contamination or carry-over of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.7.2. Validation of cleaning procedures shall reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection shall be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity and stability.

12.7.3. The cleaning validation protocol shall describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled and analytical methods. The protocol shall also indicate the type of samples to

be obtained and how they are collected and labelled.

12.7.4. Sampling shall include swabbing, rinsing or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used shall be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports for handling toxic materials and small intricate equipment such as micronisers and microfluidisers).

12.7.5. Validated analytical methods with the sensitivity to detect residues or contaminants shall be used. The detection limit for each analytical method shall be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level shall be established. Residue limits shall be practical, achievable and verifiable and be based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological or physiological activity of the API or its most deleterious component.

12.7.6. Equipment cleaning or sanitisation studies shall address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

12.7.7. Cleaning procedures shall be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise remain undetected by sampling or analysis or both.

12.8. **Validation of analytical methods-**

12.8.1. Analytical methods shall be validated unless the method employed is included in the relevant pharmacopoeia or other

recognised standard reference. The suitability of all testing methods used shall nonetheless be verified under actual conditions of use and documented.

12.8.2. Methods shall be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed shall reflect the purpose of the analysis and the stage of the API production process.

12.8.3. Appropriate qualification of analytical equipment shall be considered before starting validation of analytical methods.

12.8.4. Complete records shall be maintained of any modification of a validated analytical method. Such records shall include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. Change control:

13.1. A formal change control system shall be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.2. Written procedures shall cover the identification, documentation, appropriate review and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

13.3. Any proposals for relevant changes to GMP shall be drafted, reviewed and approved by the appropriate organisational units and reviewed and approved by the quality units.

13.4. The potential impact of the proposed change on the quality of the intermediate or API shall be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on their nature and extent and the effects these changes may have on the process. Scientific judgement shall be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.5. When implementing approved changes, measures shall be taken to ensure that all documents affected by the changes are revised.

13.6. After the change has been implemented there shall be an evaluation of the first batch produced or tested under the change.

13.7. The potential for critical changes to affect established retest or expiry dates shall be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability programme or can be added to the stability monitoring programme.

13.8. Manufacturers of the current dosage form shall be notified of changes from established production and process control procedures that can impact the quality of the API.

14.Rejection and reuse of materials:-

14.1. **Rejection-** Intermediates and APIs failing to meet established specifications shall be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials shall be recorded.

14.2. **Reprocessing**

14.2.1. Introducing an intermediate or API, including the one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallisation step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography or milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches it shall be included as part of the standard manufacturing process.

14.2.2. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

14.2.3. Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing shall be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and overreacted

materials.

14.3. **Reworking-**

14.3.1. Before a decision is taken to rework batches that do not conform to the established standards or specifications, an investigation into the reason for non-conformance shall be performed.

14.3.2. Batches that have been reworked shall be subjected to appropriate evaluation, testing, stability testing if warranted and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.3.3. Procedures shall provide for comparing the impurity profile of each reworked batch with batches manufactured by the established process. Where routine analytical methods are inadequate to characterise the reworked batch, additional methods shall be used.

14.4. **Recovery of materials and solvents-**

14.4.1. Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.4.2. Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.

14.4.3. Fresh and recovered solvents and reagents can be combined, if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.4.4. The use of recovered solvents, mother liquors and other recovered materials shall be adequately documented.

14.5. **Returns-**

14.5.1. Returned intermediates or APIs shall be identified as such and quarantined.

14.5.2. If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs shall be reprocessed, reworked or destroyed, as appropriate.

14.5.3. Records of returned intermediates or APIs shall be maintained. For each return, documentation shall include-

(i) name and address of the consignee;

(ii) intermediate or API, batch number and quantity returned;

(iii) reasons for return; and

(iv) use or disposal of the returned intermediate or API.

15. Complaints and recalls-

15.1. All quality-related complaints, whether received orally or in writing, shall be recorded and investigated according to the written procedure.

15.2. Complaint records shall include-

(i) name and address of complainant;

(ii) name (where appropriate title) and telephone number of person submitting the complaint;

(iii) nature of the complaint (including name and batch number of the API);

(iv) date on which the complaint was received;

(v) action initially taken (including dates and identity of person taking the action);

(vi) any follow-up action taken;

(vii) response provided to the originator of the complaint (including date on which the response was sent); and

(viii) final decision on intermediate or API batch or lot.

15.3. Records of complaints shall be retained in order to evaluate trends, product-related frequencies and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.4. There shall be a written procedure that defines the circumstances under which a recall of an intermediate or API shall be considered.

15.5. The recall procedure shall designate who shall be involved in

evaluating the information, how a recall shall be initiated, who shall be informed about the recall and how the recalled material shall be treated.

15.6. The recalls shall be informed to the Licencing Authorities.

16. Contract manufacturers (including laboratories):-

16.1. All contract manufacturers (including laboratories) shall comply with GMP defined in this Schedule. Special consideration shall be given to the prevention of cross-contamination and to maintaining traceability.

16.2. Contract manufacturers (including laboratories) shall be evaluated by the contract giver to ensure GMP compliance of the specific operations taking place at the contract sites.

16.3. There shall be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.4. The contract shall permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.5. Where sub-contracting is allowed, the contract acceptor shall not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.6. Manufacturing and laboratory records shall be kept at the site where the activity takes place and be readily available.

16.7. Changes in the process, equipment, test methods, specifications or other contractual requirements shall not be made unless the contract giver is informed and approves the changes.

17. Specific guidance for APIs manufactured by cell culture or fermentation:-

17.1. **General-**

17.1.1. The principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins or polypeptides or both are the same, although the degree of control will differ. Where practical, this Part shall address these differences. In general, the degree of control for

biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

17.1.2. The term "bio-technological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by bio-technological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Part. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

17.1.3. The term "classical fermentation" refers to the processes that use microorganisms existing in nature or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

17.1.4. Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. There may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation and the intended use of the API or intermediate, control of bioburden, viral contamination and endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

17.1.5. Appropriate controls shall be established at all stages of manufacturing to assure intermediate or API quality. This starts at the cell culture or fermentation step, prior steps (e.g., cell banking) shall be performed under appropriate process controls. This covers cell culture or fermentation from the point

at which a vial of the cell bank is retrieved for use in manufacturing.

17.1.6. Appropriate equipment and environmental controls shall be used to minimise the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring shall depend on the step in production and the production conditions (open, closed or contained systems).

17.1.7. In general, process controls shall take into account-

(i) maintenance of the working cell bank (where appropriate);

(ii) proper inoculation and expansion of the culture;

(iii) control of the critical operating parameters during fermentation or cell culture;

(iv) monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;

(v) harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;

(vi) monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and

(vii) viral safety concerns as described in ICH Guideline Q5A (2) [Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin].

17.1.8. Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants shall be demonstrated.

17.2. **Cell bank maintenance and record keeping-**

17.2.1. Access to cell banks shall be limited to authorised personnel.

17.2.2. Cell banks shall be maintained under storage conditions designed to maintain viability and prevent contamination.

17.2.3. Records of the use of the vials from the cell banks and storage conditions shall be maintained.

17.2.4. Where appropriate, cell banks shall be periodically monitored to determine suitability for use.

17.3. **Cell culture or fermentation-**

17.3.1. Where aseptic addition of cell substrates, media, buffers and

gases is needed, closed or contained systems shall be used where possible. If the inoculations of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there shall be controls and procedures in place to minimise the risk of contamination.

17.3.2. Where the quality of the API can be affected by microbial contamination, manipulations using open vessels shall be performed in a biosafety cabinet or similarly controlled environment.

17.3.3. Personnel shall be appropriately gowned and take special precautions handling the cultures.

17.3.4. Critical operating parameters (for example temperature, pH, agitation rates, addition of gases and pressure) shall be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity shall also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability) may not need to be monitored.

17.3.5. Cell culture equipment shall be cleaned and sterilised after use. As appropriate, fermentation equipment shall be cleaned, and sanitized or sterilised.

17.3.6. Culture media shall be sterilised before use when appropriate to protect the quality of the API.

17.3.7. There shall be appropriate procedures in place to detect contamination and determine the course of action to be taken. This shall include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes shall be identified as appropriate and the effect of their presence on product quality shall be assessed, if necessary. The results of such assessments shall be taken into consideration in the disposition of the material produced.

17.3.8. Records of contamination events shall be maintained.

17.3.9. Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as

appropriate, to minimise the risk of cross-contamination.

17.4. **Harvesting, isolation and purification-**

17.4.1. Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, shall be performed in equipment and areas designed to minimise the risk of contamination.

17.4.2. Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimising degradation, contamination and loss of quality) shall be adequate to ensure that the intermediate or API is recovered with consistent quality.

17.4.3. All equipment shall be properly cleaned and as appropriate, sanitised after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

17.4.4. If open systems are used, purification shall be performed under environmental conditions appropriate for the preservation of product quality.

17.4.5. Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate, if equipment is to be used for multiple products.

17.5. **Viral removal or inactivation steps:**

17.5.1. Viral removal and viral inactivation steps are critical processing steps for some processes and shall be performed within their validated parameters.

17.5.2. Appropriate precautions shall be taken to prevent potential viral contamination from pre-viral to post-viral removal or inactivation steps. Therefore, open processing shall be performed in areas that are separate from other processing activities and have separate air handling units.

17.5.3. The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment shall be appropriately cleaned and sanitised before reuse. Appropriate precautions shall be taken to prevent potential virus carry-over (e.g., through equipment or environment) from previous steps.

18.APIs for use in clinical trials:-

18.1. **General-**

18.1.1. Not all the controls in the previous sections of this guide are appropriate for the manufacture of a new API for investigational use during its development.

18.1.2. The controls used in the manufacture of APIs for use in clinical trials shall be consistent with the stage of development of the pharmaceutical product incorporating the API. Process and test procedures shall be flexible to allow for changes to be made as knowledge of the process increases and clinical testing of a pharmaceutical product progresses from the preclinical stages through the clinical stages. Once pharmaceutical development reaches the stage where the API is produced for use in pharmaceutical products intended for clinical trials, manufacturers shall ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

18.2. **Quality-**

18.2.1. Appropriate GMP concepts shall be applied in the production of APIs for use in clinical trials with a suitable mechanism for the approval of each batch.

18.2.2. A quality unit independent from production shall be established for the approval or rejection of each batch of API for use in clinical trials.

18.2.3. Some of the testing functions commonly performed by the quality units can be performed within other organisational units.

18.2.4. Quality measures shall include a system for testing of raw materials, packaging materials, intermediates and APIs.

18.2.5. Process and quality problems shall be evaluated.

18.2.6. Labelling for APIs intended for use in clinical trials shall be appropriately controlled and shall identify the material as being for investigational use.

18.3. **Equipment and facilities-**

18.3.1. During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures shall be in place to

ensure that equipment is calibrated, clean and suitable for its intended use.

18.3.2. Procedures for the use of facilities shall ensure that materials are handled in a manner that minimises the risk of contamination and cross- contamination.

18.4. **Control of raw materials-**

18.4.1. Raw materials used in production of APIs for use in clinical trials shall be evaluated by testing or be received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous a supplier's analysis shall be suffice.

18.4.2. In some instances the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

18.5. **Production-**

18.5.1. The production of APIs for use in clinical trials shall be documented in laboratory notebooks, batch records or by other appropriate means. These documents shall include information on the use of production materials, equipment, processing and scientific observations.

18.5.2. Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

18.6. **Validation-**

18.6.1. Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during development of an API make batch replication difficult or inexact. The combination of controls, calibration and where appropriate, equipment qualification assures quality of the API during this development phase.

18.6.2. Process validation shall be conducted in accordance with paragraph 12 when batches are produced for commercial use, even when such batches are produced on a pilot scale or small scale.

18.7. **Changes-** Changes are expected during development as knowledge is

gained and the production is scaled up. Every change in the production, specifications or test procedures shall be adequately recorded.

18.8. **Laboratory controls-**

18.8.1. While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated they shall be scientifically sound.

18.8.2. A system for retaining reserve samples of all batches shall be in place. This system shall ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.

18.8.3. Expiry and retest dating as referred to in paragraph 11.5 applies to existing APIs used in clinical trials. For new APIs paragraph 11.5 does not normally apply in early stages of clinical trials.

18.9. **Documentation-**

18.9.1. A system shall be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

18.9.2. The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials shall be appropriately documented.

18.9.3. A system for retaining production and control records and documents shall be used. This system shall ensure that records and documents are retained for an appropriate length of time after the approval, termination or discontinuation of an application.

PART XIII

REQUIREMENTS OF PLANT AND EQUIPMENT

1. **External preparations:-** The following equipment is recommended for the manufacture of 'External preparations', i.e., Ointments, Emulsions, Lotions, Solutions, Pastes, Creams, Dusting Powders and such identical products used for external applications whichever is applicable, namely:-

(1) Mixing and storage tanks preferably of stainless steel or any other appropriate material;

(2) Jacketed Kettle stainless steel container (steam, gas or electrically heated);
(3) Mixer (Electrically operated);
(4) Planetary mixer;
(5) A colloid mill or a suitable emulsifier;
(6) A triple roller mill or an ointment mill;
(7) Liquid filling equipment (Electrically operated); and
(8) Jar or tube filling equipment.

Area- A minimum area of thirty square meters for basic installation and ten square meters for ancillary area is recommended.

2. **Oral Liquid Preparations:-** The following equipment is recommended for the manufacture of oral or internal use preparations, i.e., Syrups, Elixirs, Emulsions and Suspensions, whichever is applicable, namely-
(1) Mixing and storage tanks preferably of Stainless steel or any other appropriate material;
(2) Jacketed Kettle or Stainless steel tank (steam, gas or electrically heated);
(3) Portable stirrer (Electrically operated);
(4) A colloid mill or suitable emulsifier (Electrically operated);
(5) Suitable filtration equipment (Electrically operated);
(6) Semi-automatic or automatic bottle filling machine;
(7) Pilfer proof cap sealing machine;
(8) Water distillation unit or deionizer; and
(9) Clarity testing inspection units.

Area- A minimum area of thirty square meters for basic installation and ten square meters for ancillary area is recommended.

3. **Tablets-** The Tablet section shall be free from dust and floating particles and may be air-conditioned. For this purpose, each tablet compression machine shall be isolated into cubicles and connected to a vacuum dust collector or an exhaust system. For effective operations, the tablet production department shall be divided into four distinct and separate sections as follows:-
(a) Mixing, Granulation and Drying section;
(b) Tablet compression section;
(c) Packaging section (strip or blister machine wherever required); and
(d) Coating section (wherever required).

3.1. The following electrically operated equipment are recommended for

the manufacture of compressed tablets and hypodermic tablets, namely:-

(a) **Granulation-cum-Drying section-**

(1) Disintegrator and sifter;
(2) Powder mixer;
(3) Mass mixer or Planetary mixer or Rapid mixer granulator;
(4) Granulator wherever required;
(5) Thermostatically controlled hot air oven with trays (preferably mounted on a trolley) or Fluid bed dryer; and
(6) Weighing machines;

(b) **Compression section-**

(1) Tablet compression machine, single or multi punch or rotatory;
(2) Punch and dies storage cabinets;
(3) Tablet de-duster;
(4) Tablet Inspection unit or belt;
(5) Dissolution test apparatus wherever required;
(6) In-process testing equipment like single pan electronic balance, hardness tester, friability and disintegration test apparatus; and
(7) Air-conditioning and dehumidification arrangement (wherever necessary).

(c) **Packaging section-**

(1) Strip or blister packaging machine;
(2) Leak test apparatus (vacuum system);
(3) Tablet counters (wherever applicable); and
(4) Air-conditioning and dehumidification arrangement (wherever applicable).

Area- A minimum area of sixty square meters for basic installation and twenty square meters for ancillary area is recommended for un-coated tablets.

(d) **Coating section-**

(1) Jacketed kettle stainless steel container or any other appropriate material (steam, gas or electrically heated for preparing coating suspension);
(2) Coating pan (Stainless steel);
(3) Polishing pan (where applicable);
(4) Exhaust system (including vacuum dust collector);
(5) Air conditioning and Dehumidification Arrangement; and

(6) Weighing machine.

3.2. The coating section shall be made dust free with suitable exhaust system to remove excess powder and fumes resulting from solvent evaporation. It shall be air-conditioned and dehumidified, wherever considered necessary.

Area- A minimum additional area of thirty square meters for coating section for basic installation and ten square meters for ancillary area is recommended. Separate area and equipment for mixing, granulation, drying, tablet compression, coating and packing shall be provided for Penicillin group of drugs on the lines indicated above. In case of operations involving dust and floating particles, care shall be exercised to avoid cross-contamination.

3.3. The manufacture of Hypodermic tablets shall be conducted under aseptic conditions in a separate air-conditioned room, the walls of which shall be smooth and washable. The granulation, compression and packing shall be done in this room.

3.4. The manufacture of effervescent and soluble tablets shall be carried out in air-conditioned and dehumidified areas.

4. Powders:- The following equipment is recommended for the manufacture of powders, namely:-

(1) Disintegrator;
(2) Mixer (electrically operated);
(3) Sifter;
(4) Stainless steel vessels and scoops of suitable sizes;
(5) Filling equipment; and
(6) Weighing machine.

In the case of operation involving floating particles of fine powder, a suitable exhaust system shall be provided. Workers shall be provided with suitable masks during operation.

Area- A minimum area of thirty square meters is recommended to allow for the basic installations. Where the actual blending is to be done on the premises, an additional room shall be provided for the purpose.

5. **Capsules:-** For the manufacture of capsules, separate enclosed area suitably air-conditioned and dehumidified with an airlock arrangement shall be provided. The following equipment is recommended for filling Hard Gelatin Capsules, namely:-
   (1) Mixing and blending equipment (electrically or power driven);
   (2) Capsule filling units;
   (3) Capsules counters (wherever applicable);
   (4) Weighing machine;
   (5) Disintegration test apparatus; and
   (6) Capsule polishing equipment.

   Separate equipment and filling and packaging areas shall be provided in penicillin and non-penicillin sections. In case of operations involving floating particles of fine powder, a suitable exhaust system shall be provided. Manufacture and filling shall be carried out in air-conditioned areas. The room shall be dehumidified.
   Area- A minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area each for penicillin and non-penicillin sections is recommended.

6. **Surgical dressing-** The following equipment is recommended for the manufacture of surgical dressings other than Absorbent Cotton Wool, namely-
   (1) Rolling machine;
   (2) Trimming machine;
   (3) Cutting equipment;
   (4) Folding and pressing machine for gauze;
   (5) Mixing tanks for processing medicated dressing;
   (6) Hot air dry oven;
   (7) Steam steriliser or dry heat steriliser or other suitable equipment; and
   (8) Work tables and benches for different operations.

   Area- A minimum area of thirty square meters is recommended to allow for the basic installations. In case medicated dressings are to be manufactured, another room with a minimum area of thirty square meters shall be provided.

7. **Ophthalmic preparations:-** For the manufacture of ophthalmic preparations, separate enclosed areas with air lock arrangement shall be provided. The following equipment is recommended for manufacture under

aseptic conditions of Eye Ointment, Eye lotions and other preparations for external use, namely-

(1) Thermostatically controlled hot air ovens (preferably double ended);
(2) Jacketed kettle or Stainless steel tanks (steam, gas or electrically heated);
(3) Mixing and storage tanks of stainless steel or Planetary mixer;
(4) Colloid mill or ointment mill;
(5) Tube filling and crimping equipment (semi-automatic or automatic filling machines);
(6) Tube cleaning equipment (air jet type);
(7) Tube washing and drying equipment, if required;
(8) Automatic vial washing machine;
(9) Vial drying oven;
(10) Rubber bung washing machine;
(11) Sintered glass funnel, Seitz filter or filter candle (preferably cartridge and membrane filters);
(12) Liquid filling equipment (semi-automatic or automatic filling machines);
(13) Autoclave (preferably ventilator autoclave);
(14) Air-conditioning and dehumidification arrangement (preferably centrally air-conditioned and dehumidification system); and
(15) Laminar air flow units.

Area: (1) A minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area is recommended. Manufacture and filling shall be carried out in air-conditioned areas under aseptic conditions. The rooms shall be further dehumidified as considered necessary, if preparations containing antibiotics are manufactured.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix up.

8. Pessaries and Suppositories:-

(1) The following equipment is recommended for manufacture of Pessaries and Suppositories, namely-
  (i) Mixing and pouring equipment;
  (ii) Moulding equipment; and
  (iii) Weighing machine.

Area- A minimum area of twenty square meters is recommended to allow for the basic installation.

(2) In the case of pessaries manufactured by granulation and compression, the requirements as indicated under “item 3 of Tablet” shall be provided.

9. Inhalers and Vitrallae:- The following equipment is recommended for manufacture of Inhalers and Vitrallae, namely-

(1) Mixing equipment;
(2) Graduated delivery equipment for measurement of the medicament during filling; and
(3) Sealing equipment.

Area: An area of minimum twenty square metres is recommended for the basic installations.

10. Repacking of drugs and pharmaceutical chemicals:- The following equipment is recommended for repacking of drugs and pharmaceuticals, chemicals, namely:—

(1) Powder disintegrator;
(2) Powder sifter (Electrically operated);
(3) Stainless steel scoops and vessels of suitable sizes;
(4) Weighing and measuring equipment;
(5) Filling equipment (semi-automatic or automatic machine); and
(6) Electric sealing machine.

Area- An area of minimum thirty square metres is recommended for the basic installation. In case of operations involving floating particles of fine powder, a suitable exhaust system shall be provided.

11. Parenteral Preparations:- The whole operation of manufacture of parenteral preparations (small volume injectables and large volume parenterals) in glass and plastic containers may be divided into the following separate areas or rooms, namely-

11.1. **Parenteral preparations in glass containers-**

(1) Water management area: This includes water treatment and storage;
(2) Containers and closures preparation area: This includes washing and drying of ampoules, vials, bottles and closures;
(3) Solution preparation area: This includes preparation and filtration of solution;
(4) Filling capping and sealing area: This includes filling and sealing of ampoules or filling, capping and sealing of vials and bottles;
(5) Sterilisation area;
(6) Quarantine area;
(7) Visual inspection area; and

(8) Packaging area.

The following equipment is recommended for different above mentioned areas, namely-

1. **Water management area-**
   (1) Reverse Osmosis (RO) or Electro-deionisation (EDI) water treatment unit;
   (2) Distillation (multi column with heat exchangers) unit;
   (3) Thermostatically controlled water storage tank;
   (4) Transfer pumps; and
   (5) Service lines for carrying water into user areas through continuously circulating pipe work loop. The Material of Construction (MOC) for the storage tank and circulating pipe line shall be of SS-316 L Grade.

2. **Containers and closures preparation area-**
   (1) Automatic rotary ampoule or vial or bottle washing machine having separate air, water, distilled water jets;
   (2) Automatic closures washing machine;
   (3) Storage equipment for ampoules, vials, bottles and closure;
   (4) Dryer or steriliser (double ended);
   (5) Dust proof storage cabinets; and
   (6) Stainless steel benches or stools.

3. **Solution preparation area-**
   (1) Solution preparation and mixing stainless steel tanks and other containers;
   (2) Portable stirrer;
   (3) Filtration equipment with cartridge and membrane filters or bacteriological filters;
   (4) Transfer pumps; and
   (5) Stainless steel benches or stools.

4. **Filling, capping and sealing area-**
   (1) Automatic ampoule or vial or bottle filling, sealing and capping machine under laminar air flow work station;
   (2) Gas lines (Nitrogen, Oxygen and Carbon di-oxide), wherever required; and
   (3) Stainless steel benches or stools.

5. **Sterilisation area-**

(1) Steam steriliser (preferably with computer control for sterilisation cycle along with trolley sets for loading or unloading containers before and after sterilisation);
(2) Hot Air steriliser (preferably double ended); and
(3) Pressure leak test apparatus.

6. **Quarantine area-**
(1) Storage cabinets; and
(2) Raised platforms or steel racks.

7. **Visual inspection area-**
(1) Visual inspection units (preferably conveyor belt type and composite white and black assembly supported with illumination); and
(2) Stainless steel benches or stools.

8. **Packaging area-**
(1) Batch coding machine (preferably automatic);
(2) Labeling unit (preferably conveyor belt type); and
(3) benches or stools.

Area: (1) A minimum area of one hundred and fifty square meters for the basic installation and an ancillary area of one hundred square meters for Small Volume Injectable are recommended. For Large Volume Parenterals, an area of one hundred and fifty square meters each for the basic installation and for ancillary area is recommended. These areas shall be partitioned into suitable enclosures with airlock arrangements.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix-up.

(3) Packaging materials for large volume Parenteral shall have a minimum area of one hundred square meters.

11.2. **Parenteral preparations in plastic containers by Form-Fill-Seal or Blow, Fill-Seal technology**- The whole operation of manufacture of large volume parenteral preparations in plastic containers including plastic pouches by automatic (all operations in one station) Form-Fill-Seal machine or by semi-automatic blow moulding, filling-cum-sealing machine may be divided into following separate areas or rooms, namely-

(1) Water management area;
(2) Solution preparation area;
(3) Container moulding-cum-filling and sealing area;
(4) Sterilisation area;
(5) Quarantine area;
(6) Visual inspection area; and
(7) Packaging area.

The following equipment is recommended for different above mentioned areas namely-

1. **Water management area-**
   (1) RO or Electro-deionisation (EDI) water treatment unit;
   (2) Distillation unit (multi column with heat exchangers);
   (3) Thermostatically controlled water storage tank;
   (4) Transfer pumps; and
   (5) Service lines for carrying water into user areas through continuously circulating pipe work loop. The Material of Construction (MOC) for the storage tank and circulating pipe line shall be of SS-316 L Grade.

2. **Solution preparation area-**
   (1) Solution preparation and storage tanks;
   (2) Transfer pumps; and
   (3) Cartridge and membrane filters.
3. **Container moulding-cum-filling and sealing area-**
   (1) Sterile Form-Fill-Seal machine (all operations in one station with built-in laminar air flow work station having integrated container output conveyor belt through pass box); and
   (2) Arrangement for feeding plastic granules through feeding-cum-filling tank into the machine.

4. **Sterilisation area-** Super heated steam steriliser (with computer control for sterilisation cycle along with trolley sets for loading or unloading containers for sterilisation).

5. **Quarantine area-** Adequate number of platforms or racks with storage system.

6. **Visual inspection area-** Visual inspection unit (with conveyor belt and composite white and black assembly supported with illumination).

7. **Packaging area-**
   (1) Pressure leak test apparatus (pressure belt or rotating disc type);
   (2) Batch coding machine (preferably automatic); and
   (3) Labeling unit (preferably conveyor belt type).

Area: (1) A minimum area of two hundred and fifty square meters for the basic installation and an ancillary area of one hundred and fifty square meters for large volume parenteral preparations in plastic containers by Form-Fill-Seal technology is recommended. These areas shall be partitioned into suitable enclosures with air-lock arrangements.
(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix up.
(3) Packaging materials for large volume Parenteral shall have a minimum area of one-hundred square meters.

6. These rules shall come into force for implementation as under:—

Category of manufacturers [Based on turnover (INR)]	**Time line for implementation**
Large manufacturers (Turnover>250 crores)	Six months from the date of publication of these rules.
Small and Medium manufacturers (Turnover ≤ 250 crores)	Twelve months from the date of publication of these rules.]

[1249][SCHEDULE N

[See rule 64(1)]

LIST OF MINIMUM EQUIPMENT FOR THE EFFICIENT RUNNING OF A PHARMACY

1. Entrance—The front of a pharmacy shall bear an inscription “Pharmacy" in front.

2. Premises—The premises of a pharmacy shall be separated from rooms for private use. The premises shall be well-built, dry, well-lit and ventilated and of sufficient dimensions to allow the goods in stock, especially medicaments and poisons to be kept in a clearly visible and appropriate manner. The area of the section to be used as dispensing department shall be not less than 6 square metres for one pharmacist working therein with additional 2 square metres for each additional pharmacist. The height of the premises shall be at least 2.5 metres.

The floor of the pharmacy shall be smooth and washable. The walls shall be plastered or tiled or oil painted so as to maintain smooth, durable and washable surface devoid of holes, cracks and crevices.

A pharmacy shall be provided with ample supply of good quality water.

The dispensing department shall be separated by a barrier to prevent the admission of the public.

3. Furniture and apparatus—The furniture and apparatus of a pharmacy shall be adapted to the uses for which they are intended and correspond to the size and requirements to the establishment.

Drugs, chemicals, and medicaments shall be kept in a room appropriate to their properties and in such special containers as will prevent any deterioration of the contents or of contents of containers kept near them. Drawers, glasses and other containers used for keeping medicaments shall be of suitable size and capable of being closed tightly to prevent the entry of dust.

Every container shall bear a label of appropriate size, easily readable with names of medicaments as given in the Pharmacopoeias.

A pharmacy shall be provided with dispensing bench, the top of which shall be covered with washable and impervious material like stainless steel, laminated or plastic, *etc.*

A pharmacy shall be provided with a cupboard with lock and key for the storage of poisons and shall be clearly marked with the word "POISON" in red letters on a white background.

Containers of all concentrated solution shall bear special label or marked with the word "TO BE DILUTED".

A Pharmacy shall be provided with the following minimum apparatus and books necessary for making of official preparations and prescriptions:—

Apparatus—

Balance, dispensing, sensitivity 30 mg.,
Balance, counter, capacity 3 Kgm., sensitivity 1 gm.
Beakers, lipped, assorted sizes.
Bottles, prescription, ungraduated assorted sizes.
Corks assorted sizes and tapers.
Cork, extracter.
Evaporating dishes, porcelain.
Filter paper
Funnels, glass
Litmus paper, blue and red.
Measure glasses cylindrical 10 m., 25 ml., 100 ml. and 500 m.
Mortars and pesties, glass.
Mortars and pesties, wedgwood.
Ointment pots with bakelite or suitable caps.
Ointment slab, porcelain.
Pipettes, graduated, 2 ml., 5 ml. and 10 ml.
Ring, stand (retort) iron, complete with rings.
Rubber stamps and pad.
Scissors.
Spatulas, rubber or vulcanite.
Spatulas, stainless steel.
Spirit lamp.
Glass stirring rods.

Thermometer, 0° to 200°C.
Tripod stand.
Watch glasses.
Water bath.
Water distillation still in case Eye drops and Eye lotions are prepared
Weights, Metric, 1 mg. to 100 gm.
Wire Gauze.
*Pill finisher, boxwood.
*Pill Machine
*Pill Boxes.
*Suppository mould.

Books:

The Indian Pharmacopoeia [Current Edition]
National Formulary of India [Current Edition]
The Drugs and Cosmetics Act, 1940.
The Drugs and Cosmetics Rules, 1945.
The Pharmacy Act, 1948.
The Dangerous Drugs Act, 1930.

4. General provisions—A pharmacy shall be conducted under the continuous personal supervision of a Registered Pharmacist whose name shall be displayed conspicuously in the premises.

The Pharmacist shall always put on clean white overalls.

The premises and fittings of the pharmacy shall be properly kept and everything shall be in good order and clean.

All records and registers shall be maintained in accordance with the laws in force. Any container taken from the poison cupboard shall be replaced therein immediately after use and the cupboard locked. The keys of the poison cupboard shall be kept in the personal custody of the responsible person.

Medicaments when supplied shall have labels conforming to the provisions of laws in force.

Note.— The above requirements are subject to modifications at the discretion of the Licensing Authority if he is of opinion that having regard to the nature of drugs dispensed, compounded or prepared by the licensee. It is necessary to relax the above requirements or to impose additional requirements in the circumstances of a particular case. The decision of the Licensing Authority in that regard shall be final.

* These items are to be provided only by those who intend to dispense pills or suppositories, as the case may be.]

[1250][SCHEDULE O

[See rule 126]

STANDARD FOR DISINFECTANT FLUIDS

[1251][PART I

PROVISIONS APPLICABLE TO BLACK FLUIDS AND WHITE FLUIDS

The standards for disinfectants shall conform to the Indian Standards specification (IS 1061: 1997) laid down from time to time by the Bureau of Indian Standards.]

[1252][SCHEDULE P

(See rule 96)

LIFE PERIOD OF DRUGS

Sl. No.	*Name of the drug*	*Period in months (unless otherwise specified) between date of manufacture and date of expiry which the labelled potency period of the drug shall not exceed under the conditions of storage specified in Column No. 4*	*Conditions of storage*
(1)	(2)	(3)	(4)
ANTIBIOTICS			
1.	Adramycin	30	In a cool place

SI. No.	*Name of the drug*	*Period in months (unless otherwise specified) between date of manufacture and date of expiry which the labelled potency period of the drug shall not exceed under the conditions of storage specified in Column No. 4*	*Conditions of storage*
(1)	(2)	(3)	(4)
2.	Ampicillin	36	In a cool place
3	Ampicillin Capsules	24	
4.	Ampicillin Dry Syrup	24	
5.	Ampicillin Injection	24	
6.	Ampicillin Sodium	36	In a cool place.
7.	Ampicillin Trihydrate	30	In a cool place.
8.	Amoxycillin Trihydrate	36	In a cool place.
9.	Amoxycillin Trihydrate capsules	24	
10.	Amoxycillin Trihydrate Dry Syrup	18	
11.	Bacitracin	18	In a cool place.
12.	Bacitracin or Zinc Bacitracin Tablets	12	
13.	Bacitracin Lozenges	12	
14.	Carbenicillin Sodium Injection	24	At temperature not exceeding 5°C.
15.	Carbanicillin Sodium Powder	24	At temperature not exceeding 5°C.
16.	Cephalexin	24	In a cool place.
17.	Chloramphenicol	60	In a cool place.
18.	Chloramphenicol Capsules & Tablets	48	
19.	Chloramphenicol Palmitate	48	
20.	Chloramphenicol Palmitate Oral suspension	36	
21.	Chloramphenicol Eye Drops	24	
22.	Chloramphenicol Sodium Succinate Powder	48	In a cool place.
23.	Chloramphenicol Sodium Succinate Injection	36	In a cool place.
24.	Chlortetracycline Hydrochloride	60	In a cool place.

SI. No.	*Name of the drug*	*Period in months (unless otherwise specified) between date of manufacture and date of expiry which the labelled potency period of the drug shall not exceed under the conditions of storage specified in Column No. 4*	*Conditions of storage*
(1)	(2)	(3)	(4)
25.	Chlortetracycline Hydrochloride Capsules	60	
26.	Chlortetracycline Hydrochloride Tablets	24	
27.	Chlortetracycline Hydrochloride Ointment	24	
28.	Cloxacillin (Oral)	36	In a cool place.
29.	Cloxacillin Sodium (Injection Grade)	36	In a cool place.
30.	Colistin Sulphate	60	Protected from light.
31.	D-Cycloserine	48	In a cool place.
32.	Dimethyl Chlortetracycline Hydrochloride	48	
33.	Dimethyl Chlortetracycline Hydrochloride Capsules	36	
34.	Daunoblastin Injection	36	
35.	Doxycycline Hydrochloride	48	In a cool place.
36.	Doxycycline Monohydrate	36	In a cool place.
37.	Doxycycline Monohydrate for Oral Suspension	24	
38.	Doxycycline Monohydrate Capsules	36	
39.	Erythromycin Estolate	36	In a cool place.
40.	Erythromycin Ethylsuccinate	60	In a cool place.
41.	Erythromycin Oral Suspension	36	
42.	Erythromycin Estolate for Oral Suspension	36	
43.	Erythromycin Ethyl Succinate Tablet	24	

44.	Erythromycin Estolate Tablets	24	
45.	Erythromycin Stearate	36	In a cool place.
46.	Framycetin Sulphate	48	In a well closed container with temperature not exceeding 30°C.
47.	Framycetin Sulphate Eye Drops	24	In a well closed container with temperature not exceeding 30°C.
48.	Framycetin Sulphate Ointment	24	In a well closed container with temperature not exceeding 30°C.
49.	Gentamycin Sulphate	60	In a cool place.
50.	Gentamycin Sulphate Injection	36	
51.	Gramicidin	60	In a cool place.
52.	Griseofulvin	48	In a cool place.
53.	Griseofulvin Tablets	36	
54.	Kanamycin Sulphate Injection	24	
55.	Kanamycin Acid Sulphate Powder	48	In a cool place.
56.	Mitomycin C	48	In a cool place.
57.	Neomycin Sulphate	48	In a cool place.
58.	Nystatin	36	At a temperature not exceeding 5°C.
59.	Oleandomycin Phosphate Sterile	24	In a cool place.
60.	Oleandomycin Phosphate Non-Sterile	36	In a cool place.
61.	Oxytetracycline Hydrochloride	48	In a cool place.
62.	Oxytetracycline Hydrochloride Capsules	36	
63.	Oxytetracycline Hydrochloride Tablets	24	
64.	Oxytetracycline Hydrochloride Injection	24	
65.	Oxytetracycline Hydrochloride Ointment	36	
66.	Penicillin Crystalline	36	In a cool place.
67.	Penicillin Tablets	18	In a cool place.
68.	Procaine Penicillin G	36	In a cool place.
69.	Benzathin Penicillin G	48	In a cool place.

70.	Potassium Phenoxy Methyl Penicillin	48	In a cool place.
71.	Potassium Phenoxy Methyl Penicillin Tablets	24	
72.	Polymixin B Sulphate	48	In a cool place
73.	Polymixin B Sulphate Ointment or Powder	24	In a cool place.
74.	Rifampicin	36	In a cool place.
[1253][75.	Rifampicin Capsules	36]	
76.	Spiramycin Base	24	In a cool place.
77.	Streptomycin Injection	36	In a cool place.
78.	Streptomycin Ointment	24	
79.	Streptomycin Tablets	24	
80.	Streptomycin Sulphate	48	At temperature not exceeding 20°C.
81.	Tetracycline Base	24	In a cool place.
82.	Tetracycline Hydrochloride	36	In a cool place
83.	Tetracycline Hydrochloride Capsules	36	
84.	Tetracycline Tablets	24	
85.	Tyrothricin	60	In a cool place.
	VITAMINS		
1.	Vitamin A Injection	24	
2.	Vitamin B_1 Injection	24	
3.	Thiamine Mononitrate Tablets	36	
4.	Thiamine Hydrochloride	48	In a well closed container, protected from light, in a cool place.
5.	Thiamine Mononitrate	48	In a well closed container, protected from light, in a cool place.
6.	Riboflavin	60	In a well closed container, protected from light, in a cool place.
7.	Riboflavin-5-Phosphate	24	In a well closed container, protected from light, in a cool place.
8.	Riboflavin Tablets	36	
9.	Vitamin B_2 Injection	24	

10.	Vitamin B_6	60	In a well closed container, protected from light, in a cool place.
11.	Vitamin B_6 Tablets	36	
12.	Cyanacobalamin	48	In a well closed container, protected from light, in a cool place.
13.	Hydroxycobalamin	48	In a well closed container, protected from light, in a cool place.
14.	Vitamin B_{12} Injection	36	
15.	Calcium Pantothenate	36	In a well closed container, protected from light, in a cool place.
16.	Vitamin C Injection	24	
17.	Calcium Pantothenate Tablets	36	
[1254][18.	Vitamin C	48	In a well closed container, protected from light, in a cool place.]
19.	Vitamin D_2 D_3	36	In a well closed container, protected from light, in a cool place.
20.	Vitamin E or E-Acetate	60	In a well closed container, protected from light, in a cool place.
21.	Folic Acid	60	In a well closed container, protected from light, in a cool place.
22.	Folic Acid Tablets	36	
23.	Vitamin K	60	In a well closed container, protected from light, in a cool place
24.	Vitamin K Injection	36	
25.	Niacinamide	60	In a well closed container, protected from light, in a cool place.
26.	Niacinamide Tablets	36	
27.	D-Panthenol	60	In a well closed container, protected from light, in a cool place.
INSULIN PREPARATIONS			

1.	Golbuline Zinc Insulin Injection	24	At temperature between 2°C and 8°C, must not be allowed to freeze.
2.	Insulin Injection	24	At temperature between 2°C and 8°C, must not be allowed to freeze.
3.	Insulin Zinc Suspension	24	At temperature between 2°C and 8°C, must not be allowed to freeze.
4.	Insphane Insulin Injection	24	At temperature between 2°C and 8°C, must not be allowed to freeze.
[1255][5.	Human Insulin Injection	30	At temperature between 2°C and 8°C, must not be allowed to freeze.]
NORMAL HUMAN PLASMA			
1.	Anti-Haemophillic Human Globulin	12	In a cool place.
2.	Dried Plasma	60	At temperature not exceeding 25°C.
3.	Dried Normal Human Serum		
	Albumin	60	At temperature not exceeding 25°C.
4.	Frozen Plasma	60	In deep freeze.
5.	Liquid Plasma	24	In cold place.
6.	Liquid Normal Human Serum Albumin	60	In cold place.
[1256][7.	Whole Human Blood—		
	(a) Collected in ACD Solution	21 days	At temperature between 4°C and 6°C.
	(b) Collected in CPDA Solution	35 days	At temperature between 4°C and 6°C.]
SERA TOXIN AND TOXOID			
1.	Alum Precipitated Diphtheria Toxoid	24	In cold place.
2.	Alum Precipitated Diphtheria and Tetanus Toxoid and Pertussis Vaccine combined	18	In cold place.
3.	Alum Precipitated Tetanus Toxoid	24	In cold place.
4.	Aluminium Hydroxide	24	In cold place.

	Absorbed Diphtheria Toxoid		
5.	Aluminium Hydroxide Absorbed Diphtheria Tetanus Toxoid and Pertussis Vaccine combined	18	In cold place.
6.	Aluminium Phosphate Absorbed Diphtheria Toxoid	24	In cold place.
7.	Aluminium Phosphate Absorbed Diphtheria and Tetanus Toxoid	24	In cold place.
8.	Aluminium Phosphate Absorbed Diphtheria Toxoid Tetanus Toxoid and Pertussis Vaccine combined	18	In cold place.
9.	Diagnostic Diphtheria Toxin (Schick Test)	12	In cold place.
10.	Cobra Venom in Solution	3	Between 2°C and 5°C protected from light.
11.	Diphtheria Toxoid	24	In cold place.
12.	Inactivated Diagnostic Diphtheria Toxin	12	In cold place.
13.	Liquid Serum	12	Between 2°C and 10°C preferable at the lower limit.
14.	Lyophilised Anti-Snake Venom Serum	60	
15.	Lyophilised Schick Test Toxin and control	60	
16.	Old Tuberculin	60	In cold place.
17.	Thrombin (Bovine Original)	36	In cold place.
[1257][18.	Tetanus Toxoid	36	In cold place.]
19.	Tuberculin PPD	60	In cold place.
OTHER VACCINES			
1.	Alum Precipitated Pertussis Vaccine	18	In cold place.
[1258][2.	BCG Vaccine	24	In cold place.]
3.	Cholera Vaccine	18	In cold place.
4.	DHL Vaccine (For Dog)	12	In cold place.
5.	Measles Vaccine	24	In cold place.
6.	Plague Vaccine	36	In cold place.
7.	Polio Vaccine	24	When stored at minus 20°C.
		6	When stored at Zero°C.

		3	When stored at 4°C.
8.	Rabies Vaccine	6	In cold place.
9.	Typhoid Vaccine	18	In cold place.
10.	Typhoid and Para Typhoid Vaccine	18	In cold place.
11.	Typhoid Para Typhoid A and B Vaccine	18	In cold place.
12.	Typhoid Para Typhoid A, B and C Vaccine	18	In cold place.
13.	Typhoid Para Typhoid A, B and C and Tetanus Vaccine	18	In cold place.
14.	Typhus Vaccine	12	In cold place.
15.	Yellow Fever Vaccine	12	In cold place.
[1259][16.	Anti-Rabies Vaccine (Cell Culture)	24	In cold place.]

ANTI TOXIN		
(For Serum Extracted preparations) 20% Excess potency	12	In cold place.
30% Excess potency	24	In cold place.
40% Excess potency	36	In cold place.
50% Excess potency	48	In cold place.
(for enzyme preparations) 5% Excess potency	12	In cold place.
10% Excess potency	24	In cold place.
15% Excess potency	36	In cold place.
20% Excess potency	48	In cold place.

MISCELLANEOUS DRUGS			
[1260][1.	Adrenaline for Injection	12	[As prescribed in Indian Pharmacopoeia]
2.	Chorionic Gonadotrophin for Injection (Lyopholised)	36	At temperature not exceeding 20°C
3.	Corticotrophin	24	In cold place.
4.	Corticotrophin Lyophilised	36	In cold place.
5.	Heparin Injection	36	In a cold place.

6.	Liquid Extract of Ergot	12	In cold place.
7.	Liver Extract Crude Injection	24	In a cold place.
8.	Oxytocin Injection	24	In cold place.
9.	Paraldehyde Injection	6	In cool place protected from light.
10.	Pituitary Injection	24	In cold place.
11.	Vasopressin Injection	24	In cold place.

Note: (1) The term “cool place" means place having a temperature between 10°C and 25°C.

(2) The term "cool place" means a place having a temperature not exceeding 8°C.

(3) Capsules should be kept in a well-closed container at temperature not exceeding 30°C.

(4) Wherever condition of storage is not specified in Column 4, it may be stored under normal room temperature.]

[1261][SCHEDULE P I

(*See* rule 109)

PACK SIZES OF DRUGS

Name of the Drug	Dosage form	Pack Size
(1)	(2)	(3)
Albendazole	Suspension	10 ml.
Atenolol	Tablets	14
Anti-Haemmorhoidal Topicals	Rectal Capsules	20
Aspirin (Low Dose)	Tablets	14
Cholecalciferol or Ergocalciferol	Granules	1 gm. Sachet
Ciclopiroxolamine	Vaginal Cream	30 gms.
Catalin	Ophthalmic drops	15 ml.
Famotidine	Tablets	14
[1342][ommitted]		
[1342][ommitted]		

Name of the Drug	Dosage form	Pack Size
Isoniazide	Syrup	200 ml.
Ipecacuanha	Syrup	10 ml.
Oral Rehydration Salt (ORS)	Powder	Pouches to be reconstituted to one litre in one pack or in 5 unit dose sachets in one pack.
Piperazine	Granules	5 gm.
	Syrup	30 ml.
Pyrantel Pamoate	syrup	8 ml. or 10 ml.
Potassium Chloride	Syrup	60 ml. and 200 ml.
Progestogen Qestrogen (Combinations for Oral Contraception)	Tablets	21 or 22 with or without 7 placebo
Roxatidine Acetate Hydrochloride	Tablets	14
Vitamine A Oral Drops	Drops	7.5 ml.]
[1262][Co-trimoxazole	Suspension	50 ml.
Haloperidol	Oral Solution	15 ml.
Loxapine	Oral Liquid Concentrate	15 ml.]

[1263]**[SCHEDULE Q**

[1263]**[***]**

[1264]**[SCHEDULE R**

(See rule 125)

STANDARDS FOR CONDOMS MADE OF RUBBER LATEX INTENDED FOR SINGLE USE AND OTHER MECHANICAL CONTRACEPTIVE

I. Condoms

1. Description—Condoms consist of cylindrical rubber sheaths with one end open. The open end shall terminate with an integral rim. The closed end may have a receptacle. They may be supplied rolled and shall be free from tackiness and shall be capable of being unrolled readily.

2. Materials—(1) Condoms shall be manufactured from good quality rubber latex and shall be free from embedded grit and shall be opaque or translucent prior to the application of dusting materials or lubricants;

(2) The rubber latex, colours used and any dusting materials or lubricants applied to the condoms shall neither contain nor liberate substances which are known to have toxic or other harmful effects under normal conditions of vise. Any dusting material or lubricant or colour used shall not have deleterious effect on the condoms or be harmful to the users.

3. Procedure for sampling during production—(1) Specimens constituting the test samples shall be taken at random successively from each quantum of production that is, from the quantity produced from the same finished rubber latex and under the same processing and finishing conditions of manufacture and samples from each quantum shall be tested separately to ascertain conformity of quantum with the specified requirements in accordance with the tests described in this Schedule.

(2) (a) The number of samples drawn from each quantum shall not be less than 0.5 per cent of the number.

(b) The number of samples drawn from each quantum shall be tested for Burst Volume and Pressure Test and Water Leakage Test in accordance with the method prescribed in paras 9 and 10 of this Schedule; 75 per cent of the samples drawn will be tested for Water Leakage Test and 25 per cent will be tested for Burst Volume and Pressure Test;

(c) The number of test samples 'N' and the number of rejected samples 'R' from a sequence of production quanta shall be recorded in a register. The cumulative total of test samples 'N' and the cumulative total of rejects 'R' from the test shall be recorded and the condoms shall be deemed to comply with the requirements if the cumulative total of rejects 'R' is not more than [1265][0.0025N + 3 x √0.0025N] for Water Leakage Test, and [1265][0.01N + 3 x √0.015N] for Burst Volume and Pressure Test.

(3) Each unit of 100 test samples shall be distributed for the various tests as follows:—

25 for Burst Volume Pressure Test, and;

75 for Water Leakage Test.

(4) Where the number of test samples is a multiple of 100 the distribution scale mentioned above shall be prorated.

(5) If the cumulative total of samples rejected exceeds the number of allowables at any point in the sequence of quanta, the quantum at which this occurs shall be liable to rejection. The assessment of quality of further production quanta shall include all previous test results starting from Quantum Number 1 and approval of production shall be in suspense until the condition required by the scheme is again fulfilled.

(6) At least one sample shall be taken at random from each production quantum not exceeding 10,000 condoms and shall satisfy all requirements regarding dimensions as specified in paragraph 8 of this Schedule.

4. Procedure for sampling and testing of finished products by a manufacturer.—(A) *Water Leakage Test*—(1) Statistical sampling for quality control assessment of the finished product in respect of water leakage test shall be done in accordance with the plant set out in Annexure I to this Schedule.

(2) A test sample failing in the above test is to be considered as defective. If the cumulative total of rejects 'R' is found to be equal to or greater than the number shown against 'R' in Annexure-I, the batch or lot shall be declared as not of standard quality.

(B) *Bursting Volume and Pressure Test*—(1) Sample condoms shall be tested for Bursting Volume and Pressure Test. Statistical sampling for this test shall be done in accordance with the plan set out in Annexure III to this Schedule.

Condom shall not leak or burst at a volume of less than that specified or at a pressure less than 1.0 kpa (guage), when tested as per paragraph 9, both before and after oven conditioning as specified in Annexure V. Bursting Volume minimum limit in litres shall be equal to:

$$\frac{[\text{mean condom width (mm)}^2]}{151.8}$$ rounded to the nearest 0.5 litre.

(2) A test sample failing in the above test is to considered defective. If the cumulative total of rejects 'R' is found to be equal to or greater than the number shown against 'R' in Annexure III, the batch or lot shall be declared as not of standard quality.

(C) Dimensions—At least two samples from the lot or batch shall satisfy the requirements regarding dimensions as specified in paragraph 8 of this Schedule.

5. Procedure for sampling and testing of condoms by a purchaser.—

(A) Wafer *Leakage Test.*—(1) Statistical sampling of condoms by a purchaser for Water Leakage Test shall be done in accordance with the pant set out in Annexure II to this Schedule.

(2) A test sample failing in the above test is to be considered as defective. If the cumulative total of rejects 'R' is found to be equal to or greater than the number shown against 'R' in Annexure-II, the batch or lot shall be declared as not of standard quality.

(B) *Bursting Volume and Pressure Test.*—(1) Sample condoms shall be tested for Bursting Volume and Pressure Test. Statistical sampling for this test shall be done in accordance with the plan set out in Annexure III to this Schedule. If the cumulative total of rejects 'R' is found to be equal to or greater than the number shown against 'R' in Annexure-III, the batch or lot shall be declared as not of standard quality.

Condom shall not leak or burst at a volume of less than that specified or at a pressure less than 1.0 kpa (guage), when tested as specified in paragraph 9, both before and after oven conditioning as specified in Annexure V. Bursting Volume minimum limit in litres shall be equal to

$$\frac{[\text{mean condom width (mm)}^2]}{151.8}$$ - rounded to the nearest 0.5 litre.

(C) Dimensions.—At least two samples from the lot or batch shall satisfy the requirements regarding dimensions as specified in paragraph 8 of this Schedule.

6. Sampling plan for a Drugs Inspector—(1) Where an Inspector under the Act desires to take for test samples from the premises of manufacturer or a

distribution depot; twenty containers from each batch of production may be selected by him on a random basis and from each of the containers, five samples shall be taken. The hundred samples so selected shall be distributed for various tests as specified in paragraph 7 of this Schedule. In case, the number of containers is less than twenty, the number of samples to be taken from each container shall be proportionately increased.

(2) Where an Inspector under the Act, desires to take samples from a sale premises, he shall take hundred samples from each batch of production in accordance with the procedure as specified in sub-paragraph (1).

7. Sampled condoms drawn under sub-paragraph (1) shall be distributed for the various tests as follows:—

Two samples for thickness, length and width;
Forty five samples for Water Leakage Test;
Forty five samples for Bursting Volume and Pressure Test; and
Eight samples as reserve.

The samples shall be declared as not of standard quality, if : (i) the number of condoms found defective in the Water Leakage Test exceeds one; (ii) the number of condoms found defective in Bursting Volume and Pressure Test exceeds two; (iii) samples fail to conform to the requirements of dimensions as specified in paragraph 8 of this Schedule.

8. Dimensions—(1) The length when unrolled (excluding test) shall be not less than—

(i) 170 mm

(ii) 180 mm

(2) The width of a condom when laid flat and measured at any point within 85 mm from the open end shall be:—

(i) 49 ± 2 mm for 170mm length

(ii) 53 ± 2 mm for 180mm length

(3) The single wall thickness of a condom when measured at three points, one at 30 + 2 mm from the open end, 30 + 5 mm from the close and excluding the reservoir tip and at the mid distance between these two point shall be from 0.045 mm to 0.075 mm.

Note 1.—The single-wall thickness shall be determined with a suitable micrometer dial guage graduated in intervals of 0.01 mm.

Note 2.—Condoms shall, prior to the measurements of thickness, have the dusting powder or the lubricant or both removed by means of water or Isopropanol.

9. Bursting Volume and Pressure Test—Determination of Bursting Volume and Pressure Test shall be done as specified in Annexure IV.

10. Water Leakage Test—Unroll the condom and fit the open end on a suitable mount, the condom thus being suspended open end upwards. Fill it with 300 ml water at room temperature and inspect it after a period of least 1 minute for leakage upto 25 mm from the open end. If raise the closed end until water level reaches this distance. After atleast 1 minute inspect the newly-wetted part of the condom for leakage. The condom shall be deemed to be defective if it bursts during test or shows any evidence of leakage or seepage or micro-droplets or does not hold 300 ml. water.

11. Quantity of Lubricant—(1) The condoms shall be dressed with silicone lubricant. The quantity required on each individual condom should not be less than 200 gm. and the minimum viscosity shall be 200 centistokes.

(2) Lubricated condoms in individual foil packages shall be weighed on an Analytical Balance. Each condom shall be removed from its foil package and both condom and its foil package shall be washed in denatured ethanol or isopropanol, dried and then weighed again. All weights shall be recorded to the nearest milligram (mg). Compliance with the requirement shall be determined by subtracting the weight of the washed and dried condom and its foil package from the weight of the sample condom in individual foil package prior to the removal of lubricant. Washing and drying may be repeated upto a total of four times if the lubricant quantity is less than the required minimum.

(3) At least thirteen samples shall be drawn from the lot or batch and the samples shall satisfy the requirements regarding the quantity of lubricant.

12. Colour Fastness—Not less than ten samples taken at random from each batch of coloured condoms shall pass the following test for colour fastness, namely:—

Thoroughly wet inside and outside of the condom with distilled water. Make no attempt to remove any dusting material or lubricant. Wrap the wet condom in white absorbent paper so that the largest possible surface area of the condom is in contact with the paper and seal the whole in a suitable container to prevent loss of moisture. Allow the container and its contents to stand for 16 hours to 24 hours at room temperature. After removing the absorbent paper from the container, examine it visually in natural day-light for a indication of staining. No part of the absorbent paper shall be stained. If there is any indication of staining of the absorbent paper by any colouring agent present in any of the condoms or any dusting material or lubricant, the entire batch shall be declared to be not of standard quality.

13. Labelling, packing and storage—(1) The condoms shall be individually wrapped and sealed in laminates containing atleast eight microns of aluminium foil. The individual condom shall be packed in square (non-squeeze condition)/rectangular aluminium foil. The packing shall protect the condoms from contamination and mechanical damage. The smallest packing offered to the consumer shall bear a clear permanent marking with the following particulars, namely:—

(i) Manufacturer's name and address and the trade name of the condoms, if any;
(ii) Batch number;
(iii) Date of manufacture (Month and year only);
(iv) Date of expiry (Month and year only) which shall not be more than thirty six months from the date of manufacture;
(v) The words "For single use only"

(2) The condoms shall be stored in a cool dry place away from heat and direct sunlight.

14. Integrity of individual package seals—Sample condoms in individual packages shall be placed in a sealed, transparent container (such as laboratory Bell jar) and subjected to vacuum of 50 ± 10 kpa (gauge) for a period of one minute.

Condom packages that do not inflate or remain inflated for the period of the test shall be deemed non-compliers. In doubtful cases, the test may be repeated, and both the inflation and deflation of packages may be observed on application and removal of vacuum. An AQL of 2.5 per cent will be applied in assessing the results of this test. Thirty-two samples of condoms for a batch size less than 5 lakhs and fifty samples of condoms for batch size more them 5 lakhs shall be tested for integrity test of individual package seals and the compliance limit or acceptance number shall be not more than two or three condoms respectively.

II. Other Mechanical Contraceptive

15. Standards for other mechanical contraceptive—Standards for 'Copper T' and 'Tube Ring' shall be as laid down in Annexure VI.

[1266]**[ANNEXURE I**

[See paragraph 4(A)]

SAMPLING PLAN FOR QUALITY CONTROL OF CONDOMS AT MANUFACTURERS LEVEL

BATCH SIZE : 35001 to 1.5 LAKHS	
Single Sampling Plan	
Sample Size 200 :	AQL —0.25
	AC —1
	R —2

BATCH SIZE :150001 to 5 LAKHS	
Single Sampling Plan	
Sample Size 315 :	AQL —0.25
	AC —2
	R —3

BATCH SIZE: OVER 5 LAKHS	
Single Sampling Plan	
Sample Size 500 :	AQL —0.25
	AC —3
	R —4

Note.—AQL denotes Acceptance Quality Level;

AC denotes Acceptance Number *i.e.*, the maximum allowable number of defectives for acceptance of the Batch; and

R denotes Rejection Number *i.e.*, minimum number of defectives for rejection of the Batch

ANNEXURE II

[See paragraph 5(A)]

SAMPLING PLAN FOR QUALITY CONTROL OF CONDOMS AT PURCHASER'S LEVEL

BATCH SIZE : 35001 to 1.5 LAKHS

Single Sampling Plan	
Sample Size 200 :	AQL —0.25
	AC —1
	R —2

BATCH SIZE :150001 to 5 LAKHS	
Single Sampling Plan	
Sample Size 315 :	AQL —0.25
	AC —2
	R —3

BATCH SIZE: OVER 5 LAKHS	
Single Sampling Plan	
Sample Size 500 :	AQL —0.25
	AC —3
	R —4

Note.—AQL denotes Acceptance Quality Level :

AC denotes Acceptance Number *i.e.*, the maximum allowable number of defectives for acceptance of the Batch; and

R denotes Rejection Number *i.e.*, minimum number of defectives for rejection of the Batch.

ANNEXURE III

[See paragraphs 4(B) and 5(B)]

SAMPLING PLAN FOR BURSTING VOLUME AND PRESSURE TEST

BATCH SIZE : 35001 to 1.5 LAKHS	
Single Sampling Plan	
Sample Size 200 :	AQL- 1.5
	AC —7
	R —8

BATCH SIZE :150001 to 5 LAKHS	
Single Sampling Plan	
Sample Size 315 :	AQL —1.5
	AC —10
	R —11

BATCH SIZE: OVER 5 LAKHS	
Single Sampling Plan	
Sample Size 500 :	AQL —1.5
	AC —14
	R —15

Note.—AQL denotes Acceptance Quality Level ;

AC denotes Acceptance Number *i.e.*, the maximum allowable number of defectives for acceptance of the Batch; and

R denotes Rejection Number *i.e.*, minimum number of defectives for rejection of the Batch.]

ANNEXURE IV

(See paragraphs 9)

DETERMINATION OF BURSTING VOLUME AND PRESSURE

1. Principle—Inflation of a constant length of the condom with air and recording the volume and pressure at the moment of bursting.

2. Apparatus— (1) Apparatus suitable for inflating the condom with clean air at a specified rate and provided with equipment for measuring volume and pressure.

(2) Suitable mount for fitting the condoms to the apparatus as shown in the figure annexed.

(3) Rod, 140 mm in length having a smooth sphere 20 mm in diameter at its top (see the figure) for hanging the unrolled condom when fixed to the apparatus.

3. Procedure— (1) Unroll the condom, hang it on the rod (2.3), affix to the mount (2.2) and inflate with air at a rate of 0.4 to 0.5 litre/Sec (24 to 30 litres/min.).

(2) Measure and note the Bursting Volume, in litres rounded to the nearest 0.5 litre and the bursting pressure, in kilopascals rounded to the nearest 0.1 kpa.

4. Test report—The test report shall include the following particulars :

(a) the identification of the sample;

(b) the Bursting Volume and Bursting Pressure of each tested condom;

(c) the date of testing.

ANNEXURE V

[*(See* paragraphs 4(B) and 5(B)]

OVEN CONDITIONING

1. Principle of the Method—The test consists in subjecting test samples to controlled deterioration by air at an elevated temperature and at atmospheric pressure after which Burst Volume and Pressure limits are measured.

2. Apparatus—The air oven shall be of such a size that the total volume of the test samples does not exceed 10 per cent of the free air space of the oven. Provision shall be made for slow circulation of air in the oven of not less than three changes and not more than ten changes per hour. The temperature of the oven shall be thermostatically controlled so that the test samples are kept within + 2°C of the specified ageing temperature. A thermometer shall be placed near the centre of the ageing test samples to record the actual ageing temperature.

Note.—Copper or Copper alloys shall not be used for the material of construction of the oven prescribed.

3. Test Sample—The foil laminations of individual packages should remain intact throughout all laboratory handling including over conditioning.

4. Temperature of the oven—Maintain the oven at 70 + 2°C.

5. Duration of test—96 Hours.

6. Procedure—Condition the requisite number of unopened packages of rubber condoms in the oven at 70 ± 2°C for 96 Hrs. After heating, keep the packages 23 + 5°C for atleast 12 hours but not more than 96 Hours. Open the packages and examine conditioned condoms for tackiness, brittleness, or other signs of deterioration. Within 96 hours but not sooner than 12 hours after conditioning, do the Bursting Volume and Pressure Test as described in this Schedule.

ANNEXURE VI

(*See* paragraph 15)

1. Standards for Copper T (200B) (IS-12418) (Part 4)-1991-UDC 615.477.87— Contraceptive Device Copper T (200 B) shall conform to the Indian Standards laid down from time to time by the Bureau of Indian Standards.

2. Standards for Contraceptive Tubal Ring (IS 13009:1990-UDC 615.472.6:611.656)— Contraceptive Device Tubal Ring shall conform to the Indian Standards laid down from time to time by the Bureau of Indian Standards.]

[1267][SCHEDULE R1

(See rules 109A, 109B, 109C and and 125A)

The medical devices shall conform to the Indian Standards laid down from time to time by the Bureau of Indian Standards. If there are no Bureau of Indian Standards then it shall conform to the International Standards, like International Organisation for Standardisation, or other International Pharmacopeia Standards and such other standards as may be specified for this purpose. In case national or international standards are not available, the device shall conform to the manufacturer's validated standards.]

SCHEDULE S

[1268][***]

[1269][SCHEDULE T

(See Rule 157)

GOOD MANUFACTURING PRACTICES FOR AYURVEDIC SIDDHA AND UNANI MEDICINES

The Good Manufacturing Practices (GMP) are prescribed as follows in Part I and Part II to ensure:—

(i) raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination;

(ii) the manufacturing process is as has been prescribed to maintain the standards;

(iii) adequate quality control measures are adopted;

(iv) the manufactured drug which is released for sale is of acceptable quality; and

(v) to achieve the objectives listed above, each licencee shall evolve methodology and procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection. However, under IMCC Act, 1970 registered Vaidyas, Siddhas and Hakeems who prepare medicines on their own to dispense to their patients and not selling such drugs in the market are exempted from the purview of Good Manufacturing Practices (GMP).

PART I
GOOD MANUFACTURING PRACTICES

1.1 Factory Premises:

The manufacturing plant should have adequate space for—

(i) receiving and storing raw material;
(ii) manufacturing process areas;
(iii) quality control section;
(iv) finished goods store;
(v) office; and
(vi) rejected goods/drugs store.

1.1 General Requirements:

1.1(A) *Location and surroundings*.—The factory buildings for manufacture of Ayurveda, Siddha and Unani medicines shall be so situated and shall have such construction as to avoid contamination from open sewerage, drain, public lavatory or any factory which produces disagreeable or obnoxious odour or fumes or excessive soot, dust or smoke.

1.1(B) *Buildings*.—The building used for factory shall be such as to permit production of drugs under hygienic conditions and should be free from cobwebs and insects/rodents. It should have adequate provision of light and ventilation. The floor and the walls should not be damp or moist. The premises used for manufacturing, processing, packaging and labelling will be in conformity with the provisions of the Factory Act. It shall be located so as to be:—

(I) Compatible with other manufacturing operations that may be carried out in the same or adjacent premises.

(II) Adequately provided with working space to allow orderly and logical placement of equipment and materials to avoid the risk of mix up between different drugs or components thereof and control the possibility of cross contamination by other drugs or substances and avoid the risk of omission of any manufacturing or control step.

(III) Designed, constructed and maintained to prevent entry of insects and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks and permit easy cleaning and disinfection. The walls of the room in which the manufacturing operations are carried out shall be impervious to and be capable of being kept clean. The flooring shall be smooth and even and shall be such as not to permit retention or accumulation of dust or waste products.

(IV) Provided with proper drainage system in the processing area. The sanitary fitting and electrical fixtures in the manufacturing area shall be proper and safe.

(V) Furnace/Bhatti section could be covered with tin roof and proper ventilation, but sufficient care should be taken to prevent flies and dust.

(VI) There should be fire safety measures and proper exits should be there.

(VII) Drying space.—There be separate space for drying of raw material, in process medicine or medicines require drying before packing. This space will be protected from flies/insects/dusts etc., by proper flooring, wire-mach window, glass pans or other material.

1.1(C) *Water Supply*.—The water used in manufacture shall be pure and of potable quality. Adequate provision of water for washing the premises shall be made.

1.1(D) *Disposal of waste*.—From the manufacturing sections and laboratories the waste water and the residues which might be prejudicial to the workers or public health shall be disposed off.

1.1(E) *Container's cleaning*.—In factories where operations involving the use of containers such as bottles, vials and jars are conducted, there shall be adequate arrangements separated from the manufacturing operations for washing, cleaning and drying of such containers.

1.1(F) *Stores.*—Storage should have proper ventilation and shall be free from dampness. It should provide independent adequate space for storage of different types of material, such as raw material, packaging material and finished products.

1.1(F)(A) *Raw materials.*—All raw materials procured for manufacturing will be stored in the raw materials store. The manufacture based on the experience and the characteristics of the particular raw material used in Ayurveda, Siddha and Unani system shall decide the use of appropriate containers which would protect quality of the raw material as well as prevent it from damage due to dampness, microbiological contamination or rodent and

insect infestation, etc. If certain raw materials require such controlled environmental conditions, the raw materials stores may be sub-divided with proper enclosures to provide such conditions by suitable cabinization. While designing such containers, cabins or areas in the raw materials stores, care may be taken to handle the following different categories of raw materials:—

(1) Raw material of metallic origin;
(2) Raw material of mineral origin;
(3) Raw material from animal source;
(4) Fresh Herbs;
(5) Dry Herbs or plant parts;
(6) Excipients; etc.;
(7) Volatile oils/perfumes & flavours; and
(8) Plant concentrates extracts and exudates/resins.

Each container used for raw material storage shall be properly identified with the label which indicates name of the raw material, source of supply and will also clearly state the status of raw material such as "UNDER TEST" or "APPROVED" or "REJECTED" The labels shall further indicate the identity of the particular supply in (be form of Batch No. or Lot No. and the date of receipt of the consignment.

All the raw materials shall be sampled and got tested either by the in-house Ayurvedic, Siddha and Unani experts (Quality control technical person) or by the laboratories approved by the Government and shall be used only on approval after verifying. The rejected raw material should be removed from other raw material store and should be kept in separate room. Procedure of 'First in first out' should be adopted for raw materials wherever necessary. Records of the receipt, testing and approval or rejection and use of raw material shall be maintained.

1.1(F)(B) *Packaging Materials.*—All packaging materials such as bottles, jars, capsules etc. shall be stored properly. All containers and closure shall be adequately cleaned and dried before packing the products.

1.1(F)(C) *Finished Goods Stores.*—The finished goods transferred from the production area after proper packaging shall be stored in the finished goods stores within an area marked "Quarantine". After the quality control laboratory and the experts have checked the correctness of finished goods with reference to

its packing/labelling as well as the finished product quality as prescribed, then it will be moved to "Approved Finished Goods Stock" area. Only approved finished goods shall be dispatched as per marketing requirements. Distribution records shall be maintained as required.

If any Ayurvedic, Siddha and Unani drug needs special storage conditions, finished goods store shall provide necessary environmental requirements.

1.1(G) *Working space.*—The manufacturing area shall provide adequate space (manufacture and quality control) for orderly placement of equipment and material used in any of the operations for which these are employed so as to facilitate easy and safe working and to minimize or to eliminate any risk of mix-up between different dines, raw materials and to .prevent the possibility of cross contamination of one drug by another drug that is manufactured, stored or handled in the same premises.

1.1(H) *Health Clothing, Sanitation and Hygiene of Workers.—All* workers employed in the Factory shall be free from contagious diseases. The clothing of the workers shall consist of proper, uniform suitable to the nature of work and the climate and shall be clean. The uniform shall also include cloth or synthetic covering for hands, feet and head wherever required. Adequate facilities for personal cleanliness such as clean towels, soap and scrubbing brushes shall be provided. Separate provision shall be made for lavatories to be used by men and women, and such lavatories shall be located at places separated from the processing rooms. Workers will also be provided facilities for changing their clothes and to keep their personal belongings.

1.1(I) *Medical Services.*—The manufacturer shall also provide—

(a) adequate facilities for first aid;

(b) medical examination of workers at the time of employment and periodical check up thereafter by a physician once a year, with particular attention being devoted to freedom from infections. Records thereof shall be maintained.

1.1(J) *Machinery and Equipments.*—For carrying out manufacturing depending on the size of operation and the nature of product manufactured, suitable equipment either manually operated or operated semi-automatically

(Electrical or steam based) or fully automatic machinery shall be made available. These may include machines for use in the process of manufacture such as crushing, grinding, powdering, boiling, mashing, burning, roasting, filtering, drying, filling, labelling and packing etc. To ensure ease in movement of workers and orderliness in operations a suitably adequate space will be ensured between two machines or rows of machines. These machinery and equipments have to be properly installed and maintained with proper cleaning. List of equipments and machinery recommended is indicated in Part IIA.

Proper standard operational procedures (SOPs) for cleaning, maintaining and performance of every machine should be laid down.

1.1(K) *Batch Manufacturing Records.*—The licencee shall maintain batch manufacturing record of each batch of Ayurvedic, Siddha and Unani drugs manufactured irrespective of the type of product manufactured (classical preparation or patent and proprietary medicines). Manufacturing records are required to provide an account of the list of raw materials and their quantities obtained from the store, tests conducted during the various stages of manufacture like taste, colour, physical characteristics and chemical tests as may be necessary or indicated in the approved books of Ayurveda, Siddha and Unani mentioned in the First Schedule of the Drugs and Cosmetics Act, 1940 (23 of 1940). These tests may include any in-house or pharmacopoeial test adopted by the manufacturer in the raw material or in the process material and in the finished product. These records shall be duly signed by Production and Quality Control Personnel respectively. Details of transfer of manufactured drug to the finished products store including dates and quantity of drugs transferred along with record of testing of the finished product, if any, and packaging, records shall be maintained. Only after the manufactured drugs have been verified and accepted quality shall be allowed to be cleared for sale.

It should be essential to maintain the record of date, manpower, machine and equipments used and to keep in process record of various shodhana, Bhavana, burning in fire and specific grindings in terms of internal use.

1.1 (L) *Distribution Records.*—Records of sale and distribution of each batch of Ayurveda, Siddha and Unani Drugs shall be maintained in order to facilitate prompt and complete recall of the batch, if necessary.

The duration of record keeping should be the date of expiry of the batch. Certain category of Ayurvedic, Siddha and Unani medicines like Bhasma, Rasa, Kupi-pakva, Parpati, Sindura, Karpu/uppu/puran, Kushta, Asava-arista, etc., do not have expiry date, in contrast their efficacy increases with the passage of time. Hence, records need to be maintained upto five years of the exhausting of stock.

1.1 (M) *Record of Market Complaints*.—Manufacturers shall maintain a register to record all reports of market complaints received regarding the products sold in the market. The manufacturer shall enter all data received on such market complaints, investigations carried out by the manufacturers regarding the complaint as well as any corrective action initiated to prevent recurrence of such market complaints shall also be recorded. Once in a period of six months the manufacturer shall submit the record of such complaints to the licensing authority. The Register shall also be available for inspection during any inspection of the premises.

Report of any adverse reaction resulting from the use of Ayurvedic, Siddha and Unani drugs shall also be maintained in a separate register by each manufacturer. The manufacturer shall investigate any of the adverse reaction to find if the same is due to any defect in the product, and whether such reactions are already reported in the literature or it is a new observation.

1.1(N) *Quality Control*.—Every licensee is required lo provide facility for quality control section in his own premises or through Government approved testing laboratory. The test shall be as per the Ayurveda, Siddha and Unani pharmacopoeial standard. Where the tests are not available, the test should be performed according to the manufacturers's specification or other information available. The quality control section shall verify all the raw materials, monitor in process, quality checks and control the quality of finished product being released to finished goods store/warehouse. Preferably for such quality control there will be a separate expert. The quality control section shall have the following facilities:—

(1) There should be 150 sq. feet area for quality control section.

(2) For identification of raw drugs, reference books and reference sampies should be maintained.

(3) Manufacturing record should be maintained for the various processes.

(4) To verify the finished products, controlled samples of furnished products of each batch will be kept for 3 years.

(5) To supervise and monitor adequacy of conditions under which raw materials, semi-finished products and finished products are stored.

(6) Keep record in establishing shelf life and storage requirements for the drugs.

(7) Manufacturers who are manufacturing patent proprietory Ayurveda, Siddha and Unani medicines shall provide their own specification and control references in respect of such formulated drugs.

(8) The record of specific method and procedure preparation that is, "Bhavana" "Mardana" and "Puta" and the record of every process carried out by the manufacturer shall be maintained.

(9) The standards for identity, purity and strength as given in respective pharmacopoeias of Ayurveda, Siddha and Unani systems of medicines published by Government of India shall be complied with.

(10) All raw materials will be monitored for fungal, bacterial contamination with a view to minimise such contamination.

(11) Quality control section will have a minimum of—

[1270][(i) (a) Expert in Ayurveda or Siddha or Unani medicine who possess a degree qualification recognized under Schedule II of Indian Medicine Central Council Act, 1970;

(b)Chemist, who shall possess at least a Bachelor Degree in Science or Pharmacy or Pharmacy (Ayurveda) awarded by a recognized University; and

(c) Botanist (Pharmacognosist), who shall possess at least a Bachelor Degree in Science (Medical) or Pharmacy or Pharmacy (Ayurveda) awarded by a recognized University:]

(ii) The manufacturing unit shall have a quality control section as explained under section 35(ii). Alternatively, these quality control provisions will be met by getting testing etc., from a recognised laboratory for Ayurveda, Siddha and Unani drugs; under rule 160A of the Drugs and Cosmetics Act. The manufacturing company will maintain all the records of various tests got done from outside recognised laboratory.

(iii) List of equipments recommended is indicated in Part II C.

1.2 Requirement for Sterile Product:

1.2(A) *Manufacturing Areas*.—For the manufacture of sterile Ayurvedic, Unani and Siddha drugs, separate enclosed areas specifically designed for the purpose shall be provided. These areas shall be provided with air locks for entry and shall be essentially dust free and ventilated with an air supply. For all areas where aseptic manufacture has to be carried out, air supply shall be filtered through bacteria retaining filters (HEPA Filters) and shall be at a pressure higher than in the adjacent areas. The filters shall be checked for performance on installation and periodically thereafter the record of checks shall be maintained. All the surfaces in sterile manufacturing areas shall be designed to facilitate cleaning and disinfection. For sterile manufacturing routine microbial counts of all Ayurvedic, Siddha and Unani drug manufacturing areas shall be carried out during operations. Results of such count shall be checked against established in-house standards and record maintained.

Access to manufacturing areas shall be restricted to minimum number of authorised personnel. Special procedure to be followed for entering and leaving the manufacturing areas shall be written down and displayed.

For the manufacturing of Ayurvedic, Siddha and Unani drug that can be sterilised in their final containers, the design of the areas shall preclude the possibility of the products intended for sterilisation being mixed with or taken to be products already sterilised. In case of terminally sterilised products, the design of the areas shall preclude the possibility of mix up between non-sterile and sterile products.

1.2(B) *Precautions against contamination and mix*.—

(a) Carrying out manufacturing operations in a separate block of adequately isolated building or operating in an isolated enclosure within the building.

(b) Using appropriate pressure differential in the process area.

(c) Providing a suitable exhaust system.

(d) Designing laminar flow sterile air systems for sterile products.

(e) The germicidal efficiency of UV lamps shall be checked and recorded indicating the burning hours or checked using intensity.

(f) Individual containers of liquids, and ophthalmic solutions shall be examined against black-white background fitted with diffused light after filling to ensure freedom from contamination with foreign suspended matter.

(g) Expert technical staff approved by the Licensing Authority shall check and compare actual yield against theoretical yield before final distribution of the batch.

All process controls as required under master formula including room temperature, relative humidity, volume filled, leakage and clarity shall be checked and recorded.

PART II

A. LIST OF RECOMMENDED MACHINERY, EQUIPMENT AND MINIMUM MANUFACTURING PREMISES REQUIRED FOR THE MANUFACTURE OF VARIOUS CATEGORIES OF AYURVEDIC, SIDDHA SYSTEM OF MEDICINES

One machine indicated for one category of medicine could be used for the manufacturing of other category of medicine also. Similarly some of the manufacturing areas like powdering, furnace, packing of liquids and Avaleha, Paks, could also be shared for these items.

S.No.	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended
(1)	(2)	(3)	(4)
		1200 square feet covered area with separate cabins partitions for each activity. If Unani medicines are manufactured in same premises an additional area of 400 sq. feet will be required.	
1.	Anjana/Pisti	100 sq.feet	Karel/machanised/motorised kharel, End runner/Ball-Mill Sieves/Shifier
2.	Churna/Nasya/Manjan/ Lepal/Kwath Churn	200 sq. feet	Grinder/Disintegrator/ Pulverizer/Powder mixer/ sieves/shifter
3.	Pills/Vatti/Gutika Matrica and tablets	100 sq.feet	Ball Mill, Mass Mixer/Powder mixer Granulator drier. Tablet compressing machine, pill/vati cutting machine, stainless steel trays/containers for storage and sugar-coating, polishing pan in case of sugar coated tablets, mechanised chattoo (for mixing of guggulu) where required.
4.	Kupi pakava/Ksara/ Parpati/LavanaBhasm a Satva/Sindura Karpu/ Uppu / Param	150 sq. feet	Bhatti, Karahi, Stainless Steel Vessels/Patila Flask, Multani Matti/Plaster of Paris, Copper Rod. Earthen container, Gaj put Bhatti. Muffle furnace (Electri-cally operated) End/ Edge Runner, Exhaust Fan, Wooden /S.S. Spatula
5.	Kajal	100 sq. feet	Earthen lamps for collection of Kajal. Tipple Roller Mill, End Runner, Sieves, S.S. Patila, Filling/ packing and manufacturing room should be provided with exhaust fan and ultra violet lamps.
6.	Capsules	100 sq.feet	Air Conditioner, Dehumidifier,

S.No.	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended
(1)	(2)	(3)	(4)
			hygrometer. Thermometer, Cap-sule filling machine and chemical balance
7.	Ointment/Marham Pasai	100 sq.feet	Tube filling machine, Crimping Machine /Ointment Mixer, End Runner/Mill (Where required),S.S. Storage Container S.S. Patila.
8.	Pak/Avaleh/Khand/Modak/ Lakayam	100 sq.feet	Bhatti section fitted with exhaust fan and should be fly proof, Iron Kadahi/S.S Patila and S.S. storage container
9.	Panak Syrup/ Pravahi Kwath Manapaku	150 sq. feet	Tinctum press, exhaust fan fitted and fly proof, Bhatti section. Bottle washing machine, filter press/Gravity filter liquid filling machine, P.P. Capping Machine
10.	Asava/Aristha	200 sq. feet	Same as mentioned above. Fermentation tanks containers and Distillation plant where necessary, Filler Press
11.	Sura	100 sq.feet	Same as mentioned above plus Distillation plant and Transfer pump
12.	Ark-Tinir	100 sq. feet	Maceration tank, Distillation plant, Liquid filling tank with tap/gravity Filter/Filler press Visual inspection box
13.	Tail/Ghrit Ney	100 sq. feet	Bhatti, Kadahi/S.S. Patila S.S. Storage containers, Filteration equipment, filling tank with tap/Liquid filling machine
14.	Aschyotan/Netra Malham Panir Karn Bindu, Nasabindu	100. sq. feet	Hot air oven electrically heated with thermostatic control, kettle gas or electrically heated with suitable mixing arrangements

S.No.	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended
(1)	(2)	(3)	(4)
			collation mill or ointment mill, tube filling equipment, mixing and storage tanks of stainless steel or of other suitable material sintered glass funnel, seitz filter or filter candle, liquid filling equipment, autoclave.
15.	Each manufacturing unit will have a separate area for Bhatti, furnaces, boilers, puta, etc. This will have proper ventilation, removal of smoke, prevention of flies, insects, dust etc. The furnace section could have tin roof.	200 sq. feet	

B. LIST OF MACHINERY, EQUIPMENT AND MINIMUM MANUFACTURING PREMISES REQUIRED FOR THE MANUFACTURER OF VARIOUS CATEGORIES OF UNANI SYSTEM OF MEDICINES

One machine indicated for one category of medicine could be used for the manufacturing of other category of medicine also. Similarly some of the manufacturing areas like powdering, furnace, packing of liquids could also be shared for these items.

S.No.	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended
(1)	(2)	(3)	(4)
		1200 square feet covered area with separate cabins partitions	

S.No.	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended
(1)	(2)	(3)	(4)
		for each activity. If Unani medicines are manufactured in same premises an additional area of 400 sq. feet will be required.	
1.	Itrifal Triyao/majoon/Laooq/ Jawarish Khamiras	100 sq. feet	Grinder/Pulverizer, Sieves, powder mixer (if required), S.S. Patilas, Bhatti and other accessories, Plant mixer for Khamiras
2.	Arq.	100 sq. feet	Dissilation Plant (Garembic) S.S. Storage Tank, Boiling Vessel, Gravity filter, Bottle Filling machine, Bottle washing machine, Bottle drier
3.	Habb(Pills) and tablets	100 sq. feet	Ball Mill, Mass Mixer/Powder-mixer Granulator drier, tablet compressing machine, pill/vati cutting machine, stainless steel trays/containers for storage and sugar coating polishing pan in case of sugar coated tablets, mechanised chattoo (for maxing of guggul) where required
4.	Sufoof (Powder)	200 sq. feet	Grinder /Pulveriser, Seives Trays, Scoops, Powder Mixer, (Where required)
5.	Raughan (oils) (Crushing and boiling)	100 sq. feet	Oil Expeller, S.S. Patilas, Oil filter bottle, Filling machine, Bottle drier, Bhatti
6.	Shiyaf, Surma, Kajal	100 sq. feet	End runner, mixing S.S. Vessel
7.	Marham, Zimad (Ointment)	100 sq. feet	Kharal, Bhatti, End runner, Grinder, Pulveriser, Tripple Roller Mill (if required)

S.No.	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended
(1)	(2)	(3)	(4)
8.	Qurs (Tab)	100 sq. feet	Grinder/Pulveriser, Seives, Powder Mixer, (Where needed) Gra-nulator, Drier, Tablet Compressing Machine, Die punches Trays, O.T. Apparatus, Balance with weights, Scoops, Sugar Coating Pan, polishing pan, Heater
9.	Kushta	100 sq. feet	Bhatti, Kharal, Sil Batta, Earthen pots
10.	Murabba	100 sq. feet	Aluminium Vessels 50-100 kgs. capacity, Gendna, Bhatti
11.	Capsule	100 sq. feet	Pulveriser, Powder Mixer, (Where needed), capsule filling machine, air conditioner, De-humidifier, Balance with weights, storage-containers, glass
12.	Sharbat and Jushanda	100 sq. feet	Tinctum Press, exhaust fan fitted, Bhatti section, Bottle washing machine, Filter Press, Gravity filter Liquid filling tank with tap/liquid filling machine, Hot air oven electrically heated with thermostatic control, Kettle
13.	Qutoor-e-Chashm and Marham (eye drops, eye ointment)	100 sq. feet	Hot air oven electrically heated with thermostatic control, Kettle
14.	Each manufacturing unit will have a separate area for Bhatti, furnaces, boilers,	200 sq. feet	

S.No.	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended
(1)	(2)	(3)	(4)
	putta, etc. This will have proper ventilation, removal of smoke, prevention of flies, insects, dust, etc.		

C. LIST OF EQUIPMENT RECOMMENDED FOR IN HOUSE QUALITY CONTROL SECTION

(Alternatively unit can get the testing done from the government approved laboratory)

(A) Chemistry section

1. Alcohol Determination Apparatus (complete set).
2. Volatile Oil Determination Apparatus
3. Boiling Point Determination Apparatus
4. Melting Point Determination Apparatus
5. Refractometer
6. Polarimeter
7. Viscometer
8. Tablet Disintegration Apparatus
9. Moisture Meter
10. Muffle Furnace
11. Electronic Balance
12. Magnetic Stirrer
13. Hot Air Oven
14. Refrigerator
15. Glass/Steel Distillation Apparatus
16. LPG Gas Cylinders with Burners
17. Water Bath (Temperature Controlled)
18. Heating Mantles/Hot Plates
19. TLC apparatus with all Accessories (Manual)
20. Paper Chromatography apparatus with accessories.
21. Sieve Size 10 to 120 with Sieve shaker
22. Centrifuge machine

(B) Pharmacognosy section

1. Microscope Binocular
2. Dissecting Microscope
3. Microtome
4. Physical balance
5. Aluminium Slide trays
6. Stage Micrometer
7. Camera Lucida (Prism and Mirror Type).
8. Chemicals, Glass-ware, etc.

23. De-humidifier
24. pH Meter
25. Limit Test Apparatus

[1271][D. SUPPLEMENTARY GUIDELINES FOR MANUFACTURING OF RASAUSHADHIES OR RASAMARUNTHUKAL AND KUSHTAJAT (HERBO-MINERAL-METALLIC COMPOUNDS) OF AYURVEDA, SIDDHA AND UNANI MEDICINES

These guidelines are intended to complement those provided above and should be read in conjunction with the parent guidelines. The *supplementan/ guidelines are* to provide general and minimum technical requirements for quality assurance and control in manufacturing Rasaushadhis or Rasamarunthukal and Kushtajat (Herbo-mineral-metallic formulations). These supplementary guidelines deal with Bhasmas, Sindura, Pishti, Kajjali, Khalviya Ras, Kupipakwa, Rasayan, Parpati, Potali Rasa, Satwa (of Metals and Minerals origin) Druti Parpam, Karpu, and Kushta etc. used in Ayurvedic, Siddha and Uaani Systems of medicine.

The supplementary GMP guidelines for Rasaushadhi or Rasamarunthukal and Kushtajat are needed to establish the authenticity of raw drug, minerals and metals, in-process validation and quality control parameters to ensure that these formulation are processed and prepared in accordance with classical texts and for which safety measures are complied. Only those manufacturing units which have Good Manufacturing Practices for ASU drugs and supplementary certificate of Rasaushadhies or Rasamarunthukal and Kushtajat formulations shall be allowed to manufacture the same. Supplementary Good Manufacturing Practices certificate for Rasaushadhies shall be issued by the State Licensing Authority only after thorough inspection by an expert team including Rasashstra experts nominated by the Department of AYUSH.

2. Manufacturing Process Areas.—For the manufacture of Bhasma and Kupipakawa and Rasaushadhi preparations made from metals and minerals the following specific areas shall be provided, which should be completely segregated from the production area used for preparation of plants and animal byproduct based formulation to avoid cross-contamination. The following exclusive areas are required for Rasaushadhies or Rasamarunthukal and Kushtajat:—

2.2. (a) *Bhatti or Heating Devise section for Bhasma and Rasaushadhies.*—100 Sq. feet for heating, burning, putta and any heat related work with proper ventilation, exhaust and chimney. This could be tin shed also.

(b) *Grinding, Drying and Processing section for Bhasma and Rasaushadhies.*—100 Sq. feet (Manual or Mechanical, oven etc.). Drying [1] [shall be] done in a space which is covered by glass or other transparent material to allow entry of sunrays on the material to keep for the purpose. If drying is being done in oven the temperature of the same may be selected specific temperature.

(c) *Rashaushadi Related Store.*—100 Sq. feet.

The size and dimensions of each Bhatti section would be so designed to suit the batch size or quantity of materials to be processed, keeping in mind the processing is done as per the conditions of Drug and Cosmetics Act mentioned under Schedule I official books.

In addition to the fuels prescribed in the schedule books namely coal, fire wood, cow dung cakes etc., use of other heating devices *e.g.*, electrical heating, oil or gas fired furnaces and others [1272] [shall be] employed so as to provide the required temperature as per the nature of material and object of heating. Depending on the formulation being manufactured, manufacturers may adopt aerobic or anaerobic process. Properly baked and clean earthen pots of other crucibles and glass containers or appropriate design shall be used.

The manufacturing area should be designed with special attention to process the products that generate toxic fumes like $S0_2$ arsenic and mercury vapour, etc. When heating and boiling of the materials is necessary, suitable ventilation and air exhaust flow mechanism should be provided to prevent accumulation of unintended fumes and vapours. Such areas may be provided with properly designed chimneys or ducts fitted with exhaust system and suitable scrubbing system to remove fumes and smoke, so that safety of personnel and environment is taken care of.

Since processing of Rasaushadhis may introduce heavy metal contamination and cross-contamination etc., therefore, cleaning of equipment is particularly important after every process by using appropriate cleaning agent which should

not react with material of equipment and must be free from unwanted properties *e.g.*, corrosiveness.

2.3 Records shall be maintained specially for temperatures attained during the entire process of Bhasmikaran, while employing different kinds of classical puta, furnaces using oil, gas or electricity. Appropriate temperature measuring instrument should be employed such as pyrometer and, pyrograph for manual reading or recording by heat sensors, connected to computer as the case may be.

In order to handle large quantities, appropriate technology like use of hand operated extruders for making chakrikas or pellets may be adopted. However, such equipments made of aluminium or its alloys should not be used.

Access to manufacturing areas shall be restricted to minimum number of authorized personal only.

3. Quality Control.—

A. In Process Quality Control:

The registers as indicated below should exclusively be maintained for ready reference:

(a) Shodhan Register with following details:—

1. SI. No.
2. Batch No. and Size
3. Date, time and duration
4. Name of the Raw-material with Quality reference and quantity
5. Quantity of Shodhana Dravya
6. Book Reference followed
7. Methodology

(b) Bhavana and Putta Register with following details:—

1. SI. No.
2. Batch No.
3. Date, time
4. Name of the material and quantity of starting materials
5. Quantity of Nirvapya Dravya

6. Quantity of Bhavana Dravya
7. Date and Time of Starting and completion of Bhavana or Mardana and duration
8. Type and Number of Puttas
9. Time and Date of completion Puttas
10. Colour and texture of the product or standards
11. In process tests followed (Bhasma Pariksha and any other tests)
12. In case heating at a particular temperature is required, record of attainment of that temperature.

(c) Grinding Record Register.—(Finished Product/Intermediate procedure)—

1. SI. No
2. Batch No
3. Date and time
4. Name of the material and quantity
5. Name of the equipment (SS/granite)
6. Duration of grinding
7. Repeat the grinding if required (Number of repetition)

(d) Packing details—

1. Name of Rasaushadhi
2. Type of Dosage Form (e.g., Powder, pill, tablet etc.)
3. Weight of Rasaushadhi in each unit.

B. Product Quality Control:

The specifications for finished Rasaushadhi are primarily intended to define the quality rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the quality. Consistent quality for Rasaushdhi can only be assured if the starting material-metals and minerals are used of pharmacopoeial standards. In some cases more detailed information may be needed on aspects of their process. The manufacture will ensure in-house standards for the uniform quality of product.

Quality testing will be carried out as per official Pharmacopoeia or Schedule books for texts namely, colour, taste, varitaratwa, Rekhapurnatwa, Laghutva,

Nirdhumatwa, Dutagre Kachakacha, Niruttha, Apunarbhava and Nischandratwa.

The Particle size of the product should be tested by adopting microscope fitted with micrometer or particle size analyzer or any appropriate other techniques. Required physio-chemical characterization of the product should be undertaken by appropriate analytical equipment. The Standard Manufacturing Process of the product should be evolved/ follow up. The disintegration time of pills-vati and tablets should also be recorded.

4. Product recalls.—Literature inserted inside the product package should indicate the name address of the manufacturing unit [1273][and] telephone number for reporting of any adverse drug reaction by physicians or patients. On receipt of such Adverse Drug Reaction report, it will be the responsibility of the manufacturer to ensure the recall the product from the market.

Standard operating procedures (SOP) should be included for storage of recalled Rasaushadhies in a secure segregated area, complying with the requirements specified for storage, till their final disposal.

5. Medical examination of the employees.—Employees engaged in manufacturing should be medically examined periodically at least once a year for any adverse effect of the drug during manufacturing process for which necessary investigations [1274][shall be] carried out for ensuring that there is no effect of material on the vital organs of the employees. Annual examination reports of the employees shall be made available to statutory inspectors during Good Manufacturing Practices inspections.

6. Self-Inspection.—The release of Rasaushadhis should be under the control of a person who has been trained in the specific features of the processing and quality assurance of Rasaushadhis. Personnel dealing with the production and quality assurance of Rasaushadhis manufacturing section should have an adequate training in the specific subject of Rasaushadhis manufacturing. He will be at least a degree holder in Ayurveda/ Siddha/Unani medicine or B. Pharma degree holder in Ayurveda/Siddha/Unani medicine.

7. Dosage form of Rasaushadhi.—The Rasaushadhies may be made into an acceptable dosage forms such as, churna, vati, guti, tablet, capsule or Capsule etc., after adding suitable permissible fillers or binding agents as

permissible under the Ayurvedic Pharmacopoeia of India or Indian Pharmacopoiea as updated from time to time. In such cases the label must indicate the quantity of Ayurveda, Siddha and Unani medicine in one Tablet or Pill or Capsule in addition to the filler. The crystalline product may be grinded before packing in the individual dispensing size". All the Rasushadhi or Rasamaruthukal or Kushtajat shall be packed in a dosage form which is ready for use for the consumer. Grinding and weighting of individual does of potentially poisonous products will not be permissible in patient consumer pack. This arrangement may reduce the Adverse Drug Reaction of Rasaushadhi which takes place due to does variation. However for hospital bulk pack, it will not be applicable and label will clearly indicate the "Hospital pack".

8. Area Specifications/requirement for an applicant companies only to have GMP of Rasaushadhies or Rasamarunthukal and Kushtajat (Herbo-mineral/metallic compounds) of Ayurveda, Siddha and Unani medicines:—

S. No.	Category of Medicine/ Manufacturing area	Minimum Manufacturing Space required (1500 sq. ft.)	Machinery equipment recommended
1.	Pisti/Grinding area for Bhasma, Pishti, Kushtajat.	100 sq. ft.	Kharal/mechanized/motorized Kharal, End runner/Ball-Mill Sieves/Shifter.
2.	Powdering area for raw drugs of plant origin giving in Rasaushadhies (Herbo-metalic formulations)	200 sq. ft.	Grinder/Dis tin tegra tor/Pul verisar/Powder mixer/Sieves/ Shifter.
3.	Pills/Vati/Gutika Matrica and tablets/Habb making area.	100 sq. ft.	Ball Mill, Mass Mixer/Powder mixer, Granulator drier, tablet compressing machine, pill/vati cutting machine, stainless steel trays/container for storage and sugar coating, polishing pan in case of sugar coted tablets, mechanized chatee, (for mixing of guggulu) where required.
4.	Kupi pakva /Ksara /Parpati/Lavana Bhasma Satva /Sindura Karpu/ Uppu/Param/Qushta/Jawhar	150 sq. ft.	Bhatti, Karahi/stainless steel vessels/patila flask, Multani Matti/ Plaster of Paris, Copper Rod, Earthen container, Gaj Put Bhatti, Muffle furnace (electrically operated)

S. No.	Category of Medicine/ Manufacturing area	Minimum Manufacturing Space required (1500 sq. ft.)	Machinery equipment recommended
			End/Edge Runner, Exhaust Fan, Wooden, S.S. Spatula.
5.	Receiving and storing raw material	200 sq. ft.	
6.	Quality Control Section	150sq. ft.	
7.	Quarantine/observation	50 sq. ft.	
8.	Finished goods store	150 sq. ft.	
9.	Rejected goods store	50 sq. ft.	
10.	Bhatti-putta area	200 sq. ft.	
11.	Area for water and washing etc.	50 sq. ft.	
12.	Office	100 sq. ft.	
	Total	**1500 Sq. ft.]**	

Note.—The above requirements of machinery, equipments, space, are made subject to the modification at the discretion of the Licensing Authority; if he is of the opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter then in the circumstances in a particular case [1275][he may do so after recording reasons in writing].

[1276][*SCHEDULE TA*

(See rule 157A)

FORM FOR RECORD OF UTILIZATION OF RAW MATERIAL BY AYURVEDA OR SIDDHA OR UNANI LICENSED MANUFACTURING UNITS DURING THE FINANCIAL YEAR

Identification Particulars:

Manufacturing License No.....

Issued by.....

Name.....

Address.....
State.....Pin Code.....
Telephone .....Fax.....
Email.....

1. Quantity of Medicinal Plants/Extracts/Essential Oils/Metals/Animal By-Products/Minerals Used During 1st April, to 31st March, of the proceeding year (For Productions at the identified facility)

(a) Herbs Used

Common Name as in AFI/API*	Plant's Botanical Name	Quantity Used/per annum (in Kgs.)	Sources of Supply					Part Used			
			Traders/ Manufacturers	Forest Collectors	Cultivators	Imported	Total	Whole plants	Root	Leaf	Others

* Ayurvedic Formulary of India/Ayurvedic Pharmacopoeia of India

(b) Extracts Used

Name of Extracts		Quantity Used/per annum (in Kgs.)	Sources of Supply			
Common Name as in AFI/API*	Botanical Name		In-House	Export Suppliers	Imported	Total

* Ayurvedic Formulary of India /Ayurvedic Pharmacopoeia of India

(c) Metals/Minerals Used

Name of Mineral		Quantity Used/per annum (in Kgs.)	Sources of Supply			
Common Name	Chemical Name		Manufacturers Traders (Domestic)		Importers	Total

(d) Animal By-Products Used

Name of By-Product		Quantity Used/per annum (in Kgs.)	Sources of Supply			
Common Name	Biological /Chemical Name (if any)		Manufacturers Traders (Domestic)		Importers	Total

2. Shortage of raw material(s)/inputs during the preceding year.

Yes No

If yes, please indicate name(s) of such raw material(s) by level of importance starting from most important to least important, reason for shortage [availability, quality or any other (please specify)]

Name of Raw Material		Appro. Qty of shortage (in Kgs.)	Reason
Name of the drug and part used as mentioned in official formulary/ Pharmacopoeial/Schedule I books	Biological/Chemical Name (if any)		

[1277][SCHEDULE U

(See rules 74, 74A, 74B, 78 and 78A)

I. PARTICULARS TO BE SHOWN IN MANUFACTURING RECORDS

A. SUBSTANCES OTHER THAN PARENTERAL IN PREPARATIONS IN GENERAL

1. Serial number.
2. Name of the product.
3. Reference of Master Formula Records.
4. Lot/Batch Size
5. Lot/Batch Number.
6. Date of commencement of manufacture and date of completion of manufacture and the assigned date of expiry.

7. Name of ail ingredients, specifications quantities requires for the lot/Batch size and quantities actually used. All weighings and measurements shall be carried out by a responsible person and initialled by him and shall be counter checked and signed by the competent technical staff under whose personal supervision the ingredients are used for manufacture.
8. Control Numbers of raw materials used in the formulation.
9. Date, time and duration of mixing.
10. Details of environmental controls like room temperature, relative humidity.
11. Date of granulation, wherever applicable.
12. Theoretical weight and actual weight of granules/powder blend.
13. Records of in-processes controls (Periodically whenever necessary).
    (a) Uniformity of mixing.
    (b) Moisture content of granules/powder in case of Tablet/Capsules.
    (c) pH of solution in case of liquid.
    (d) Weight variation.
    (e) Disintegration time.
    (f) Hardness.
    (g) Friability test.
    (n) Leak test in case of strip packing.
    (i) Filled volume of liquids.
    (j) Quantity of tablets/capsules in the final container.
    (k) Content of ointment in the filled containers.

14. Date of compression in case of Tablets/date of filling in case of capsules.

15. Date of sealing/coating/polishing in case of capsules/tablets wherever applicable.

16. Reference to analytical Report number stating the result of test and analysis.

17. Separate records of the disposal of the rejected batches and of batches withdrawn from the market.

18. The theoretical yield and actual productions yield and packing particulars indicating the size and quantity of finished packings.

19. Specimen of label/strip, carton with batch coding information like Batch Number, date of manufacture, date of expiry, retail price as applicable, stamped thereon and inserts used in the finished packings.

20. Signature with date of competent technical staff responsible for the manufacture.

21. Counter signature of the head of the testing units or other approved person-in-charge of testing for having verified the batch records and for having released the batch for sale and distribution, the quantity released and date of release.

22. Date of release of finished packings and quantity released for sale and distribution.

23. Quantity transferred to warehouse.

24. For Hypodermic tablets and ophthalmic preparations, which are required to be manufactured under aseptic conditions, records snail be maintained indicating the precautions taken during the process of manufacture to insure that aseptic conditions are maintained.

B. PARENTERAL PREPARATIONS

1. Serial Number.
2. Name of the product.
3. Reference of the master formula record.
4. Batch/Lot size.
5. Batch No. and/or Lot No.
6. Date of commencement of manufacture and date of completion.
7. Names of all ingredients, specifications and quantity required for the Lot/Batch size and quantity actually used. All weighings and measurements shall be carried out by a responsible person and initialled by nim and shall be countersigned by the technical staff under whose personal supervision the stocks are issued and by another competent technical staff under whose supervision the ingredients are used for manufacture.
8. Control numbers of raw materials used in the formulation.
9. Date, time and duration of mixing.

10. Details of environmental controls like temperature, humidity, microbial count in the sterile working areas.
11. pH of the solution, wherever applicable.
12. Date and method of filtration.
13. Sterility test, reference on bulk batch wherever applicable
14. Records of check on volume filled.
15. Date of filling.
16. Records of tests employed—
    (a) To ensure that sealed ampoules are leak proof.
    (b) To check the presence of foreign particles.
    (c) Pyrogen test, wherever applicable.
    (d) Toxicity test wherever applicable.

17. Records of checking of instruments and apparatus of sterilisation (Indicators).

18. Records of cleaning and sterilisation of containers and closures, if necessary.

19. Records of sterilisation in case of parenteral preparations which are heat sterilised including particulars of time, temperature and pressure employed. Such records should be marked to relate to the batch sterilised.

20. Number and size of containers filled and quantity rejected.

21. The theoretical yield and actual yield and the percentage yield thereof.

22. Reference to Analytical report numbers stating whether of standard quality or otherwise.

23. Specimen of labels, cartons *etc.* with Batch coding information like batch number, date of manufacture, date of expiry,, as applicable, stamped thereon, and inserts used in the finished packings.

24. Signature with date of the component technical staff responsible for manufacture.

25. Particulars regarding the precautions taken during the manufacture to ensure that aseptic conditions are maintained.

26. *Counter*—Signature of head of the testing unit or person in charge of testing for having verified the documents and for having released the product for sale ana distribution, the quantity released and date of release.

27. Records for having transferred to warehouse giving packing and quantities.

28. Separate records of the disposal of the rejected batches and of all batches withdrawn from the market.

29. Records of reprocessing if any and particulars of reprocessing.

II. RECORDS OF RAW MATERIALS

Records in respect of each raw material shall be maintained indicating the date of receipt, invoice number, name and address of manufacturer/supplier, batch number, quantity received, pack size, date of manufacture, date of expiry, if any, date of analysis and release/rejection by quality control, analytical report number, with special remarks, if any, quantity issued, date of issue and the particulars of the name and batch numbers of products for the manufacture of which issued and the proper disposal of the stocks.

III. PARTICULARS TO BE RECORDED IN THE ANALYTICAL RECORDS

A. TABLETS AND CAPSULES

1. Analytical report number.
2. Name of the sample.
3. Date of receipt of sample.
4. Batch/Lot number.
5. Protocols of tests applied.
    (a) Description.
    (b) Identification.
    (c) Uniformity of weight.
    (d) Uniformity of diameter (if applicable).
    (e) Disintegration test (time in minutes).
    (f) Any other tests.
    (g) Results of Assay.

Note.— Records regarding various tests applied (including readings and calculations) should be maintained and necessary reference to these records should be entered in Col. 5 above whenever necessary.

6. Signature of the Analyst.
7. Opinion and signature of the approved Analyst.

B. PARENTERAL PREPARATIONS

1. Analytical Report Number.
2. Name of the sample.
3. Batch number.
4. Date of receipt of samples.
5. Number of containers filled.
6. Number of containers received.
7. Protocols of tests applied.
   (a) Clarity.
   (b) pH wherever applicable.
   (c) Identification.
   (d) Volume in container.
   (e) Sterility—(i) Bulk sample wherever applicable (ii) container sample.
   (f) Pyrogen test, wherever applicable.
   (g) Toxicity test, wherever applicable.
   (n) Any other tests.
   (i) Results of Assay.

Note.— Records regarding various tests applied (including readings and calculations) should be maintained and necessary reference to these records should be entered in Col. 7 above whenever necessary.

8. Signature of the Analyst.
9. Opinion and signature of the approved Analyst.

PYROGEN TEST

1. Test Report Number.
2. Name of the sample.
3. Batch number.

4. Number of rabbits used.
5. Weight of each rabbit.
6. Normal temperature of each rabbit.
7. Mean initial temperature of each rabbit.
8. Dose and volume of solution injected into each rabbit and time of injection.
10. Maximum Temperature.
11. Response.
12. Summed response.
13. Signature of the Analyst.
14. Opinion and signature of the approved Analyst.

TOXICITY TEST

1. Test Report Number.
2. Name of the sample.
3. Batch Number.
4. Number of mice used and weight of each mouse.
5. Strength and volume of the drugs injected.
6. Date of injection.
7. Results and remarks.
8. Signature of Analyst.
9. Opinion and signature of the approved Analyst.

C. FOR OTHER DRUGS

1. Analytical report number.
2. Name of the sample.
3. Batch/Lot number.
4. Date of receipt of sample.
5. Protocol of tests applied.
   (a) Description
   (b) Identification
   (c) Any other tests.
   (d) Results'-of Assay.

Note.— Particulars regarding various tests applied (including readings and calculations) shall be maintained and necessary reference to these records shall be entered in Column 5 above, whenever necessary.

6. Signature of the Analyst.
7. Opinion and signature of the approved Analyst.

D. RAW MATERIALS

1. Serial number.
2. Name of the materials.
3. Name of manufacturer/supplier.
4. Quantity received.
5. Invoice/Challan number and date.
6. Protocols of tests applied.

Note.— Particulars regarding various tests applied (including readings and calculations) shall be maintained and necessary reference to these records shall be entered in Column 6 above, whenever necessary.

E. CONTAINER, PACKING MATERIALS, ETC.

1. Serial number.
2. Name of the item.
3. Name of the manufacturer/supplier
4. Quantity received.
5. Invoice/Challan number and date.
6. Protocols of tests applied.

Note.— Particulars regarding various tests applied shall be maintained and necessary reference to these records shall be entered in Column 6 above, whenever necessary.

7. Remarks.
8. Signature of the examiner.

Note.—1. The foregoing provisions represent the minimum requirements to be complied with the licensee. The Licensing Authority, may how'ever, direct the nature of records to be maintained by the licensee for such products as are not covered by the categories described above.

2. The Licensing Authority may permit the licensee to maintain records in such manner as are considered satisfactory, provided the basic requirements laid down above are complied with.

3. The Licensing Authority may at its discretion direct the licensee to maintain records for such additional particulars as it may consider necessary in the circumstances of a particular case.]

[1278][SCHEDULE U (I)

[1278][***]

[1279][SCHEDULE V

(See rule 124B)

STANDARDS FOR PATENT OR PROPRIETARY MEDICINES

[1280][***]

[1281][2. *Standards for patent or proprietary medicines, containing vitamins*—Patent or proprietary medicines containing vitamins for prophylactic, therapeutic or paediatric use shall contain the vitamins in quantities not less than and not more than those specified below in single or in two divided daily doses, namely:—[See table on next page].

[1280][***]

[1282][4. *General Standards for Different Categories of Patent or Proprietary Medicine*—In the case of Pharmaceutical products containing several active ingredients, the selection shall be such that the ingredients do not interact with one another, and do not affect the safety and therapeutic efficacy of the product. The combination shall not also lead to analytical difficulties for the purpose of assaying the content of such ingredient separately. The substances added as additives shall be innocuous, shall not affect the safety or therapeutic efficacy of the active ingredients, and shall not affect the assays and identity tests in the amount present.]

Vitamin	Unit	Patent or proprietary medicines containing vitamins for prophylactic use	Patent or proprietary medicines containing vitamins for therapeutic use	Patent or proprietary medicines containing vitamins for paediatric use	
(In single dose or in two divided doses) per daily dose					
		For adults		For infants less than one year	For children above one year upto adults
1	2	3	4	5	6
Vitamin A	I.U.	Not less than 1,600 and not more than 2,500.	Not less than 5,000 and not more than 10,000.	Not less than 750 and not more than 3,000.	Not less than 1,500 and not more than 5,000.
Vitamin D	I.U.	Not less than 100 and not more than 200.	Not less than 400 and not more than 1,000.	Not less than 200 and not more than 400.	Not less than 100 and not more than 400.
Vitamin B1	mg.	Not less than 1 and not more than 2.	Not less than 4.5 and not more than 10.	Not less than 0.5 and not more than 1.	Not less than 1 and not more than 4.5.
Vitamin B2	mg.	Not less than 1 and not more than 3	Not less than 5 and not more than 10.	Not less than 0.5 and not more than 1.5.	Not less than 1 and not more than 5.
Vitamin B6	mg.	Not less than 0.5 and not more than 1.5.	Not less than 1.5 and not more than 3.	Not less than 0.5 and not more than 1.5.	Not less than 1 and not more than 3.
Niacinamide	mg.	Not less than 15 and not more than 26.	Not less than 45 and not more than 100.	Not less than 5 and not more than 15.	Not less than 10 and not more than 40.
d —Pantothenic acid or its salts and panthenol	mg.	Not less than 1 and not more than 5.	Not less than 5 and not more than 50.	Not less than 1 and not more than 3.	Not less than 2.5 and not more than 10.
Folic acid	mg.	Not less than 50 and not more than 300.	Not less than 1,000 and not more than 1,500.	Not less than 25 and not more than 100.	Not less than 100 and not more than 500.
Vitamin B12	[1283][mcg]	Not less than 05 and not more than 1.0.	Not less than 5 and not more than 15.	Not less than 1 and not more than 3.	Not less than 1 and not more than 5.
Vitamin C	mg	Not less than 25 and not more than 50.	Not less than 75 and not more than 150.	Not less than 20 and not more than 40.	Not less than 30 and not more than 80.
Vitamin E	I.U.	Not less than 5 and not more than 10.	Not less than 15 and not more than 25.	Not less than 2.5 and not more than 10.	Not less than 5 and not more than 20

Note 1.—*Patent or proprietary medicines containing vitamins intended for prophylactic, therapeutic or paediatric use shall bear on the label the words "For Prophylactic Use", "For Therapeutic Use" or "For Paediatric Use" as the case may be. In the cases of paediatric preparations the age of the infant or the child for whose use it is intended, shall be given in addition to the particulars required to be given under these rules.*

Note 2.—*The above standards shall not apply to any preparation containing a single vitamin only and also to any preparation containing vitamins intended for parenteral use :*

Provided, however, that in the case of patent or proprietary medicines containing vitamins which are intended for the treatment of certain specific conditions or diseases, the Licensing Authority specified in clause (b) or Rule 21, may permit the addition of vitamins therein in relaxation of the limits specified above, if satisfactory evidence is produced in justification of such relaxation.]

Subject to the provisions of these rules, patent or proprietary medicines shall comply with the following standards, namely:—

1. Patent or proprietary medicines shall comply with the general requirements of the dosage form under which it falls as given in the Indian Pharmacopoeia. If the dosage form is not included in the Indian Pharmacopoeia, but is included in any other pharmacopoeia, prescribed for the purpose of the Second Schedule to the Act, it shall comply with the general requirements of the dosage of such pharmacopoeia. Without prejudice to the generality of the foregoing requirements, general requirements shall include compliance with colour consistency, clarity, stability, freedom from contamination with foreign matter or fungal growth, defects like chipping and capping of tablets, cracking of the coating, mottled appearance and other characteristic defects that can be perceived by visual inspection.

2. Without prejudice to the generality of the following paras, dosage forms of patent or proprietary medicines shall comply with the following requirements, namely:—

(a) *Tablets :* Medicines shall comply with requirements for tablets as laid down in the Indian Pharmacopoeia. The nature of coating shall be indicated on the label. Permitted colours may, however, be added and declared on the label. Nature of tablets, such as uncoated, sugar coated or filmcoated, shall also be declared on the label.

[1284][***]

(b) *Capsules :* Medicines shall comply with the requirements for capsules laid down in the Indian Pharmacopoeia. However, the capsules, shall be free from distortion of shape, discolouration and other physical defects like leakage of power joints, pinholes or cracks in the capsules;

(c) *Liquid oral dosage forms :* Emulsions and suspensions shall dispose uniformly on shaking. Homogeneous solutions shall contain no sediments. The volume of the product (net content) in the container shall be not less than the labelled volume. The limited for ethanol content of pharmaceutical products shall be not less than 90 per cent and not more than 110 per cent of the labelled contents.

(d) *Injections :* Medicines shall comply with the requirements for injections as laid down in the Indian Pharmacopoeia.

(e) *Ointments :* Medicines shall comply with the requirements for ointments as laid down in Indian Pharmocopoeia.

3. The content of active ingredients, other than vitamins, enzymes and antibiotics, in patent or proprietary medicines shall be not less than 90 per cent and not more than 110 per cent of the labelled content; however, for enzymes and vitamins, only for lower limit of 90 per cent shall apply. In all dry formulations containing antibiotics, the limit shall be 90 to 130 per cent of the labelled contents and in case of liquid antibiotic formulations, the limit shall be 90 to 140 per cent of labelled contents.

Fiducial limits for error for microbiological assay of antibiotics may be estimated depending upon the design of assay procedure. Methods used for assaying active ingredients shall employ the same basic principles and shall use same organisms as given in the latest edition of the Indian Pharmacopoeia or shall follow any other methods as approved by the authority competent to grant licence to manufacture.

4. All patent or proprietary medicines containing aspirin shall be subjected to "Free Salicylic Acid Test" and the limit of such acid shall be 0.75 per cent. Except in case of soluble type aspiring in which case the limit of such acid shall be 3 per cent.

5. Patent or proprietary medicine to be tested under the provisions of rule 121A for pyrogen shall be tested by injecting into rabbits not less than the human dose of the medicine based on body weight of a 60 kg. human being. Methodology and limits shall be based on the method recorded in the Indian Pharmacopoeia. Dose selected shall be indicated in the protocol but the dose shall be not greater than 5 times the human dose based on body weight of 60 kg. for man.

6. In injectable patent or proprietary medicines, the test for freedom from toxicity, shall be performed as described in the Indian Pharmacopoeia. Dose selected shall be indicated in the protocol but the dose shall not be less than five times the human dose based on body weight of 60 kg. human being.]

[1285][***]

[1286][SCHEDULE X

(See rules 23, 61, 75, 97 and 105A)

Amobarbital	Phencyclidine	Dexamphetamine
Glutethimide	Barbital	Methylphenidate
Pentobarbital	Methamphetamine	Secobarbital
[1287][Ketamine	Phenometrazine	Ethclorvynol
hydrochloride]	Cyclobarbital	Methylphenobarbital
Amphetamine	[1288][***]	
Meprobamate	[1289][***]	

Notes.—l.Any stereiosometric form of the substance specified in this Schedule, any salt of the substance and preparation containing such substances are also covered by this Schedule.

2. Preparations containing the above substances are also covered by this Schedule:

Provided, however, preparations containing Meprobamate [1289][***] in combination with other drugs may be exempted by the Licensing Authority specified in clause (b) of rule 21, from the provisions of this Schedule, if satisfactory evidence is adduced that these preparations are not liable to be misused.]

[1290][SCHEDULE Y

[See rules 122A, 122B, 122D, 122DA, 122DAA and 122E]

REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT AND/OR MANUFACTURE OF NEW DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS

1. Application for permission.—(1) Application for permission to import or manufacture new drugs for sale or to undertake clinical trials shall be made in Form 44 accompanied with following data in accordance with the appendices, namely:—

(i) chemical and pharmaceutical information as prescribed in Item 2 of Appendix I;

(ii) animal pharmacology data as prescribed in Item 3 of Appendix I and Appendix IV;

(a) specific pharmacological actions as prescribed in Item 3.2 of Appendix I, and demonstrating, therapeutic potential for humans shall be described according to the animal models and species used. Wherever possible, dose-response relationships and ED 50s shall be submitted. Special studies conducted to elucidate mode of action shall also be described (Appendix IV);

(b) general pharmacological actions as prescribed in Item 3.3 of Appendix I and Item 1.2 of Appendix IV;

(c) pharmacokinetic data related to the absorption, distribution, metabolism and excretion of the test substance as prescribed in Item 3.5 of Appendix I. Wherever possible, the drug effects shall be corelated to the plasma drug concentrations;

(iii) animal toxicology data as prescribed in Item 4 of Appendix I and Appendix III;

(iv) human Clinical Pharmacology Data as prescribed in Items 5, 6 and 7 of Appendix I and as stated below:

(a) for new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as required imder Items 1, 2, 3, 4, 5 (data, if any, from other countries) and 9 of Appendix I;

(b) for new drug substances discovered in countries other than Indio, Phase I data as required under Items 1, 2, 3, 4, 5 (data from other countries) and 9 of Appendix I should be submitted alongwith the application. After submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with other global trials for that drug. Phase III trials are

required to be conducted in India before permission to market the drug in India is granted;

(c) the data required will depend upon the purpose of the new drug application. The number of study subjects and sites to be involved in the conduct of clinical trial will depend upon the nature and objective of the study. Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier Phase(s);

(d) application for permission to initiate specific phase of clinical trial should also accompany Investigator's brochure, proposed protocol (Appendix X), case record form, study subject's informed consent document(s) (Appendix V), investigator's undertaking (Appendix VII) and ethics committee clearance, if available (Appendix VIII);

(e) reports of clinical studies submitted under Items 5-8 of Appendix I should be in consonance with the format prescribed in Appendix II of this Schedule. The study report shall be certified by the Principal Investigator or, if no Principal Investigator is designated, then by each of the Investigators participating in the study. The certification should acknowledge the contents of the report, the accurate presentation of the study as undertaken, and express agreement with the conclusions. Each page should be numbered;

(v) regulatory status in other countries as prescribed in Item 9.2 of Appendix I, including information in respect of restrictions imposed, if any, on the use of the drug in other countries, *e.g.* dosage limits, exclusion of certain age groups, warning about adverse drug reactions, etc. (Item 9.2 of Appendix I). Likewise, if the drug has been withdrawn in any country by the manufacturer or by regulatory authorities, such information should also be furnished along with the reasons and their relevance, if any, to India. This information must continue to be submitted by the sponsor to the Licensing Authority during the course of marketing of the drug in India;

(vi) the full prescribing information should be submitted as part of the new drug application for marketing as prescribed in Item 10 of Appendix I. The prescribing information (package insert) shall comprise the following sections: generic name; composition, dosage form/s; indications; dose and method of administration; use in special populations (such as pregnant women, lactating

women, pediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions. All package inserts, promotional literature and patient education material subsequently produced are required to be consistent with the contents of the approved full prescribing information. The drafts of label and carton texts should comply with provisions of Rules 96 and 97. After submission and approval by the Licensing Authority, no changes in the package insert shall be effected without such changes being approved by the Licensing Authority; and

(vii) complete testing protocol/s for quality control testing together with a complete impurity profile and release specifications for the product as prescribed in Item 11 of Appendix I should be submitted as part of new drug application for marketing. Samples of the pure drug substance and finished product are to be submitted when desired by the regulatory authority.

(2) If the study drug is intended to be imported for the purposes of examination, test or analysis, the application for import of small quantities of drugs for such purpose should also be made in Form 12.

(3) For drugs indicated in life threatening/serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

2. Clinical Trial

(1) *Approval for Clinical trial—*

(i) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under Rule 21(b), and the approval obtained from the respective ethics committee(s). The Licensing Authority as defined shall be informed of the approval of the respective institutional ethics committee(s) as prescribed in Appendix VIII, and the trial initiated at each respective site only after obtaining such an approved for that site. The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an

independent ethics committee (constituted as per Appendix VIII), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

(ii) All trial Investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified physician (or dentist, when appropriate) who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

Laboratories used for generating data for clinical trials should be compliant with Good Laboratory Practices. If services of a laboratory or a facilities outside the country are to be availed, its/their name(s), address(es) and specific services to be used should be stated in the protocol to avail Licensing Authority's permission to send clinical trial related samples to such laboratory(ies) and/or facility(ies). In all cases, information about laboratory(ies)/facilities to be used for the trial, if other than those at the investigation site(s), should be furnished to the Licensing Authority prior to initiation of trial at such site(s).

(iii) Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the Ethics Committee which has granted the approval for the study. No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and the Licensing Authority except when it is necessary to eliminate immediate hazards to the trial subject(s) or when change(s) involve(s) only logistic or administrative aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Licensing Authority. Administrative and/or logistic changes in the protocol should be notified to the Licensing Authority within 30 days.

(2) *Responsibilities of Sponsors*—

(i) The clinical trial sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP). Guidelines issued by the Central Drugs Standard Control Organization, Directorate-General of Health Services, Government of India as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity.

(iii) In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions (Appendix XI), if any, and the reason for discontinuation of the study or non-pursuit of the new drug application.

[1291][(iv) Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Licensing Authority as referred to in clause (b) of rule 21, the Chairman of the Ethics Committee and the head of the institution where the trial has been conducted, within fourteen days of the occurrence of the serious adverse event.]

[1292][(v) in case of injury or death occurring to the clinical trial subject, the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever nad obtained permission from the Licensing Authority for conduct of the clinical trial, shall make payment for medical management of the subject and also provide financial compensation for the clinical trial related injury or death in the manner as prescribed in Appendix XII;]

[1293][(vi) the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, shall submit details of compensation provided or paid for clinical trial related injury or death, to the Licensing Authority within thirty days of the receipt of the order of the Licensing Authority.]

[1294][(3)(i)] *Responsibilities of the Investigator(s)*—

The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII. Standard operating procedures are required to be documented by the investigate 3 for the tasks performed by them. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events. Investigator(s) shall report all serious and unexpected adverse events to the [1295][Licensing Authority defined under clause (b) of rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence. [1296][In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish tne reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the Investigator to the Licensing Authority as referred to in clause (b) of rule 21, the Chairman of the Ethics Committee and the Head of the institution where the trial has been conducted within fourteen days of the occurrence of the serious adverse event.]].

[1297][(ii) The Investigator shall provide information to the clinical trial subject through informed consent process as provided in Appendix V about the essential elements of the clinical trial and the subject's right to claim compensation in case of trial related injury or death. He shall also inform the subject or his/her nominee(s) of their rights to contact the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical

trial for the purpose of making claims in the case of trial related injury or death.]

(4) *Informed Consent—*

(i) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The subject's consent must be obtained in writing using an 'Informed Consent Form'. Both the patient information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is not able to give informed consent *(e.g.* an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative [a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India]. If the subject or his/her legally acceptable representative is unable to read/write - an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(iii) A checklist of essential elements to be included in the study subject s informed consent document as well as a format for the Informed Consent Form for study subjects is given in Appendix V.

[1298][(iv) An audio-video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record:

Provided that in case of clinical trial of anti-HIV and anti-Leprosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall De maintained by the investigator for record.]

(5) *Responsibilities of the Ethics Committee—*

(i) It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well being of all trial subjects. The ethics committee should exercise particular care to protect the rights, safety and well being of all vulnerable subjects participating in the study, *e.g.*, members of a group with hierarchical structure *(e.g.* prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent. Ethics committee(s) should get document 'standard operating procedures' and should maintain a record of its proceedings.

(ii) Ethics Committee(s) should make, at appropriate intervals, an ongoing review of the trials for which they review the protocol(s). Such a review may be based on the periodic study progress reports furnished by the investigators and/or monitoring and internal audit reports furnished by the sponsor and/or by visiting the study sites.

(iii) In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so ana at once communicate such a decision to the Investigator as well as to the Licensing Authority.

[1299][(iv) In case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as referred to in clause (b) of rule 21 for

conducting the clinical trial, to the Licensing Authority within thirty days of the occurrence of the serious adverse event.]

[1300]*[5(A) Serious Adverse Events—*

(1) A serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalisation (in case the study was being conducted on out-patient), prolongation of hospitalisation (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.

(2) The Investigator shall report all serious [1301][***] adverse events to the Licensing Authority as defined under clause (b) of rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence as per Appendix XI, and the said Licensing Authority shall determine the cause of injury or death as per the procedure prescribed under Appendix XII and pass orders as deemed necessary.] [1302][In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event.]

(6) *Human Pharmacology (Phase I*)—

(i) The objective of studies in this phase is the estimation of safety and tolerabiiity with the initial administration of an investigational new drug into human(s). Studies in this phase of development usually have non-therapeutic objectives and may be conducted in heallhy volunteers subjects or certain types of patients. Drugs will, significant potential toxicity *e.g.* cytotoxic drugs are usually studied in patients. Phase I trials should preferably be carried out by investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the subjects.

(ii) Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives:—

(a) *Maximum Tolerated Dose:* To determine the tolerabiiity of the dose range expected to be needed later clinical studies and to determine tlie nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.

(b) Pharmacokinetics, *i.e.*, characterization of drug's absorption, distribution, metabolism and excretion. Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) *Pharmacodynamics:* Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic/pharmacodynamic studies) may be conducted in healthy volunteer subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

(d) *Early Measurement of Drug Activity:* Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

(7) *Therapeutic Exploratory Trials (Phase II*)—

(i) The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who

are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this phase is to determine the dose(s) and regimen for Phase m trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations *(e.g.* mild versus severe disease) for further studies in Phase II or Phase III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

(iii) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

(8) *Therapeutic Confirmatory Trials (Phase III)*—

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s). Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).

(ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies need to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

(iv) If the application is for the conduct of clinical trials as a part of multi national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Licensing Authority along with the application.

(9) *Post Marketing Trials (Phase IV)*—

Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), *e.g.* mortality/morbidity studies, epidemiological studies, etc.

3. Studies in Special Populations.—Information supporting the use of the drug in children, pregnant women, nursing women, elderly patients, patients with renal or other organ systems failure, and those on specific concomitant medication is required to be submitted if relevant to the clinical profile of the drug and its anticipated usage pattern. Any claim sought to be made for the drug product that is not based on data submitted under preceding items of this Schedule should be supported by studies included under this item of the Schedule (Appendix I, Item 8.3).

(1) *Geriatrics*—Geriatric patients should be included in Phase III clinical trials (and in Phase II trials, at the sponsor's option) in meaningful numbers, if—

(a) the disease intended to be treated is characteristically a disease of aging; or

(b) the population to be treated is known to include substantial numbers of geriatric patients; or

(c) when there is specific reason to expect that conditions common in the elderly are likely to be encountered; or

(d) when the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

(2) *Paediatrics.*—(i) The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

(ii) If the new drug is for diseases predominantly or exclusively affecting paediatric patients, clinical trial data should be generated in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

(iii) If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

(iv) If the new drug has a potential for use in paediatric patients - paediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post-marketing surveillance in adults if a safety concern exists. In cases where there is limited paediatric data at the time

of submission of application -more data in paediatric patients would be expected after marketing authorisation for use in children is granted.

(v) The paediatric studies should include—

(a) clinical trials,

(b) relative bioequivalence comparisons of the paediatric formulation with the adult formulation performed in adults, and

(c) definitive pharmacokinetic studies for dose: selection across the age ranges of paediatric patients in whom the drug is likely to be used. These studies should be conducted in the paediatric patient population with the disease under study.

(vi) If the new[r] drug is a major therapeutic advance for the paediatric population -the studies should begin early in the drug development, and this data should be submitted with the new drug application.

(vii) Paediatric subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies, for serious or life-threatening diseases in which,, in the opinion of the Investigator and parent(s)/ legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental/legal guardian consent should be sufficient'to allow participation in the study.

(viii) For clinical trials conducted in the paediatric pdpulation, the reviewing ethics committee should include members who are knowledgeable about paediatric, ethical, clinical and psychosocial issues.

(3) *Pregnant or Nursing Women.*—(i) Pregnant or'nursing women should be includes in clinical trials only when the drug is intended for use by pregnant/nursing women or foetuses/nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.

(ii) For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, foetus and child will be required. Where applicable, excretion of the drug: or iits metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug.

[1303][(4) *Post Marketing Surveillance* — (i) The applicant shall have a pharmacovigilance system in place for collecting, processing and forwarding the report to the licensing authority for, information on adverse drug reactions emerging from the use of the drug manufactured or marketed by the applicant in the country.

(ia) The system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction

(ib) Subsequent to approval of the product, new drug shall be closely monitored for its clinical safety once it is marketed.

(ic) The applicant shall furnish Periodic Safety Update Reports (PSURs) in order to—

(a) report all relevant new information from appropriate sources;

(b) relate the data to patient exposure;

(c) summarise the market authorisation status in different countries and any significant variations related to safety; and

(d) indicate whether changes shall be made to product information in order to optimise the use of product.]

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR. Within the single PSUR separate

presentations of data for different dosage forms, indications or separate population need to be given.

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The PSURs shall be: submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two. years -the PSURs need to be submitted annually. Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(iv) New studies specifically planned or conducted to examine a safety issue should be described in the PSURs.

(v) A PSUR should be structured as follows:—

(a) *A title page stating:* Periodic safety update report for the product; applicant's name, period covered by the report, date of approval of new drug, date of marketing of new drug and date of reporting;
(b) Introduction;
(c) Current worldwide market authorization status
(d) Update of actions taken for safety reasons;
(e) Changes to reference safety information;
(f) Estimated patient exposure;
(g) Presentation of individual case histories;
(h) Studies;
(i) Other information;
(j) Overall safety evaluation;
(k) Conclusion;
(l) Appendix providing material relating to indications, dosing, pharmacology and other related information.

(5) *Special studies: Bioavailability/Bioequivalence studies:*

(i) drugs approved elsewhere in the world and absorbed systemically, Bioequivalence With the reference formulation should be carried out wherever applicable. These studies should be conducted under the labelled conditions of administration. Data on the extent of systemic absorption may be required for formulations other than those designed for systemic absorption.

(ii) Evaluation of the effect of food on absorption following oral administration should be carried out. Data from dissolution studies should also be submitted for all solid oral dosage forms.

(iii) Dissolution and bioavailability data submitted with the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulation(s) sought to be marketed and those used for clinical trials during clinical development of the product. *(See* Items 8.1, 8.2 and 8.3 of Appendix I).

(iv) All bioavailability and bioequivalence studies should be conducted according to the Guidelines for bioavailability and bioequivalence studies as prescribed.

Note.—The data requirements stated in this Schedule are expected to provide adequate information to evaluate the efficacy, safety and therapeutic rationale of new drugs (as defined under rule 122-E) prior to the permission for sale. Depending upon the nature of new drugs and disease(s), additional information may be required by the Licensing Authority. The applicant shall certify the authenticity of the data and documents submitted in support of an application for new drug. The Licensing Authority reserves the right to reject any data or any document(s) if such data or contents of such documents are found to be of doubtful integrity.

APPENDIX I

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS/IMPORT/MANUFACTURE OF NEW DRUGS FOR MARKETING IN THE COUNTRY

1. *Introduction*

A brief description of the drug and the therapeutic class to which it belongs

2. *Chemical and pharmaceutical information*

2.1. Information on active ingredients

Drug information (Generic name, Chemical name or INN)

2.2 Physicochemical Data

(a) Chemical name and structure

Empirical formula

Molecular weight

(b) Physical properties

Description

Solubility

Rotation

Partition coefficient

Dissociation constant

2.3. Analytical Data

Elemental analysis

Mass spectrum

NMR spectra

IR spectra

UV spectra

Polymorphic identification

2.4. Complete monograph specification including

Identification

Identity/quantification of impurities

Enantiomeric purity

Assay

2.5. Validations

Assay method

Impurity estimation method

Residual solvent/other volatile impurities (OVI) estimation method

2.6. Stability studies (for details refer Appendix IX)

Final release specification

Reference standard characterization
Material safety data sheet

2.7. Data on Formulation

Dosage form Composition
Master manufacturing formula
Details of the formulation (including inactive ingredients)
In process quality control check
Finished product specification
Excipient compatibility study
Validation of the analytical method
Comparative evaluation with international brand(s) or approved Indian brands, if applicable
Pack presentation
Dissolution
Assay
Impurities
Content uniformity
pH
Force degradation study
Stability evaluation in market intended pack at proposed storage conditions
Packing specifications
Process validation

When the application is for clinical trials only, the international non-proprietary name (INN) or generic name, drug category, dosage form and data supporting stability in the intended container-closure system for the duration of the clinical trial (information covered in Item Nos. 2.1, 2.3, 2.6, 2.7) are required.

3. *Animal Pharmacology (for details refer Appendix IV)*

3.1 Summary
3.2 Specific pharmacological actions
3.3 General pharmacological actions
3.4 Follow-up and Supplemental Safety Pharmacology Studies
3.5 Pharmacokinetics: absorption; distribution; metabolism; excretion

4. *Animal Toxicology (for details refer Appendix III)*

4.1 General Aspects
4.2 Systemic Toxicity Studies
4.3 Male Fertility Study
4.4 Female Reproduction and Developmental Toxicity Studies
4.5 Local toxicity
4.6 Allergenicity/Hypersensitivity
4.7 Genotoxicity
4.8 Carcinogenicity

[1304][Note.—Where the data on animal toxicity as per the specifications of Appendix-III has been submitted and the same has been considered by the regulatory authority of the country which had earlier approved the drug, the animal toxicity studies shall not be required to be conducted in India except in cases where there are. specific concerns recorded in writing.]

5. *Human/Clinical pharmacology (Phase I)*

5.1 Summary
5.2 Specific Pharmacological effects
5.3 General Pharmacological effects
5.4 Pharmacokinetics, absorption, distribution, metabolism, excretion
5.5 Pharmacodynamics/early measurement of drug activity

6. *Therapeutic exploratory trials (Phase II)*

6.1 Summary
6.2 Study report(s) as given in Appendix II

7. *Therapeutic confirmatory trials (Phase III)*

7.1 Summary
7.2 Individual study reports with listing of sites and investigators

8. *Special studies*

8.1 Summary
8.2 Bioavailability/Bioequivalence
8.3 Other studies *e.g.* geriatrics, paediatrics, pregnant or nursing women

9. *Regulatory status in other countries*

9.1. Countries where the drug is

(a) Marketed
(b) Approved
(c) Approved as IND
(d) Withdrawn, if any, with reasons

9.2. Restrictions on use, if any, in countries where marketed/approved

9.3 Free sale certificate or certificate of analysis, as appropriate

10. *Prescribing information*

10.1 Proposed full prescribing information
10.2 Drafts of labels and cartons

11. *Samples and Testing Protocol/s*

11.1 Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Licensing Authority), with testing protocol/s, full impurity profile and release specifications.

[1305][12. New Chemical Entity and Global Clinical Trial:

12.1 Assessment of risk versus benefit to the patients
12.2 Innovation vis-a-vis existing therapeutic option
12.3 Unmet medical need in the country.]

Notes.—(1) All items may not be applicable to all drugs. For explanation, refer text of Schedule Y.

(2), For requirements of data Jo be submitted with application for clinical trials refer text of this Schedule.

APPENDIX IA

DATA REQUIRED TG BE SUBMITTED BY AN APPLICATION FOR GRANT OF PERMISSION TO IMPORT AND/OR MANUFACTURE A NEW DRUG ALREADY APPROVED IN THE COUNTRY

1. ***Introduction***

A brief description of the drug and the therapeutic class

2. ***Chemical and pharmaceutical information***

2.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

2.2 Dosage form and its composition

2.3 Test specifications

(a) active ingredients

(b) inactive ingredient

2.4 Tests for identification of the active ingredients and method of its assay

2.5 Outline of the method of manufacture of active ingredients

2.6 Stability data

3. Marketing information

3.1 Proposed package insert/promotional literature

3.2 Draft specimen of the label and carton

4. ***Special studies conducted with approval of Licensing Authority***

4.1 Bioavailability/Bioequivalence and comparative dissolution studies for oral dosage forms

4.2 Sub-acute animal toxicity studies for intravenous infusions and injectables.

[1306][APPENDIX IB

DATA TO BE SUBMITTED ALONG WITH APPLICATION TO CONDUCT CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF A PHYTOPHARMACEUTICAL DRUG IN THE COUNTRY

PART I

1. Data to be submitted by the applicant:

1.1. A brief description or summary of the phytopharmaceutical drug giving the botanical name of the plant (including vernacular or scriptural name, wherever applicable), formulation and route of administration, dosages, therapeutic class for Which it is indicated and the claims id be'made for the phytopharmaceutical product.

1.2. Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethno medicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.

1.3. Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine literature or reports on current usage of the formulation.

1.4. Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed,—

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

1.5. Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years, wherever applicable.

1.6. Present usage of the phytopharmaceutical drug, - to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

2. Human or clinical pharmacology information:

2.1. Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed,—

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

2.2. Pharmacodynamic information (if available).

2.3. Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with english translation to be attached.)

PART II

DATA GENERATED BY APPLICANT

3. Identification, authentication and source of plant used for extraction and fractionation:

3.1. Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.

3.2. Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. (Furnish certificate of confirmation of botanical identity by a qualified taxonomist).

3.3. Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.

3.4. Season or time of collection.

3.5. Source of the plant including its geographical location and season or time of collection.

3.6. A statement indicating whether the species is any of the following, namely:—

(a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species (CITES) of wild Fauna and Flora;

(b) entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);

(c) any known genotypic, chemotypic and ecotypic variability of species.

3.7. A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely:—

(a) harvest location;
(b) growth conditions;
(c) stage of plant growth at harvest;
(d) harvesting time;
(e) collection, washing, drying and storage conditions;
(f) handling, garbling and transportation;
(g) grinding, pulverising of the plant material; and
(h) sieving for getting uniform particle size of powdered plant material.

3.8. Quality specifications, namely:—

(a) foreign matter;
(b) total ash;
(c) acid insoluble ash;
(d) pesticide residue;

(e) heavy metal contamination;
(f) microbial load;
(g) chromatographic fingerprint profile with phytochemical reference marker;
(h) assay for bio-active or phytochemical compounds; and
(i) chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).

3.9. An undertaking to supply specimen sample of plant duly labeled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.

4. Process for extraction and subsequent fractionation and purification:

4.1. Quality specifications and test methods for starting material.

4.2. Steps involved in processing.

(a) details of solvent used, extractive values, solvent residue tests or limits, physico-chemical tests, microbial loads, heavy metal contaminants, chromatographic finger-print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;

(b) characterisation of final purified fraction;

(c) data on bio-active constituent of final purified fraction;

(d) information on any excipients or diluents or stabiliser or preservative used, if any.

4.3. Details of packaging of the purified and characterised final product, storage conditions and labeling.

5. Formulation of phytopharmaceutical drug applied for:

5.1. Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per unit dose, name and

proportions of all excipients, Stabilisers and any other agent used and packaging materials.

5.2. Test for identification for the phytopharmaceutical drug

5.3. Quality specifications for active anfil inactive phytopharmaceutical chromatographic finger-print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.

6. Manufacturing process of formulation:

6.1. The outline of the method of manufacture of the dosage form/ along with environmental controls, in-process quality control tests and limits for acceptance.

6.2. Details of all packaging materials used, packing steps and description of the final packs.

6.3. Finished product's quality specifications, including tests specific for the dosage form, quality and chromatographic finger-print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.

7. Stability data:

7.1. Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature at 40 +/- 2 deg. C and humidity at 75% RH +/- 5%RH for 0, 1, 2, 3 and 6 months.

7.2. Stability data of the phytopharmaceutical drug in dosage form or formulation stored at room temperature at 40 +/- 2 deg. C and humidity at 75%RH +/-5%RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.

8. Safety and pharmacological information:

8.1. Data on safety and pharmacological studies to be provided.

8.2. Animal toxicity and safety data:

(a) 28 to 90 days repeat dose oral toxicity on two species of animals;

(b) *In*-vitro genotoxicity data (Ame's test and Chromosomal aberration test as per Schedule Y);

(c) dermal toxicity tests for topical use products;

(d) teratogenicity study (only if phytopharmaceutical drug is intended for use during pregnancy).

9. Human studies: -

9.1. Clinical trials for phytopharmaceutical drugs to be conducted as per applicable rules and guidelines for new drugs. ;

9.2. For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.

9.3. Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies: Provided that in the case pf phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.

10. Confirmatory clinical trials

10.1. Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.

10.2. Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable rules and guidelines.

10.3. Submit information on how the quality of the formulation would be maintained during the above studies.

11. Regulatory status:

11.1. Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as traditional medicine or as an approved drug.

12. Marketing information:

12.1. Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.

12.2. Draft of the text for label and carton.

13. Post marketing surveillance (PMS):

13.1. The applicant shall furnish periodic safety update reports eyery six months for the first two years after approval the drug is granted.

13.2. For subsequent two years the periodic safety update reports need to be submitted annually.

14. Any other relevant information:

Any other relevant information which the applicant considers that it will help in scientific evaluation of the application.

APPENDIX II

STRUCTURE, CONTENTS AND FORMAT FOR CLINICAL STUDY REPORTS

1. *Title Page***.—**This page should cdntain information about the title of the study, the protocol code, name of the investigational product tested, development phase, indication studied, a brief description of the trial design, the start and end date of patient accrual and the names of the sponsor and the participating institutes (investigators).

2. *Study Synopsis* (1 to 2 pages).—A brief overview of the study from the protocol development to the trial closure should be given here. This section will only summarize the important conclusions derived from the study.

3. *Statement of compliance with the 'Guidelines for Clinical Trials on Pharmaceutical Products in India*—GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India.

4. *List of Abbreviations and Definitions.*

5 *Table of contents*

6. *Ethics Committee.*—This section should document that the study was conducted in accordance with the ethical principles of Declaration of Helsinki. A detailed description of the Ethics Committee constitution and date(s) of approvals of trial documents for each of the participating sites should be provided. A declaration should state that EC notifications as per Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization and Ethical Guidelines for Biomedical Research on Human subjects, issued by Indian Council of Medical Research have been followed.

7. *Study Team.*—Briefly describe the administrative structure of the study (Investigators, site staff, sponsor/designates, Central laboratory etc.).

8. *Introduction.*—*A* brief description of the product development rationale should be given here.

9. *Study objective.*—A statement describing the overall purpose of the study and the primary and secondary objectives to be achieved should be mentioned here.

10. *Investigational Plan.*—This section should describe the overall trial design, the subject selection criteria, the treatment procedures, blinding/randomization techniques, if any, allowed/disallowed concomitant treatment, the efficacy and safety criteria assessed, the data quality assurance procedures and the statistical methods planned for the analysis of the data obtained.

11. *Trial Subjects.*-—*A* clear accounting of all trial subjects who entered the study will be given here. Mention should also be made of all cases that were dropouts or protocol deviations. Enumerate the patients screened, randomised, and prematurely discontinued. State reasons for premature discontinuation of therapy in each applicable case.

12. *Efficacy Evaluation.*—The results of evaluation of all the efficacy variables will be described in this section with appropriate tabular and graphical representation. A brief description of the demographic characteristics of the trial patients should also be provided alongwith a listing of patients and observations excluded from efficacy analysis.

13. *Safety Evaluation.*—This section should include the complete list

13.1 All serious adverse events, whether expected or unexpected, and

13.2 Unexpected adverse events whether serious or not (compiled from data received as per Appendix XI).

The comparison of adverse events across study groups may be presented in a tabular or graphical form. This section should also give a brief narrative of all important events considered related to the investigational product.

14. *Discussion and Overall Conclusion.*—Discussion of the important conclusions derived from the trial and scope for further development.

15. *List of References*

16. *Appendices.*—List of Appendices to the Clinical Trial Report—

(a) Protocol and amendments
(b) Specimen of Case Record Form
(c) Investigators' name(s) with contact addresses, phone, e-mail etc.
(d) Patient data listings
(e) List of trial participants treated with investigational product
(f) Discontinued participants
(g) Protocol deviations
(h) CRFs of cases involving death and life threatening adverse event cases
(i) Publications from the trial
(j) Important publications referenced in the study
(k) Audit certificate, if available

(1) Investigator's certificate that he/she has read the report and that the report accurately describes the conduct and the results of the study.

APPENDIX III

ANIMAL TOXICOLOGY (NON-CLINICAL TOXICITY STUDIES)

1. *General principles.*—Toxicity studies should comply with the norms of Good Laboratory Practice (GLP). Briefly, these studies should be performed by suitably trained and qualified staff employing properly calibrated and standardized equipment of adequate size and capacity. Studies should be done as per written protocols with modifications (if any) verifiable retrospectively. Standard Operating Procedures (SOPs) should be followed for all managerial and laboratory tasks related to these studies. Test substances and test systems (in-vitro or in-vivo) should be properly characterized and standardized. All documents belonging to each study, including its approved protocol, raw data, draft report, final report, and histology slides and paraffin tissue blocks should be preserved for a minimum of 5 years after marketing of the drug.

Toxicokinetic studies (generation of pharmacokinetic data either as an integral component of the conduct of non-clinical toxicity studies or in specially designed studies) should be conducted to assess the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study. Other objectives of toxicokinetic studies include obtaining data to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety, to support the choice of species and treatment regimen in non-clinical toxicity studies and to provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies.

1.1 *Systemic Toxicity Studies*

1.1.1 *Single-dose Toxicity Studies:* These studies (see Appendix I, Item 4.2) should be carried out in 2 rodent species (mice and rats) using the same route as intended for humans. In addition, unless the intended route of administration in humans is only intravenous, at least one more route should be used in one of the species to ensure systemic absorption of the drug. This route should depend on the nature of the drug. A limit of 2g/kg (or 10 times the normal dose that is

intended in humans, whichever is higher) is recommended for oral dosing. Animals should be observed for 14 days after the drug administration, and minimum lethal dose (MLD) and maximum tolerated dose (MTD) should be established. If possible, the target organ of toxicity should also be determined. Mortality should be observed for up to 7 days after parenteral administration and up to 14 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD_{10} and LD_{50} should be reported preferably with 95 per cent confidence limits. If LD_{50}s cannot be determined, reasons for the same should be stated.

The dose causing severe toxic manifestations or death should be defined in the case of cytotoxic anticancer agents, and the post-dosing observation period should be up to 14 days. Mice should first be used for determination of MTD. Findings should then be confirmed in rat for establishing linear relationship between toxicity and body surface area. In case of nonlinearity, data of the more sensitive species should be used to determine the Phase I starting dose. Where rodents are known to be poor predictors of human toxicity *(e.g.*, antifolates), or where the cytotoxic drug acts by a novel mechanism of action, MTD should be established in non-rodent species.

1.1.2 *Repeated-dose Systemic Toxicity Studies:* These studies *(see* Appendix I, Item 4.2) should be carried out in at least two mammalian species, of which one should be a non-rodent. Dose ranging studies should precede the 14-, 28-, 90- or 180-day toxicity studies. Duration of the final systemic toxicity study will depend on the duration, therapeutic indication and scale of the proposed clinical trial *(see* Item 1.8). If a species is known to metabolize the drug in the same way as humans, it should be preferred for toxicity studies.

In repeated-dose toxicity studies the drug should be administered 7 days a week by the route intended for clinical use. The number of animals required for these studies, *i.e.* the minimum number of animals on which data should be available, is shown in Item 1.9.

Wherever applicable, a control group of animals given the vehicle alone should be included, and three other groups should be given graded doses of the drug. The highest dose should produce observable toxicity; the lowest dose should not cause observable toxicity, but should be comparable to the intended

therapeutic dose in humans or a multiple of it. To make allowance for the sensitivity of the species the intermediate dose should cause some symptoms, but not gross toxicity or death, and should be placed logarithmically between the other two doses.

The parameters to be monitored and recorded in long-term toxicity studies should include behavioural, physiological, biochemical and microscopic observations. In case of parenteral drug administration, the sites of injection should be subjected to gross and microscopic examination. Initial and final electrocardiogram and fundus examination should be carried out in the non-rodent species.

In the case of cytotoxic anticancer agents dosing and study design should be in accordance with the proposed clinical schedule in terms of days of exposure and number of cycles Two rodent species may be tested for initiating Phase I trials. A non-rodent species should be added if the drug has a novel mechanism of action, or if permission for Phase II, III or marketing is being sought.

For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half life, incomplete elimination or unanticipated organ toxicity.

Notes.—(i) *Single Dose Toxicity Study:* Each group should contain at least 5 animals of either sex. At least four graded should be given. Animals should be exposed to the test substance in a single bolus or by continuous infusion or several doses within 24 hours. Animals should be observed for 14 days. Signs of intoxication, effect on body weight, gross pathological changes should be reported. It is desirable to include histo-pathology of grossly affected organs, if any.

(ii) *Dose-ranging Study:* Objectives of this study include the identification of target organ of toxicity and establishment of MTD for subsequent studies.

(a) Rodents: Study should be performed in one rodent species (preferably rat) by the proposed clinical route of administration. At least four graded doses including control should be given, and each dose group as well as the vehicle control should consist of a minimum of 5 animals of each sex. Animals should be exposed to the test substance daily for 10 consecutive days. Highest dose should be the maximum tolerated dose of single-dose study. Animals should be observed daily for signs of intoxication (general appearance, activity and behaviour etc.), and periodically for the body weight and laboratory parameters. Gioss examination of Viscera and microscopic examination of affected organs should be done.

(b) *Non-rodents:* One male and one female are to be taken for ascending phase MTD study. Dosing should start after initial recording of cage-side and laboratory parameters. Starting dose may be 3 to 5 times the extrapolated effective dose or MTD (whichever is less), and dose escalation in suitable steps should be done every third day after drawing the samples for laboratory parameters. Dose should be lowered appropriately when clinical or laboratory evidence of toxicity are observed. Administration of test substance should then continue for 10 days at the well-tolerated dose level following which, samples for laboratory parameters should be taken. Sacrifice, autopsy and microscopic examination of affected tissues should be performed as in the case of rodents..

(iii) *14-28 Day repeated-dose toxicity studies:* One rodent (6-10/sex/group) and one non-rodent (2-3/sex/group) species are needed. Daily dosing by proposed clinical route at three dose levels should be done with highest dose having observable toxicity, mid- dose between high and low dose, and low dose. The doses should preferably be multiples of the effective dose and free from toxicity. Observation parameters should include cage- side observations, body weight changes, food/water intake, blood biochemistry, haematology, and gross and microscopic studies of all viscera and tissues.

(iv*)* *90-Day repeated-dose toxicity studies:* One rodent (15-30/sex/group) and one non- rodent (4-6/sex/group) species are needed. Daily dosing by proposed clinical route at three graded dose levels should be done. In addition to the control a “high-dose-reversal” group and its control group should be also

included. Parameters should include signs of intoxication (general appearance, activity and behaviour etc), body weight, food intake, blood biochemical parameters, haematological values, urine analysis, organ weights, gross and microscopic study of viscera and tissues. Half the animals in "reversal" groups (treated and control) should be sacrificed after 14 days of stopping the treatment. The remaining animals should be sacrificed after 28 days of stopping the treatment or after the recovery of signs and/or clinical pathological changes – whichever comes later, and evaluated for the parameters used for the main study.

(v) *180-Day repeated-dose toxicity studies:* One rodent (15-30/sex/group) and one non-rodent (4-6/sex/group) species are needed. At least 4 groups, including control, should be taken. Daily dosing by proposed clinical route at three graded dose levels should be done. Parameters should include signs of intoxication, body weight, food intake, blood biochemistry, hematology, urine analysis, organ weights, gross and microscopic examination of organs and tissues.

1.2 Male Fertility Study:

One rodent species (preferably rat) should be used. Dose selection should be done from the results of the previous 14 or 28-day toxicity study in rat. Three dose groups, the highest one showing minimal toxicity in systemic studies, and a control group should be taken. Each group should consist of 6 adult male animals. Animals should be treated with the test substance by the intended route of clinical use for minimum 28 days and maximum 70 days before they are paired with female animals of proven fertility in a ratio of 1:2 for mating.

Drug treatment of the male animals should continue during pairing. Pairing should be continued till the detection of vaginal plug or 10 days, whichever is earlier. Females getting thus pregnant should be examined for their fertility index after day 13 of gestation. All the male animals should be sacrificed at the end of the study. Weights of each testis and epididymis should be separately recorded. Sperms from one epididymis should be examined for their motility and morphology. The other epididymis and both testes should be examined for their histology.

1.3 Female Reproduction and:Developmental Toxicity Studies:

These studies (see Appendix I, item 4.4) need to be carried out for all drugs proposed to be studied or used in women of child bearing age. Segment I, II and III studies (see below) are to be performed in albino mice or rats, and segment II study should include albino rabbits also as a second test species.

On the occasion, when the test article is not compatible with the rabbit (e.g. antibiotics which are effective against gram positive, anaerobic organisms and protozoas) the Segment II data in the mouse may be substituted.

1.3.1 *Female Fertility Study (Segment I):* The study should be done in one rodent species (rat preferred). The drug should be administered to both *males*and females, beginning a sufficient number of days (28 days in males and 14 days in females) before mating. Drug treatment should continue during mating and, subsequently, during the gestation period. Three graded doses should be used, the highest dose (usually the MTD obtained from previous systemic toxicity studies) should not affect general health of the parent animals. At least 15 males and 15 females should be used per dose group. Control and the treated groups should be of similar size. The route of administration should be the same as intended for therapeutic use.

Dams should be allowed to litter and their mcdication should be continued till the weaning of pups. Observations on body weight, food intake, clinical signs of intoxication, mating behaviour, progress of gestation/parturition periods, length of gestation, parturition, post-partem health and gross pathology (and histopathology of affected organs) of dams should be recorded. The pups from both treated and control groups should be observed for general signs of intoxication, sex-wise distribution in different treatment groups, body weight, growth parameters, survival, gross examination, and autopsy. Histopathology of affected organs should be done.

1.3.2 *Teratogenicity Study (Segment II):* One rodent (preferably rat) and one non-rodent (rabbit) species are to be used. The drug should be administered throughout the period of organogenesis, using three dose levels as described for Segment I. The highest dose should cause minimum material toxicity and the lowest one should be proportional to the proposed dose for clinical use in humans or a multiple of it. The route of administration should be the same as intended for human therapeutic use.

The control and the treated groups should consist of at least 20 pregnant rats (or mice) and 12 rabbits, on each dose level. All foetuses should to be subjected to gross examination, one of the foetuses should be examined for skeletal abnormalities and the other half for visceral abnormalities. Observation parameters should include: (Dams) signs of intoxication, effect on body weight, effect on food intake, examination of uterus, ovaries and uterine contents, number of corpora lutea, implantation sites, resorption (if any); and for the foetuses, the total number, gender, body length, weight and gross/ visceral/skeletal abnormalities, if any.

1.3.3 *Perinatal Study (Segment III):* This study is specially recommended if the drug is to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development. One rodent species (preferably rat) is needed. Dosing at levels comparable to multiples of human dose should be done by the intended clinical route. At least 4 groups (including control), each consisting of 15 dams should be used. The drug should be administered throughout the last trimester of pregnancy (from day 15 of gestation) and then the dose that causes low foetal loss should be continued throughout lactation and weaning. Dams should then be sacrificed and examined as described below.

One male and one female from each litter of F_1 generation (total 15 males and 15 females in each group) should be selected at weaning and treated with vehicle or test substance (at the dose levels described above) throughout their periods of growth to sexual maturity, pairing, gestation, parturition and lactation. Mating performance and fertility of F_1 generation should thus be evaluated to obtain the F_2 generation whose growth parameters should be monitored till weaning. The criteria of evaluation should be the same as described earlier (3.4.1).

Animals should be sacrificed at the end of the study and the observation parameters should include (Dams) body weight, food intake, general signs of intoxication, progress of gestation/ parturition periods and gross pathology (if any); and for pups, the clinical signs, sex-wise distribution in dose groups, body weight, growth parameters, gross examination, survival and autopsy (if needed) and where necessary, histopathology.

1.4 Local Toxicity

These studies (see Appendix I, item 4.5) are required when the new drug is proposed to be used by some special route (other than oral) in humans. The drug should be applied to an appropriate site (e.g., skin or vaginal mucous membrane) to determine local effects in a suitable species. Typical study designs for these studies should include three dose levels and untreated and/ or vehicle control, preferably use of 2 species, and increasing group size with increase in duration of treatment. Where dosing is restricted due to anatomical or humane reasons, or the drug concentration cannot be increased beyond a certain level due to the problems of solubility, pH or tonicity, a clear statement to this effect should be given. If the drug is absorbed from the site of application, appropriate systemic toxicity studies will also be required.

Notes (i) *Dermal toxicity study*: The study should be done in rabbit and rat. [1307][The initial toxicity study shall be carried out by non—animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines.] Test material should be applied on shaved skin covering not less than 10% of the total body surface area. Porous gauze dressing should be used to hold liquid material in place. Formulations with different concentrations (at least 3) of test substance, several fold higher than the clinical dosage form should be used. Period of application may vary from 7 to 90 days depending on the clinical duration of use. Where skin irritation is grossly visible in the initial studies, a recovery group should be included in the subsequent repeated-dose study. Local signs (erythema, oedema and eschar formation) as well as histological examination of sites of application should be used for evaluation of results.

(ii) *Photo-allergy or dermal photo-toxicity*: It should be tested by Armstrong/ Harber Test in guinea pig. This test should be done if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential (e.g., drugs to be used in treatment of leucoderma). Pretest in 8 animals should screen 4 concentrations (patch application for 2 hours ±15 min.) with and without UV exposure (10 J/cm^2). Observations recorded at 24 and 48 hours should be used to ascertain highest nonirritant dose. Main test should be performed with 10 test animals and 5 controls. Induction with the dose selected from pretest should use 0.3 ml/patch for 2 hour ±15 min. followed by 10 J/cm2 of UV exposure. This should be repeated on day 0, 2,4,7,9 and 11 of the test.

Animals should be challenged with the same concentration of test substance between day 20 to 24 of the test with a similar 2-hour application followed by exposure to 10 J/cm^2 of UV light. Examination and grading of erythema and oedema formation at the challenge sites should be done 24 and 48 hours after the challenge. A positive control like musk ambrett or psoralin should be used.

(iii) *Vaginal Toxicity Test*: Study is to be done in rabbit or dog. Test substance should be applied topically (vaginal mucosa) in the form of pessary, cream or ointment. Six to ten animals per dose group should be taken. Higher concentrations or several daily applications of test substance should be done to achieve multiples of daily human dose. The minimum duration of drug treatment is 7 days (more according to clinical use), subject to a maximum of 30 days. Observation parameters should include swelling, closure of introitus and histopathology of vaginal wall.

(iv) *Rectal Tolerance Test*: For all preparations meant for rectal administration this test may be performed in rabbits or dogs. Six to ten animals per dose group should be taken. Formulation in volume comparable to human dose (or the maximum possible volume) should be applied once or several times daily, per rectally, to achieve administration of multiples of daily human dose. The minimum duration of application is 7 days (more according to clinical use), subject to a maximum of 30 days. Size of suppositories may be smaller, but the drug content should be several fold higher than the proposed human dose. Observation parameters should include clinical signs (sliding on backside), signs of pain, blood and/or mucus in faeces, condition of anal region/sphincter, gross and (if required) histological examination of rectal mucosa.

(v) *Parenteral Drugs:* For products meant for intravenous or intramuscular or subcutaneous or intradermal injection the sites of injection in systemic toxicity studies should be specially examined grossly and microscopically. If needed, reversibility of adverse effects may be determined on a case to case basis.

(vi) *Ocular toxicity studies (for products meant for ocular instillation):* These studies should be carried out in two species, one of which should be the albino rabbit which has a sufficiently large conjunctival sac. Direct delivery of drug onto the cornea in case of animals having small conjunctival sacs should be ensured. Liquids, ointments, gels or soft contact lenses (saturated with drug) should be used. Initial single dose application should be done to decide the

exposure concentrations for repeated-dose studies and the need to include a recovery group. [1308][Such initial toxicity studies shall be carried out by non-animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines].Duration of the final study will depend on the proposed length of human exposure subject to a maximum of 90 days. At least two different concentrations exceeding the human dose should be used for demonstrating the margin of safety. In acute studies, one eye should be used for drug administration and the other kept as control. A separate control group should be included in repeated-dose studies.

Slit-lamp examination should be done to detect the changes in cornea, iris and aqueous humor. Fluorescent dyes (sodium fluorescein, 0.25 to 1.0%) should be used for detecting the defects in surface epithelium of cornea and conjunctiva. Changes in intra-ocular tension should be monitored by a tonometer. Histological examination of eyes should be done at the end of the study after fixation in Davidson‘s or Zenker‘s fluid.

(vii) *Inhalation toxicity studies:* The studies are to be undertaken in one rodent and one non-rodent species using the formulation that is to be eventually proposed to be marketed. Acute, subacute and chronic toxicity studies should be performed according to the intended duration of human exposure. Standard systemic toxicity study designs (described above) should be used. Gases and vapours should be given in whole body exposure chambers; aerosols are to be given by nose-only method. Exposure time and concentrations of test substance (limit dose of 5mg/l) should be adjusted to ensure exposure at levels comparable to multiples of intended human exposure. Three dose groups and a control (plus vehicle control, if needed) are required. Duration of exposure may vary subject to a maximum of 6 hours per day and five days a week. Food and water should be withdrawn during the period of exposure to test substance.

Temperature, humidity and flow rate of exposure chamber should be recorded and reported. Evidence of exposure with test substance of particle size of 4 micron (especially for aerosols) with not less that 25% being 1 micron should be provided. Effects on respiratory rate, findings of bronchial lavage fluid examination, histological examination of respiratory passages and lung tissue should be included along with the regular parameters of systemic toxicity studies or assessment of margin of safety.

1.5 Allergenicity/Hypersensitivity

Standard tests include guinea pig maximization test (GPMT) and local lymph node assay (LLNA) in mouse. Any one of the two may be done.

Notes (i) *Guinea Pig Maximization Test*: The test is to be performed in two steps; first, determination of maximum nonirritant and minimum irritant doses, and second, the main test. The initial study will also have two components. To determine the intradermal induction dose, 4 dose levels should be tested by the same route in a batch of 4 male and 4 female animals (2 of each sex should be given Freund's adjuvant). The minimum irritant dose should be used for induction. Similarly, a topical minimum irritant dose should be determined for challenge. This should be established in 2 males and 2 females. A minimum of 6 male and 6 female animals per group should be used in the main study. One test and one control group should be used. It is preferable to have one more positive control group. Intradermal induction (day 1) coupled with topical challenge (day 21) should be done. If there is no response, re-challenge should be done 7-30 days after the primary challenge. Erythema and oedema (individual animal scores as well as maximization grading) should be used as evaluation criteria.

(ii) *Local Lymph Node Assay*: Mice used in this test should be of the same sex, either only males or only females. Drug treatment is to be given on ear skin. Three graded doses, the highest being maximum nonirritant dose plus vehicle control should be used. A minimum of 6 mice per group should be used. Test material should be applied on ear skin on three consecutive days and on day 5, the draining auricular lymph nodes should be dissected out 5 hours after i.v. H-thymidine or bromo-deoxy-uridine (BrdU). Increase in H-thymidine or BrdU incorporation should be used as the criterion for evaluation of results.

1.6 Genotoxicity

Genotoxic compounds, in the absence of other data, shall be presumed to be trans-species carcinogens, implying a hazard to humans. Such compounds need not be subjected to long-term carcinogenicity studies. However, if such a drug is intended to be administered for chronic illnesses or otherwise over a long period of time - a chronic toxicity study (up to one year) may be necessary to detect early tumorigenic effects.

Genotoxicity tests are in vitro and in vivo tests conducted to detect compounds which induce genetic damage directly or indirectly. These tests should enable a hazard identification with respect to damage to DNA and its fixation.

The following standard test battery is generally expected to be conducted:

(i) A test for gene mutation in bacteria.

(ii) An in-vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an in vitro mouse lymphoma tic assay.

(iii) An in-vivo test for chromosomal damage using rodent hematopoietic cells. Other genotoxicity tests *e.g.* tests for measurement of DNA adducts, DNA strand breaks, DNA repair or recombination serve as options in addition to the standard battery for further investigation of genotoxicity test results obtained in the standard battery. Only under extreme conditions in which one or more tests comprising the standard battery cannot be employed for technical reasons, alternative validated tests can serve as substitutes provided sufficient scientific justification should be provided to support the argument that a given standard battery test is not appropriate.

Both in-vitro and in-vivo studies should be done. In-vitro studies should include Ames' Salmonella Assay and Chromosomal Aberrations (CA) in cultured cells. In-vivo studies should include Micronucleus Assay (MNA) or CA in rodent bone marrow. Data analysis of CA should include analysis of 'gaps'.

Cytotoxic Anticancer Agents: Genotoxicity data are not required before Phase I and II trials. But these studies should be completed before applying for Phase III trials.

Notes.—*Ames' Test (Reverse Mutation Assay in Salmonella):* S. typhimurium tester strains such as TA98, TA100, TA102, TA1535, TA97 or Escherichia coli WP2 uvrA or Escherichia coli WP2 uvrA (pKM101) should be used.

(i) In-vitro exposure (with and without metabolic activation, S9 mix) should be done at a minimum of 5 log dose levels. "Solvent" and "positive" control should

be used. Positive control may include 9-amino-acridine, 2-nitrofluorine, sodium azide and mitomycin C, respectively, in the tester strains mentioned above. Each set should consist of at least three replicates. A 2.5 fold (or more) increase in number of revertants in comparison to spontaneous revertants would be considered positive.

(ii) *In-vitro Cytogenetic Assay:* The desired level of toxicity for in-vitro cytogenetic tests using cell lines should be greater than 50% reduction in cell number or culture confluency. For lymphocyte cultures, an inhibition of mitotic index by greater than 50% is considered sufficient. It should be performed in CHO cells or on human lymphocyte in culture. In-vitro exposure (with and without metabolic activation, S9 mix) should be done using a minimum of 3 log doses. "Solvent" and "positive" control should be included. A positive control like Cyclophosphamide with metabolic activation and Mitomycin C for without metabolic activation should be used to give a reproducible and detectable increase clastogenic effect over the background which demonstrates the sensitivity of the test system. Each set should consist of at least three replicates. Increased number of aberrations in meta Phase chromosomes should be used as the criteria for evaluation.

(iii) *In-vivo Micronucleus Assay:* One rodent species (preferably mouse) is needed. Route of administration of test substance should be the same as intended for humans. Five animals per sex per dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. A positive control like mitomycin C or cyclophosphamide should be used. Dosing should be done on day 1 and 2 of study followed by sacrifice of animals 6 hours after the last injection. Bone marrow from both the femora should be taken out, flushed with fetal bovine serum (20 min.), pelletted and smeared on glass slides. Giemsa-MayGruenwald staining should be done and increased number of micronuclei in polychromatic erythrocytes (minimum 1000) should be used as the evaluation criteria.

(iv) *In-vivo Cytogenetic Assay:* One rodent species (preferably rat) is to be used. Route of administration of test substance should be the same as intended for humans. Five animals/sex/dose groups should be used. At least three dose levels, plus "solvent' and "Positive" control should be tested. Positive control may include cyclophosphamide. Dosing should be done on day I followed by intra-peritoneal colchicine administration at 22 hours. Animals should be

sacrificed 2 hours after colchicine administration. Bone marrow from both the femora should be taken out, flushed with hypotonic saline (20 min.), pelletted and resuspended in Carnoy's fluid. Once again the cells should be pelletted and dropped on clean glass slides with a Pasteur pipette. Giemsa staining should be done and increased number of aberrations in metaphase chromosomes (minimum 100) should be used as the evaluation criteria.

1.7 Carcinogenicity (See Appendix 1, Item 4.8)

Carcinogenicity studies should be performed for all drugs that are expected to be clinically used for more than 6 months as well as for drugs used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. Carcinogenicity studies are also to be performed for drugs if there is concern about their carcinogenic potential emanating from previous demonstration of carcinogenic potential in the product class that is considered relevant to humans or where structure-activity relationship suggests carcinogenic risk or when there is evidence of preneoplastic lesions in repeated dose toxicity studies or when long-term tissue retention of parent compound or metabolite(s) results in local tissue reactions or other pathophysiological responses. For pharmaceuticals developed to treat certain serious diseases, Licensing Authority may allow carcinogenicity testing to be conducted after marketing permission has been granted.

In instances where the life-expectancy in the indicated population is short *(i.e.,* less than 2-3 years) - no long-term carcinogenicity studies may be required. In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When such drugs are intended for adjuvant therapy in tumour free patients or for prolonged use in non-cancer indications, carcinogenicity studies may be/are needed. Completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical trials, unless there is special concern for the patient population.

Carcinogenicity studies should be done in a rodent species (preferably rat). Mouse may be employed only with proper scientific justification. The selected strain of animals should not have a very high or very low incidence of spontaneous tumors.

At least three dose levels should be used. The highest dose should be sub-lethal, and it should not reduce the life span of animals by more than 10% of expected normal. The lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, *e.g.* 2.5x; to make allowance for the sensitivity of the species. The intermediate dose is to be placed logarithmically between the other two doses. An untreated control and (if indicated) a vehicle control group should be included. The drug should be administered 7 days a week for a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Generally, the period of dosing should be 24 months for rats and 18 months for mice.

Observations should include macroscopic changes observed at autopsy and detailed histopathology of organs and tissues. Additional tests for carcinogenicity (short-term bioassays, neonatal mouse assay or tests employing transgenic animals) may also be done depending on their applicability on a case to case basis.

Note**.**—Each dose group and concurrent control group not intended to be sacrificed early should contain at least 50 animals of each sex. A high dose satellite group for evaluation of pathology other than neoplasia should contain 20 animals of each sex while the satellite control group should contain 10 animals of each sex. Observation parameters should include signs of intoxication, effect on body weight, food intake, clinical chemistry parameters, hematology parameters, urine analysis, organ weights, gross pathology and detailed histopathology. Comprehensive descriptions of benign and malignant tumour development, time of their detection, site, dimensions, histological typing etc. should be given.

1.8 Animal toxicity requirements for clinical trials and marketing of a new drug.

Systemic Toxicity Studies

Route of administration	Duration of proposed human administration	Human phase(s) for which study is proposed to be conducted	Long-term toxicity requirements
[1309][Oral, or parentral or transdermal	Single dose or several doses in one day, Upto 1 wk	I, II, III	2 sp, 2 wks

	>1 wk but upto 2 wks	I, II, III	2 sp; 2 wks
	Upto 2 wks	Marketing permission	2 sp; 4 wks
	>2 wks but upto 4 wks	I, II, III	2 sp; equal to duration of human exposure
		Marketing permission	2 sp; 12 wks
	> 4 wks but upto 12 wks	I, II, III	2 sp; equal to duration of human exposure
		Marketing permission	2 sp; 24 wks
	> 12 wks but upto 24 wks	I, II, III	2 sp; equal to duration of human exposure
		Marketing permission	2 sp; Rodent 24 wks, non-rodent 36 wks
	> 24 wks	I, II, III	2 sp; Rodent 24 wks, non-rodent 36 wks
		Marketing permission	2 sp; Rodent 24 wks, non-rodent 36 wks]
Inhalation (general Anaesthetics, aerosols)	Up to 2 wk	I, II, III	2 sp; I mo (Exposure time 3h/d, 5d/wk)
	Up to 4 wk	I, II, III	2 sp; 12 wk (Exposure time 6h/d, 5d/wk)
	> 14 wk	I, II, III	2 sp; 24 wk (Exposure time 6h/d, 5d/wk)
Local Toxicity Studies Dermal	Up to 2 wk	I, II	1 sp; 4 wk
		III	2 sp; 4 wk
	> 2 wk	I, II, III	2 sp: 12 wk
Ocular or Otic or Nasal	Up to 2 wk	I, II	1 sp; 4 wk
		III	2 sp; 4 wk
	> 2 wk	I, II, III	2 sp: 12 wk
Vaginal or Rectal	Up to 2 wk	I, II	1 sp; 4 wk
		III	2 sp. 4 wk
	> 2 wk	I, II, III	2 sp; 12 wk

Special Toxicity Studies

Male Fertility Study:

- [1310][Phase III in male volunteers/patients]

Female Reproduction and Developmental Toxicity Studies:

- Segment II studies in 2 species; Phase II, III involving female patients of child-bearing age.
- Segment I study; Phase III involving female patients of child-bearing age.
- Segment III study; Phase III for drugs to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development.

Allergenicity / Hypersensitivity: Phase I, II, III - When there is a cause of concern or for parenteral drugs (including dermal application)

Photo-allergy or Dermal Photo-toxicity:

• Phase I, II, III - If the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential.

Genotoxicity:

- In-vitro studies - Phase I
- Both in-vitro and in-vivo - Phase II, III

Arcinogenicity:

- Phase III - When there is a cause for concern, or when the drug is to be used for more than 6 months.

Abbreviations: sp-species; mo-month; wk-week; d-day; h-hour, I, II, III - Phases of clinical trial.

Note.—1. Animal toxicity data generated in other countries may be accepted and may not be asked to be repeated/duplicated in India on a case to case basis depending upon the quality of data and the credentials of the laboratory(ies) where such data has been generated.

2. Requirements for fixed dose combinations are given in Appendix VI.

1.9 Number of animals required for repeated-dose toxicity studies

Group	14-28 days				84-182 days			
	Rodent (Rat)		Non-rodent (Dog or Monkey)		Rodent (Rat)		Non-rodent (Dog or Monkey)	
	M	F	M	F	M	F	M	F
Control	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Low dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Intermediate dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
High dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6

2.0 Laboratory parameters to be included in toxicity studies

Haematological parameters

• Haemoglobin	• Total RBC Count	• Haematocrit	• Reticulocyte Count
• Total WBC Count	• Differential WBC Count	• Platelet Count	• Terminal Bone Marrow Examination
• ESR (Non-rodents only)	• General Blood Picture: A special mention of abnormal and immature cells should be made		
• Coagulation Parameters (Non-rodents only): Bleeding Time, Coagulation Time, Prothrombin Time Activated Partial Thromboplastin Time.			

Urinalysis Parameters

• Colour	• Appearance	• Specific Gravity	• 24-hour urinary output
• Reaction (pH)	• Albumin	• Sugar	• Acetone
• Bile pigments	• Urobilinogen	• Occult Blood	

Blood Biochemical Parameters

•Glucose	• Cholesterol	• Triglycerides	• HDL Cholesterol (Non-rodents only)
•LDL Cholesterol (Non-rodents only)	• Bilirubin	• SGPT(ALT)	• SGOT (AST)
•Alkaline Phosphatase	• GGT (Non-rodents (ALP) only)	• Blood Urea Nitrogen	• Creatinine
• Total Proteins	• Albumin	• Globulin (Calculated values)	• Sodium
• Potassium	• Phosphorus	• Calcium	

Grass and Microscopic Pathology

• Brain*: Cerebrum, Cerebellum, Midbrain	• (Spinal Cord)	• Eye	• (Middle Ear)
• Thyroid	• (Parathyroid)	• Spleen*	• Thymus
• Adrenal*	• (Pancreas)	• (Trachea)	• Lung*
• Heart*	• Aorta	• Oesophagus	• Stomach
• Duodenum	• Jejunum	• Terminal ileum	• Colon
• (Rectum)	• Liver*	• Kidney*	• Urinary bladder
• Epididymis	• Testis*	• Ovary	• Uterus*
• Skin	• Mammary gland	• Mesenteric lymph node	• Skeletal muscle

* Organs marked with an asterisk should be weighed.

( ) Organs listed in parenthesis should be examined if indicated by the nature of the drug or observed effects.

Non-clinical toxicity testing and safety evaluation data of an IND needed for the conduct of different phases of clinical trials.

Note.—Refer Appendix III (Points 1.1 through 1.7 and tables 1.8 and 1.9) for essential features of study designs of the non-clinical toxicity studies listed below.

For Phase I Clinical Trials Systemic Toxicity studies

(i) Single dose toxicity studies.

(ii) Dose Ranging Studies.

(iii) Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Male fertility study

In-vitro genotoxicity tests—

Relevant local toxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure).

Allergenicity/Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application).

Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential).

For *Phase II Clinical Trials*

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I trial, with appropriate references.

In case of an application for directly starting a Phase II trial - complete details of the non-clinical safety data needed for obtaining the permission for Phase I trial, as per the list provided above must be submitted.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

In-vivo genotoxicity tests—

Segment II reproductive/developmental toxicity study (if female patients of child bearing age are going to be involved).

For Phase III Clinical Trials

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permission for Phase I and II trials, with appropriate references.

In case of an application for directly initiating a Phase III trial - complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and Phase II trials, as per the list provided above must be provided.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Reproductive/developmental toxicity studies

Segment I (if female patients of child bearing age are going to be involved), and Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development).

Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).

For Phase IV Clinical Trials

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I, II and III trials, with appropriate references.

In case an application is made for initiating the Phase IV trial, complete details of the non-clinical safety data needed for obtaining the permissions for Phase I, II and III trials, as per the list provided above must be submitted.

Application of Good Laboratory Practices (GLP)—

The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

APPENDIX IV

ANIMAL PHARMACOLOGY

1. *General principles*

Specific and general pharmacological studies should be conducted to support use of therapeutics in humans. In the early stages of drug development enough information may not be available to rationally select study design for safety assessment. In such a situation, a general approach to safety pharmacology studies can be applied. Safety pharmacology studies are studies that investigate potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range or above.

1.1 Specific Pharmacological Actions

Specific pharmacological actions are those which demonstrate the therapeutic potential for humans.

The specific studies that should be conducted and their design will be different based on the individual properties and intended uses of investigational drug.

Scientifically validated methods should be used. The use of new technologies and methodologies in accordance with sound scientific principles should be preferred.

1.2 General Pharmacological Actions

1.2.1 Essential Safety Pharmacology

Safety pharmacology studies need to be conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range and above. These studies should be designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; to evaluate adverse pharmacodynamic and/or pathophysiological effects observed in toxicology and/or clinical studies; and to investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected.

The aim of the essential safety pharmacology is to study the effects of the test drug on vital functions. Vital organ systems such as cardiovascular, respiratory and central nervous systems should be studied. Essential safety pharmacology studies may be excluded or supplemented based on scientific rationale. Also, the exclusion of certain test(s) or exploration(s) of certain organs, systems or functions should be scientifically justified.

1.2.1.1 Cardiovascular System

Effects of the investigational drug should be studied on blood pressure, heart rate and the electrocardiogram. If possible in-vitro, in-vivo and/or ex-vivo methods including electrophysiology should also be considered.

1.2.1.2 Central Nervous System

Effects of the investigational drug should be studied on motor activity, behavioural changes, coordination, sensory and motor reflex responses and body temperature.

1.2.1.3 Respiratory System

Effects of the investigational drug on respiratory rate and other functions such as tidal volume and haemoglobin oxygen saturation should be studied.

1.3 Follow-up and Supplemental Safety Pharmacology Studies

In addition to the essential safety pharmacological studies, additional supplemental and follow-up safety pharmacology studies may need to be conducted as appropriate. These depend on the pharmacological properties or chemical class of the test substance, and the data generated from safety pharmacology studies, clinical trials, pharmacovigilance, experimental in-vitro or in-vivo studies, or from literature reports.

1.3.1 Follow-up Studies for Essential Safety Pharmacology

Follow-up studies provide additional information or a better understanding than that provided by the essential safety pharmacology.

1.3.1.1 Cardiovascular System

These include ventricular contractility, vascular resistance and the effects of chemical mediators, their agonists and antagonists on the cardiovascular system.

1.3.1.2 Central Nervous System

These include behavioural studies, learning and memory, electrophysiology studies, neurochemistry and ligand binding studies.

1.3.1.3 Respiratory System

These include airway resistance, compliance, pulmonary arterial pressure, blood gases and blood pH.

1.3.2 Supplemental Safety Pharmacology Studies

These studies are required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety pharmacological studies and are a cause for concern.

1.3.2.1 Urinary System

These include urine volume, specific gravity, osmolality, pH, proteins, cytology and blood urea nitrogen, creatinine and plasma proteins estimation.

1.3.2.2 Autonomic Nervous System

These include binding to receptors relevant for the autonomic nervous system, and functional response to agonist or antagonist responses in-vivo or in-vitro, and effects of direct stimulation of autonomic nerves and their effects on cardiovascular responses.

1.3.2.3 Gastrointestinal System

These include studies on gastric secretion, gastric pH measurement, gastric mucosal examination, bile secretion, gastric emptying time in-vivo and ileocaecal contraction in-vitro.

1.3.2.4 Other Organ Systems

Effects of the investigational drug on organ systems not investigated elsewhere should be assessed when there is a cause for concern. For example dependency potential, skeletal muscle, immune and endocrine functions may be investigated.

1.4 *Conditions under which Safety Pharmacology Studies are not necessary*

Safety pharmacology studies are usually not required for locally applied agents *e.g.* dermal or ocular, in cases when the pharmacology of the investigational drug is well known, and/or when systemic absorption from the site of application is low. Safety pharmacology testing is also not necessary, in the case of a new derivative having similar pharmacokinetics and pharmacodynamics.

1.5 *Timing of Safety Pharmacology Studies in relation to Clinical Development*

1.5.1 Prior to First Administration in Humans

The effects of an investigational drug on the vital functions listed in the essential safety pharmacology should be studied prior to first administration in humans. Any follow-up or supplemental studies identified, should be conducted if necessary, based on a cause for concern.

1.5.2 During Clinical Development

Additional investigations may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development.

1.5.3 Before applying for marketing approval

Follow-up and supplemental safety pharmacology studies should be assessed prior to approval unless not required, in which case this should be justified. Available information from toxicology studies addressing safety pharmacology endpoints or information from clinical studies can replace such studies.

1.6 *Application of Good Laboratory Practices (GLP)*

The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

APPENDIX V

INFORMED CONSENT

1. Checklist for study subject's informed consent documents—

1.1 Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research.

2. Expected duration of the subject's participation.
3. Description of the procedures to be followed, including all invasive procedures.
4. Description of any reasonably foreseeable risks or discomforts to the subject.
5. Description of any benefits to the subject or others reasonably expected from research. If no benefit is expected subject should be made aware of this.
6. Disclosure of specific appropriate alternative procedures or therapies available to the subject.
7. Statement describing the extent to which confidentiality of records identifying the subject will be maintained and who will have access to subject's medical records.
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials).

[1311][(9) Statement describing the financial compensation and medical management as under:

[1312][(a) In case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.

(b) In the event of a trial related injury or death, the Sponsor or his representative, whosoever has obtained permission from the Licensing Authority for conduct of the clinical trial, shall provide financial compensation for the injury or death.

10. An explanation about whom to contact for trial related queries, rights of subjects and in the event of any injury.
11. The anticipated prorated payment, if any, to the subject for participating in the trial.
12. Subject's responsibilities on participation in the trial.
13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled.

[1313][14. Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

[1313][15. Statement that in the case of placebo controlled trial, the placebo administered to the subjects shall not have any therapeutic effect.

[1313][16. Any other pertinent information.

1.2 Additional elements, which may be required:

(a) Statement of foreseeable circumstances under which the subject's participation may be terminated by the Investigator without the subject's consent.

(b) Additional costs to the subject that may result from participation in the study.

(c) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by subject.

(d) Statement that the subject or subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the subject's willingness to continue participation will be provided.

(e) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or foetus, if the subject is or may become pregnant), which are currently unforeseeable.

(f) Approximate number of subjects enrolled in the study.

2. Format of informed consent form for subjects participating in a clinical trial—

Informed Consent form to participate in a clinical trial Study Title:
Study Number:
Subject's Initials:.....Subject's Name:.....
Date of Birth/Age:.....
[1314][Address of the Subject.....
Qualification.....
Occupation: Student/Self-Employed/Service/Housewife/Others (Please tick as appropriate)
Annual Income of the subject.....
Name and address of the nominee(s) and his relation to the subject.....(for the purpose of compensation in case of trial related death).]

Please initial box
(Subject)

(i)	I confirm that I have read and understood the information sheet dated..... for the above study and have had the opportunity to ask questions	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected	[ ]
(iii)	I understand that the sponsor of the clinical trial, others working on the sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).	[ ]
(v)	I agree to take part in the above study.	[ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

Date:...../.... ../.....

Signatory's Name:_____

Signature of the Investigator:_____

Date:...../.... ../.....

Study Investigator's Name:_____

Signature of the Witness.....

Date:...../.... ../.....

Name of the Witness:_____

[1315][(Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the subject or his/her attendant).]

APPENDIX VI

FIXED DOSE COMBINATIONS (FDCs)

Fixed Dose Combinations refer to products containing one or more active ingredients used for a particular indication(s). FDCs can be divided into the following groups and data required for approval for marketing is described below:

(a) The first group of FDCs includes those in which one or more of the active ingredients is a new drug. For such FDCs to be approved for marketing data to be submitted will be similar to data required for any new drug (including clinical trials) *[See* Rule 122E, item (a)].

(b) (i) The second group FDCs includes those in which active ingredients already approved/ marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature [See Rule 122-E, item (c)]. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated (See Appendix 1, Item 9).

(ii) For marketing permission, appropriate chemical and pharmaceutical data will be submitted. In case such a combination is not marketed anywhere in the world but these drugs are already in use concomitantly (not as an FDC but individually) for the said claim, marketing permission may be granted based on chemical and pharmaceutical data. Data showing the stability of the proposed dosage form will also have to be submitted.

(iii) For any other such FDCs, clinical trials may be required. For obtaining permission to carry out clinical trials with such FDCs a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio.

(c) The third group of FDCs includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such FDCs, the appropriate rationale including published reports (if any) should be submitted to obtain marketing permission. Permission will be granted depending upon the nature of the claim and data submitted.

(d) The fourth group of FDC includes those whose individual active ingredients (or drugs from the same class) have been widely used in a particular indication(s) for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience. It will have to be demonstrated that the proposed dosage form is stable and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

No additional animal or human data are generally required for these FDCs, and marketing permission may be granted if the FDC has an acceptable rationale.

APPENDIX VII

UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator [or Investigator(s) when there is no Principal Investigator].

2. Name and address of the medical college, hospital or other facility where the clinical trial will be conducted: Education, training and experience that qualify the Investigator for the clinical trial [Attach details including Medical Council registration number, and/or any other statement(s) of qualification(s)].

3. Name and address of all clinical laboratory facilities to be used in the study.

4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.

5. Names of the other members of the research team (Co- or sub-investigators) who will be assisting the Investigator in the conduct of the investigation(s).

6. Protocol title and Study number (if any) of the clinical trial to be conducted by the Investigator.

7. Commitments:

(i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary Ethics Committee and regulatory approvals have been obtained.

(ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the sponsor and prior review and documented approval/ favourable opinion from the Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to the trial subjects or when the change(s) involved are only logistical or administrative in nature.

(iii) I agree to personally conduct and/or supervise the clinical trial at my site.

(iv) I agree to inform all subjects, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and Ethics Committee review and approval specified in the GCP guidelines are met.

(v) I agree to report to the sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory and GCP guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit/inspection by the sponsor, Ethics Committee, Licensing Authority or their authorized representatives, in accordance with

regulatory and GCP provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized representatives of the sponsor.

(ix) I agree to promptly report to the Ethics Committee all changes in the clinical trial activities and all unanticipated problems involving risks to human subjects or others.

(x) I agree to inform all unexpected serious adverse events to the sponsor as well as the Ethics Committee within seven days of their occurrence.

(xi) I will maintain confidentiality of the identification of all participating study patients and assure security and confidentiality of study data.

(xii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials.

8. Signature of Investigator with date.

APPENDIX VIII

ETHICS COMMITTEE

[1316]**[I. Requirements and guidelines for registration of Ethics Committee**

1. Scope:

Ethics Committee shall review every clinical trial proposal and evaluate the possible risks to the subjects, expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice. In the case of any serious adverse event occurring to the clinical trial subjects during the clinical trial, the Ethics. Committee shall analyse and forward us opinion as per procedures specified in APPENDIX XII of Schedule Y.

2. Composition of Ethics Committee:

(a) Ethics Committee shall consist of not less than seven members and one among its members, who is from outside the institute, shall be appointed as Chairman; one member as a Member Secretary and rest of the

members shall be from Medical, Scientific, Non-medical and Non-scientific fields including lay public.

(b) The committee shall include at least one member whose primary area of interest or specialization is Non-scientific and at least one member who is independent of the institution. Besides, there should be appropriate gender representation on the Ethics Committee.

(c) The Ethics Committee can have as its members, individuals from other Institutions or Communities, if required.

(d) Members should be conversant with the provisions of clinical trials under this Schedule, Good Clinical Practice Guidelines lor clinical trials in India and other regulatory requirements to safeguard the rights, safety and well-being of the trial subjects.

(e) For review of each protocol the quorum of Ethics Committee shall be at least five members with the following representations:

(i) basic medical scientist (preferably one pharmacologist);
(ii) clinician;
(iii) legal expert;
(iv) social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person;
(v) lay person from community.

(f) The members representing medical scientists and clinicians should have Post graduate qualification and adequate experience in their respective fields and aware of their role and responsibilities as committee members.

(g) As far as possible, based on the requirement of research area such as HIV, Genetic disorder, etc., specific patient group may also be represented in the Ethics Committee.

(h) There should be no conflict of interest. The members shall voluntarily withdraw from the Ethics Committee meeting while making a decision on an application which evokes a conflict of interest which may be indicated in writing to the Chairman prior to the review and be recorded so in the minutes, All members shall sign a declaration on conflict of interest,

(i) Subject experts or other experts may be invited to the meetings for their advice. But no such expert shall have voting rights.

3. Information required to be submitted by the applicant for registration of Ethics Committee:

(a) Name of the Ethics Committee.

(b) Authority under which the Ethics Committee has been constituted, membership requirements, the term of reference, conditions of appointment and the quorum required.

(c) The procedure for resignation, replacement or removal of members.

(d) Address of the office of the Ethics Committee.

(e) Name, address, qualification, organisational title, telephone number, fax number, e-mail, mailing address and brief profile of the Chairman.

(f) Names, qualifications, organisational title, telephone number, fax number, e-mail and mailing address of the members of the Ethics Committee. The information shall also include member's specialty (primary, scientific or non-scientific), member's affiliation with institutions and patient group representation, if any.

(g) Details of the supporting staff.

(h) In the case of Ethics Committees existing before the publication of the Drugs and Cosmetics (Third Amendment) Rules, 2013,—

(i) type of clinical research reviewed by the committee *(e.g.* Pharmaceuticals, devices, epidemiological, retrospective, herbals, etc.)

(ii) documents reviewed for every clinical trial protocol including Informed Consent documents.

(iii) information in respect of number of meetings of the committee and documentation of the minutes of meetings of these committees concerning clinical trials.

(iv) information regarding review of serious adverse events reported during the conduct of the trial.

(i) The standard operating procedures to be followed by the committee in general.

(j) standard operating procedures to be followed by the committee for vulnerable population.

(k) Policy regarding training for new and existing committee members along with standard operating procedures.

(1) Policy to monitor or prevent the conflict of interest along with standard operating procedures.

(m) If the committee has been audited or inspected before, give details.

4. Maintenance of Record:

All documentation and communication of an Ethics Committee are to be dated, filed and preserved according to the standard operating procedures. Strict confidentiality shall be maintained during access and retrieval procedures. Records should be maintained for the following, namely:—

(a) The constitution and composition of the Ethics Committee;
(b) The curriculum vitae of all the committee members;
(c) Standard operating procedures followed by the committee;
(d) National and international guidelines;
(e) Copies of the protocol, data collection formats, Case Report Forms, Investigator's brochures, etc., submitted for review;
(f) All correspondence with committee members and Investigators regarding application, decision and follow up;
(g) Agenda of all Ethics Committee meetings;
(h) Minutes of all Ethics Committee meetings with signature of the Chairman;
(i) Copies of decisions communicated to the applicants;
(j) Record of all notification issued for premature termination of a study with a summary of the reasons;

(k) Final report of the study including microfilms, compact disks or Video recordings.

All records shall be safely maintained after the completion or termination of the study for not less than five years from the date of completion or termination of the trial (Both in hard and soft copies).

5. The Ethics Committee shall be open to inspection by the officers authorised by the Central Drugs Standard Control Organisation, who may include an officer of the State Drug Control Authority concerned, to verify compliance to the requirements of Schedule Y, Good Clinical Practices guidelines and other applicable regulation for safeguarding the rights, safety and well-being of the trial subjects.]

[1317]**[III. Format for According Approval to clinical trial protocol by the Ethics Committee]**

To

Dr

Dear Dr._____

The Institutional Ethics Committee/Independent Ethics Committee (state name of the committee, as appropriate) reviewed and discussed your application to conduct the clinical trial entitled "....." on ..... (date).

The following documents were reviewed:—

(a) Trial Protocol (including protocol amendments), dated .....Version No.(s) .....

(b) Patient Information Sheet and Informed Consent Form (including updates, if any) in English and/or vernacular language.

(c) Investigator's Brochure, dated ..... Version No.....

(d) Proposed methods for patient accrual including advertisement(s) etc. proposed to be used for the purpose.

(e) Principal Investigator's current CV.

(f) Insurance Policy/Compensation for participation and for serious adverse events occurring during the study participation.

(g) Investigator's Agreement with the sponsor.

(h) Investigator's Undertaking (Appendix VII).

The following members of the Ethics Committee were present at the meeting held on (date, time, place).

.....Chairman of the Ethics Committee.

.....Member-Secretary of the Ethics Committee.

.....Name of each member with designation.

We approve the trial to be conducted in its presented form.

The Institutional Ethics Committee/Independent Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

Yours sincerely,

Member-Secretary, Ethics Committee.

APPENDIX IX

STABILITY TESTING OF NEW DRUGS

Stability testing is to be performed to provide evidence on how the quality of a drug substance or formulation varies with time under the influence of various environmental factors such as temperature, humidity and light, and to establish shelf life for the formulation and recommended storage conditions.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/ or efficacy. In case of formulations the testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content *(e.g.*, antioxidant, antimicrobial preservative), and functionality tests *(e.g.*, for a dose delivery system).

Validated stability indicating analytical procedures should be applied. For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance.

In general, a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen should be sufficient to cover storage, shipment and subsequent use.

Stress testing of the drug substance should be conducted to identify the likely degradation products, which in turn establish the degradation pathways, evaluate the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of formulation involved.

Stress testing may generally be carried out on a single batch of the drug substance. It should include the effect of temperature(s), humidity where appropriate, oxidation and photolysis on the drug substance.

Data should be provided for (a) Photostability on at least one primary batch of the drug substance as well as the formulation, as the case may be, and (b) the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.

Long-term testing should cover a minimum of 12 months' duration on at least three primary batches of the drug substance or the formulation at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Accelerated testing should cover a minimum of 6 months duration at the time of submission.

In case of drug substances, the batches should be manufactured to a minimum of pilot scale by the same synthetic route and using a method of manufacture that simulates the final process to be used for production batches. In case of formulations, two of the three batches should be at least pilot scale and the third one may be smaller. The manufacturing process(es) used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specifications as that intended for marketing.

The stability studies for drug substances should be conducted either in the same container-closure system as proposed for storage and distribution or in a container-closure system that simulates the proposed final packaging. In case of

formulations, the stability studies should be conducted in the final container-closure system proposed for marketing.

Stability testing of new drug substances and formulations:

(i) Study conditions for drug substances and formulations intended to be stored under general conditions

Study	Study conditions	Duration of study
Long-term	30° C ± 2° C/65% RH ± 5% RH	12 months
Accelerated	40° C ± 2° C/75% RH ± 5% RH	6 months

If at any time during 6 months' testing under the accelerated storage condition, such changes occur that cause the product to fail in complying with the prescribed standards, additional testing under an intermediate storage condition should be conducted and evaluated against significant change criteria.

(ii) Study conditions for drug substances and formulations intended to be stored in a refrigerator

Study	*Study conditions*	*Duration of study*
Long-term	5° C ± 3° C	12 months
Accelerated	25° C ± 2° C/60% RH ± 5% RH	6 months

(iii) Study conditions for drug substances and formulations intended to be stored in a freezer

Study	*Study conditions*	*Duration of study*
Study	Study conditions	Duration of study
Long-term	-20° C° ± 5° C	12 months

(iv) Drug substances intended for storage below -20° C shall be treated on a case-by-case basis.

(v) Stability testing of the formulation after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period.

APPENDIX X

CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL TRIALS

1. Title Page—

(a) Full title of the clinical study.
(b) Protocol/Study number and protocol version number with date.
(c) The IND name/number of the investigational drug.
(d) Complete name and address of the sponsor and contract research organization, if any.
(e) List of the Investigators who are conducting the study, their respective institutional affiliations and site locations.
(f) Name(s) of clinical laboratories and other departments and/or facilities participating in the study.

2. Table of Contents—

A complete Table of Contents including a list of all Appendices.

1. Background and Introduction

(a) Pre-clinical experience
(b) Clinical experience

Previous clinical work with the new drug should be reviewed here and a description of how the current protocol extends existing data should be provided. If this is an entirely new indication, how this drug was considered for this should be discussed. Relevant information regarding pharmacological, toxicological and other biological properties of the drug/ biologic/medical device and previous efficacy and safety experience should be described.

2. Study Rationale

This section should describe a brief summary of the background information relevant to the study design and protocol methodology. The reasons for performing this study in the particular population included by the protocol should be provided.

3. Study objective(s) (primary as well as secondary) and their logical relation to the study design.

4. Study Design—

(a) *Overview of the Study Design:* Including a description of the type of study *(i.e.*, double-blind, multicentre, placebo controlled, etc.), a detail of the specific treatment groups and number of study subjects in each group and investigative site, subject number assignment, and the type, sequence and duration of study periods.

(b) Flow chart of the study.

(c) A brief description of the methods and procedures to be used during the study.

(d) Discussion *of Study Design.*—This discussion details the rationale for the design chosen for this study.

5. Study Population: The number of subjects required to be enrolled in the study at the investigative site and by all sites along with a brief description of the nature of the subject population required is also mentioned.

6. Subject Eligibility—

(a) Inclusion Criteria.
(b) Exclusion Criteria.

7. *Study Assessments*—Plan, procedures and methods to be described in detail.

8. Study Conduct stating the types of study activities that would be included in this section would be: medical history, type of physical

examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom measurement, dispensation and retrieval of medication, subject cohort assignment, adverse event review, etc.

Each visit should be described separately as Visit 1, Visit 2, etc.

Discontinued Subjects: Describes the circumstances for subject withdrawal, drop-outs, or other reasons for discontinuation of subjects. State how drop-outs would be managed and if they would be replaced, describe the method of handling of protocol waivers, if any. The person(s) who approves all such waivers should be identified and the criteria used for specific waivers should be provided.

Describes how protocol violations will be treated, including conditions where the study will be terminated for non-compliance with the protocol.

9. Study Treatment—

(a) Dosing schedule (dose, frequency and duration of the experimental treatment). Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency and duration of concomitant treatment should be stated.

(b) *Study drug supplies and administration:* A statement about who is going to provide the study medication and that the investigational drug formulation has been manufactured following all regulations. Details of the product stability, storage requirements and dispensing requirements should be provided.

(c) *Dose modification for study drug toxicity:* Rules for changing the dose or stopping the study drug should be provided.

(d) Possible drug interactions.

(e) *Concomitant therapy:* The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a subject is not allowed to use during parts of or

the entire study. If any washout periods for prohibited medications are needed prior to enrolment, these should be described here.

(f) *Blinding procedures: A* detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the subject.

(g) *Unblinding procedures:* If the study is blinded, the circumstances in which unblinding may be done and the mechanism to be used for unblinding should be given.

10. *Adverse Events* (See *Appendix XT):* Description of expected adverse events should be given.

Procedures used to evaluate an adverse event should be described.

11. Ethical Considerations: Give the summary of—

(a) Risk/benefit assessment:
(b) Ethics Committee review and communications:
(c) Informed consent process:
(d) Statement of subject confidentiality including ownership of data and coding procedures:

12. *Study Monitoring and Supervision: A* description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected to perform monitoring.

Case Record Form (CRF) completion requirements, including who gets which copies of the forms and any specifics required in filling out the forms, CRF correction requirements, including who is authorized to make corrections on the CRF and how queries about study data are handled and how errors, if any, are to be corrected should be stated.

Investigator study files, including what needs to be stored following study completion should be described.

13. Investigational Product Management—

(a) Give Investigational product description and packaging (stating all ingredients and the formulation of the investigational drug and any placebos used in the study).

(b) The precise dosing required during the study.
(c) Method of packaging, labelling and blinding of study substances.
(d) Method of assigning treatments to subjects and the subject identification code numbering system.
(e) Storage conditions for study substances.
(f) *Investigational product accountability:* Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed and returned / destroyed.
(g) Describe policy and procedure for handling unused investigational products.

14. Data Analysis—

Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.

Statistical Analysis: Give complete details of how the results will be analyzed and reported along with the description of statistical tests to be used to analyze the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data; method of evaluation of the data for treatment failures, non-compliance, and subject withdrawals, rationale and conditions for any interim analysis, if planned.

Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable.

15. Undertaking by the Investigator *(See* Appendix VII).

16. Appendices.—Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

APPENDIX XI

DATA ELEMENTS FOR REPORTING SERIOUS ADVERSE EVENTS OCCURRING IN A CLINICAL TRIAL

1. Patient Details—

Initials and other relevant identifier (hospital/OPD record number etc.)*
Gender
Age and/or date of birth
Weight
Height

2. Suspected Drug(s)—

Generic name of the drug*
Indication(s) for which suspect drug was prescribed or tested Dosage form and strength
Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)
Route of administration
Starting date and time of day
Stopping date and time or duration of treatment

3. Other Treatment(s)—

Provide the same information for concomitant drugs (including non-prescription/OTC drugs) and non-drug therapies, as for the suspected drug(s).

4. Details of Suspected Adverse Drug Reaction(s)—

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.*

Start date (and time) of onset of reaction
Stop date (and time) or duration of reaction
Dechallenge and rechallenge information
Setting *(e.g.*, hospital, out-patient clinic, home, nursing home)

5. Outcome—

Information on recovery and any sequelae; results of specific tests and/or treatment that may have been conducted.

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; Any post-mortem findings,

Other information: Anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.

6. Details about the Investigator*—

Name**:**
Address**:**
Telephone number:
Profession (Speciality):
Date of reporting the event to Licensing Authority:
Date of reporting the event to Ethics Committee overseeing the site:
Signature of the Investigator

Note.—Information marked* must be provided.]

[1318][APPENDIX XII

COMPENSATION IN CASE OF INJURY OR DEATH DURING CLINICAL TRIAL

[1319][(1) In case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.]

(2) In case the injury occurring to the trial subject is related to the clinical trial, such subject shall also be entitled for financial compensation as per order of the Licensing Authority defined under clause (b) of rule 21, and the financial compensation will be over and above any expenses incurred on the medical management of the subject. [1320][In case, there is no permanent injury, the

quantum of compensation shall be commensurate with the nature of the nonpermanent injury and loss of wages.]

(3) In the case of clinical trial related death of the subject, his/her nominee(s) would be entitled for financial compensation, as per the order of the Licensing Authority defined under clause (b) of rule 21, and the financial compensation will be over and above any expenses incurred on the medical management of the subject.

(4) The financial compensation for clinical trial related injury or death could be in the form of:—

(a) payment for medical management;
(b) financial compensation for trial related injury;
(c) financial compensation to nominee(s) of the trial subject in case of death;
(d) financial compensation for the child injured in-utero because of the participation of parent in clinical trial.

(5) The Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, shall provide financial compensation, if the injury or death has occurred because of any of the following reasons, namely:—

(a) adverse effect of investigational product(s);

(b) any clinical trial procedures involved in the study;

(c) violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the Investigator;

(d) failure of investigational product to provide intended therapeutic effect [1320][where, the standard care, though available, was not provided to the subject as per the clinical trial protocal];

(e) use of placebo in a placebo-controlled trial [1320][where, the standard care, though available, was not provided to the subject as per the clinical trial protocal];

(f) adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;

(g) Injury to the child in-utero because of the participation of parent in clinical trial.

(6) Procedure for payment of financial compensation

(a) The Investigator shall report all serious [1321][***] adverse events to the Licensing Authority as defined under clause (b) of rule 21, the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence as per Appendix XI. [1322][In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event.]

(b) (i) The cases of serious adverse events of death shall be examined as under:

(A)An independent Expert Committee shall be constituted by the licensing Authority as defined under rule 21 (b) to examine the cases and recommend to the Licensing Authority for the purpose of arriving at the cause of death and quantum of compensation in case of clinical trial related death.

(B) The Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, and the Investigator shall forward their reports on serious adverse event of death after due analysis to Chairman of the Ethics Committee and [1323][***] the Licensing Authority as defined under rule 21 (b) and the head of the Institution where the trial has been conducted, within [1324][fourteen days] of occurrence of the serious adverse event of death.

(C)The Ethics Committee shall forward its report on serious adverse event of death after due analysis along with its opinion on the

financial compensation, if any, to be paid by the Sponsor or his representative, 'whosoever had obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial, [1325][***] to the Licensing Authority within [1326][thirty days] of the occurrence of the serious adverse event of death.

[1327][(CA) The Licensing Authority shall forward the report of the Investigator, Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conducting clinical trial and the Ethics Committee to the Chairman of the Expert Committee.]

(D) The Expert Committee shall examine the report of serious adverse event of death and give its recommendations to the Licensing Authority for the purpose of arriving at the cause of the adverse event within [1328][one hundred and five days of the occurrence of the adverse event] and the Expert Committee while examining the event, may take into consideration, the reports of the Investigator, Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conducting the clinical trial and the Ethics Committee.

(E) In the case of clinical trial related death, the Expert Committee shall also recommend the quantum of compensation to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial.

(F) The Licensing Authority shall consider the recommendations of the Expert Committee and shall determine the cause of death and pass orders as deemed necessary.

(G) In case of clinical trial related death, the Licensing Authority, after considering the recommendations of the Expert Committee, shall decide the quantum of compensation to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial and shall pass orders as deemed necessary within [1329][one hundred and fifty days of the occurrence of the adverse event].

(ii) Cases of serious adverse events, other than deaths, shall be examined as under:

(A) The Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, and the Investigator shall forward their reports on serious adverse event, after due analysis, to the Licensing Authority as defined under rule 21(b), Chairman of the Ethics Committee and the head of the Institution where the trial has been conducted within [1330][fourteen days] of occurrence of the serious adverse event.

(B) The Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion regarding the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial, to the Licensing Authority within [1331][thirty days] of occurrence of the serious adverse event.

(C) The Licensing Authority shall determine the cause of injury and pass order as deemed necessary. The Licensing Authority shall have the option to constitute an independent Expert Committee, wherever considered necessary, to examine such serious adverse events of injury, which will recommend to the Licensing Authority for arriving at the cause of the injury and also the quantum of compensation in case of clinical trial related injury, to be paid by the Sponsor or his representative whosoever haa obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial.

(D) In case of clinical trial related injury, the Licensing Authority, shall decide the quantum of compensation to be paid by the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, and shall pass orders as deemed necessary within [1332][one hundred and fifty days of the occurrence of the adverse event].

(c) The Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, shall pay the compensation in case of clinical trial related injury or death as per the order of

the Licensing Authority as defined under rule 21(b) within thirty days of the receipt of such order.]

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REFERENCES

1. Vide Notification No. F.28-10/45H (1), dated 21st December, 1945.
2. Subs. By G.S.R. 370(E), dated 7th April, 1994 (w.e.f. 7-4-1994).
3. The words “and cosmetics” omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier it was inserted by G.S.R. 1183, dated 17th August, 1964.
4. The words "except the State of Jammu and Kashmir" omitted by G.S.R. 358, dated 5th March, 1975.
5. Sub-rule (3) omitted by G.S.R.19, dated 15th December, 1977(w.e.f. 7-1-1978).
6. Ins. By G.S.R. 327(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).
7. Subs. By G.S.R. 579(E), dated 20th September, 2006, for clause (b) (w.e.f. 20-09-2006). Earlier clause (b) was omitted by G.S.R. 19, 15th December, 1977 (w.e.f. 7-1-1978) and was again inserted by G.S.R. 973(E), dated 14th December, 1992 (w.e.f. 14-12-1992).
8. Subs. By S.O. 4816, dated 19th November, 1969.
9. Ins. by G.S.R. 101(E), dated 11th February, 2020 (w.e.f. 1-3-2021).
10. Ins. by G.S.R. 680(E), dated 5th December, 1980 (w.e.f. 5-12-1980).
11. Clause (ea) re-lettered as clause (eb) by G.S.R. 101(E), dated 11th February, 2020 (w.e.f. 1-3-2021).
12. Ins. by G.S.R. 918(E), dated 30th November, 2015 (w.e.f. 30-11-2015).
13. Clause (eb) re-lettered as clause (ec) by G.S.R. 101(E), dated 11th February, 2020 (w.e.f. 1-3-2021).
14. Added by Notification No. F. 1-22/59-D, dated 9th April, 1960.
15. Ins. by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
16. Subs. Notification No. F. 1-3/51-D.S., dated 15th October, 1954.
17. Ins. by G.S.R. 681(E), dated 6th June, 1988 (w.e.f. 6-6-1988).
18. Subs. by Notification No. F. 1-16/57-D, dated 15th June, 1957.
19. Subs. by Notification No. F. 28-10/45-H(1), dated 31st March, 1957.
20. Clause (j) omitted by G.S.R. 592(E), dated 13th August, 2008 (w.e.f. 13-8-2008). Clause (j), before omission, stood as under:
“(j) “Poisonous substance specified in Schedule E”.
21. Clause (ii) omitted by Notification No. F. 1-16/57-D, dated 15th June, 1957.
22. Subs. by Notification No. F. 4-1/60-D, dated 15th May, 1961.
23. Subs. by G.S.R. 445(E), dated 30th April, 1992 (w.e.f. 30-4-1992).
24. Ins. by G.S.R. 445(E), dated 30th April, 1992 (w.e.f. 30-4-1992).
25. Ins. by G.S.R. 249(E), dated 4th April, 2002. (w.e.f. 4-4-2002).
26. Added by Notification No. F 1-6/62-D, dated 2nd July, 1969.
27. Subs, by G.S.R. 651(E), dated 9th September, 2009, for sub-rule (3) (w.e.f. 9-9-2009). Earlier sub-rule (3) was added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972). Sub-rule (3), before substitution, stood as under:
"(3) The functions of the Laboratory in respect of condoms shall be carried out at the Central Indian Pharmacopoeia Laboratory, Ghaziabad and the functions of the Director in respect of the said condoms shall be exercised by the Director of the said Laboratory.".
28. Added by G.S.R. 2655, dated 25th October, 1975 (w.e.f. 25-10-1975).
29. Sub-rule (4) omitted and (5) renumbered as sub-rule (4) by G.S.R. 62€, dated 15th February, 1982 (w.e.f. 15-12-1982).
30. Subs. by G.S.R. 242(E), dated 18th March, 1998 (w.e.f. 6-5-1998).
31. Ins. by G.S.R. 16(E), dated 16th January, 1990.
32. Ins. by G.S.R. 246(E), dated 1st May, 1991 (w.e.f. 1-5-1991), (inadvertently mentioned as (7) in Gazette Notification).
33. Subs. By G.S.R. 202(E), dated 22nd March, 2021, for “Homoeopathic Pharmacopoeia Laboratory, Ghaziabad” (w.e.f. 23-3-2021).
34. Subs. By G.S.R. 908(E), dated 22nd December, 2014, for sub-rule (8) (w.e.f. 22-12-2014). Earlier sub-

rule (8) was inserted by G.S.R. 249(E), dated 4th April, 2002 (w.e.f. 4-4-2002). Sub-rule (8), before substitution, stood as under:

"(8) The functions of the Laboratory in respect of Blood Grouping reagents and diagnostic kits for Human Immunodeficiency Virus, Hepatitis B Surface Antigen and Hepatitis C Virus shall be carried out at the National Institute of Biologicals, Noida and the functions of the Director in respect of the said drugs shall be exercised by the Director of the said laboratory."

35. Ins. By G.S.R. 250(E) , dated 15th March , 2017 (w.e.f. 15-3-2017)
36. Ins. By G.S.R. 213(E) , dated 11th March , 2019 (w.e.f. 11-3-2019)
37. Subs. By G.S.R. 604(E) , dated 24th August , 2001 for the heading "IMPORT" (w.e.f. 1-1-2003).
38. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
39. The words "specified in Schedules C and C(1)" omitted by G.S.R. 604(E) dated 24th August, 2001 (w.e.f. 1-1-2003)
40. Ins. By G.S.R. 604(E), dated 24th August, 2001 (w.e.f. 1-1-2003).
41. Subs. By G.S.R. 604(E), dated 24th August, 2001, for "power to sign licences and" (w.e.f. 1-1-2003).
42. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
43. Subs. By G.S.R. 604(E), dated 24th August, 2001, for "import of any biological or other special product specified in Schedule C or C(1)" (w.e.f. 1-1-2003).
44. Subs. By G.S.R. 604(E), dated 24th August, 2001, for rule 24 (w.e.f. 1-1-2003).
45. Subs. By G.S.R. 1193(E), dated 12th December, 2018 for "one thousand rupees for a single drug and an additional fee at the rate of one hundred rupees" (w.e.f. 12-12-2018)
46. Subs. By G.S.R. 1193(E), dated 12th December, 2018 for "one hundred rupees" (w.e.f. 12-12-2018)
47. Ins. by G.S.R. 35(E), dated 20th January, 2005 (w.e.f. 20-1-2005)
48. Subs, by G.S.R. 1193(E), dated 12th December, 2018 for "two hundred and fifty rupees shall be paid" (w.e.f. 12-12-2018).
49. The words "or for a duplicate copy of the licence issued under this rule, if the original is defaced, damaged or lost" omitted by G.S.R. 839(E), dated 29th November, 2021 (w.e.f. 29-11-2021).
50. Ins. by G.S.R. 604(E) dated 24th August, 2001 (w.e.f. 1-1-2003).
51. Subs, by G.S.R. 1193(E), dated 12th December, 2018 for "one thousand and five hundred US dollars" (w.e.f. 12-12-2018).
52. Subs, by G.S.R. 1193(E), dated 12th December, 2018 for "one thousand US dollars" (w.e.f. 12-12-2018).
53. Subs, by G.S.R. 1193(E), dated 12th December, 2018 for "five thousand US dollars" (w.e.f. 12-12-2018).
54. Subs, by G.S.R. 1193(E), dated 12th December, 2018, for "three hundred US dollars or its equivalent in Indian rupees shall be paid" (w.e.f. 12-12-2018). Earlier these words were amended by G.S.R. 35(E), dated 20th January, 2005 (w.e.f. 20-1-2005).
55. Added by Notification No. F.1-19/48-D, dated 27th October, 1949.
56. Sub-rule (2) omitted by S.O.R. 2136, dated 15th June, 1957
57. Subs. By G.S.R. 462(E, dated 22ng June 1982, for rule 25A (w.e.f. 22-6-1982). Earlier rule 25A was inserted by Notification No. F1-9/52-D, dated 3rd November, 1958.
58. Subs. By G.S.R. 604(E) dated 24th August, 2001, for sub clause (i) (w.e.f. 1-1-2003)
59. Ins. By G.S.R. 604(E) dated 24th August, 2001(w.e.f. 1-1-2003)
60. Ins. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
61. Ins. By G.S.R. 604(E) dated 24th August, 2001(w.e.f. 1-1-2003)
62. Subs. by Notification No. F.1-10/62-D, dated 19th April, 1964.
63. Subs. By G.S.R. 604(E) dated 24th August, 2001, for "valid upto the 31st December pf the year following the year in which it is granted" (w.e.f. 1-1-2003)
64. Ins. By G.S.R. 604(E) dated 24th August, 2001(w.e.f. 1-1-2003)
65. Subs. By G.S.R. 604(E) dated 24th August, 2001, for the proviso (as given below)(w.e.f. 1-1-2003). "Provided that a person who is aggrieved by the suspension or cancellation of his licence may, within three months of the date of the order, appeal to the district judge of the district in which the right of appeal accrues or if there is no district judge of that disctrict such judicial officer as the Central Government may appoint in this behalf having jurisdiction whose decision shall be final."
66. Omitted by G.S.R. 944(E), dated 21st September, 1988 (w.e.f. 21-9-1988). Earlier rule 30A was added by Notification No. F. 1-30/48, dated 14th April, 1952.
67. Added by Notification No. F. 1-30/48, dated 14th April, 1952.

68. Subs, by G.S.R. 680(E), dated 5th December, 1980 (w.e.f. 5-12-1980).

69. Added by Notification No. F. 1-45, dated 4th January, 1951.

Subs, by G.S.R. 604(E), dated 24th August, 2001, for rule 31 (w.e.f. 1-1-2003). Rule 31, before substitution, stood as under:

"31. Standard for certain imported drugs.—No biological or other special products specified in Schedule C or C(l) shall be imported unless it complies with the standard of strength, quality and purity, if any, specified, and the tests prescribed in that Schedule shall be applicable for determining whether any such imported drugs complies with the said standards:

70.

Provided that in the case of biological and other special products intended for veterinary use the standards of strength, quality and purity, if any, shall be those that are specified in Schedule F(l) and the tests prescribed in that Schedule shall be applicable for determining whether any such imported drug complies with the said standards and where no standards are specified in Schedule F(l) for any veterinary drug, the standards for such drug shall be those specified in the current edition, for the time being in force, of the British Pharmacopoeia (Veterinary)."

71. Subs, by S.O. 2889, dated 2nd July, 1969 (w.e.f. 19-7-1969).

72. The words "and Schedule F", omitted by G.S.R. 663(E), dated 3rd July, 1992, (w.e.f. 3-7-1992).

73. Added by S.O. 2139, dated 5th June, 1972, (w.e.f. 12-8-1972).

74. Ins. By G.S.R. 604(E) dated 24th August, 2001(w.e.f. 1-1-2003)

75. Subs. By G.S.R. 604(E) dated 24th August, 2001, for sub-rule(3) (w.e.f. 1-1-2003). Earlier sub-rule (3) was added by S.O. 903, dated 10th February, 1976 (w.e.f. 28-2-1976)

76. Subs, by G.S.R. 1193(E), dated 12th December, 2018 for "one hundred rupees for a single drug and an additional fee of fifty rupees" (w.e.f. 12-12-2018).

77. Ins. By G.S.R. 604(E) dated 24th August, 2001(w.e.f. 1-1-2003)

78. Subs, by G.S.R. 1193(E), dated 12th December, 2018 for "one hundred rupees for a single drug and an additional fee of fifty rupees" (w.e.f. 12-12-2018).

79. Ins. By G.S.R. 604(E) dated 24th August, 2001(w.e.f. 1-1-2003)

80. Ins. By S.R.O. 560, dated 3rd March, 1955

81. Ins. by G.S.R. 521(E), dated 1st June , 2018 (w.e.f. 1-6-2018).

82. Ins. by G.S.R. 103(E), dated 2nd February, 2017 (w.e.f. 2-2-2017).

83. Subs, by Notification No. F. 1-3/51-D.S. (S.R.O. 3262), dated 15th October, 1954.

84. Ins. by Notification No. F. 1-45/58-D, (S.O. 115), dated 4th January, 1961 (w.e.f. 14-2-1961).

85. Subs, by Notification No. F. 1-99/52-D.S., dated 3rd November, 1953.

86. Subs, by Notification No. F. 7-7/47-D, dated 5th January, 1954.

87. Added by Notification No. F. 7-11-47/D, dated 15th January, 1951.

88. Rule 42 omitted by Notification No. F. 1-9/52-D.S., dated 3rd November, 1953

89. Subs. By G.S.R. 478(E) dated 6th August, 1981, for rule 43A (w.e.f. 6-8-1981). Earlier rule 43A was inserted by Notification No. F.7-7/47-D, dated 5th January, 1954.

90. Ins. By G.S.R. 116(E), dated 24th February, 2009 (w.e.f. 24-2-2009).

91. Ins. By G.S.R. 120(E), dated 5th March, 1998 (w.e.f 5-3-1998)

92. Subs. By G.S.R. 532(E) dated 18th May, 2016, (w.e.f. 18-5-2016). Earlier these words were substituted by G.S.R.575(E) dated 17th July, 2012 (w.e.f. 17-7-2012), G.S.R. 101(E) dated 18th February 2011 (w.e.f. 18-2-2011), G.S.R. 45(E) dated 21st January , 2010 (w.e.f. 21-1-2010), G.S.R. 504(E) dated 18th July, 2002 (w.e.f. 18-2-2002)and G.S.R. 647(E) dated 28th October, 1998 (w.e.f. 28-10-1998).

93. Subs. By G.S.R. 41(E) dated 17th January , 2017, for “Chennai, Kolkata, Mumbai, Cochin, Nhava Sheva, Kandla, Inland Container Depots at Tuglakabad and Patparganj in Delhi, Tuticorin in Tamil Nadu, Murmugao Port in Goa and Visakhapatnam in Andhra Pradesh: in respect of drugs imported by sea into India;” (w.e.f. 17-1-2017)

94. Subs. By G.S.R. 20(E) dated 10th January 2019, for “Tuticorin” (w.e.f. 10-1-2019)

95. Subs. By G.S.R. 20(E) dated 10th January 2019, for “Gandhinagar” (w.e.f. 10-1-2019)

96. Ins. By G.S.R. 653(E) dated 13th September , 2019 (w.e.f. 13-9-2019)

97. Subs. By G.S.R. 848(E) dated 9th December, 2021, for “Inland container Depot Dhannad” (w.e.f. 9-12-2021).

98. Added by S.O. 1056(E) dated 19th March, 1964 (w.e.f. 28-3-1964)

99. Subs. By G.S.R. 443(E) dated 12th April, 1989 (w.e.f. 12-4-1989).

100. Subs. By G.S.R. 1427(E) dated 10th October, 1977 (w.e.f. 22-10-1977)

101. Subs. by G.S.R. 71(E) dated 30th January, 1987 (w.e.f. 30.01.1987).
102. Subs. By G.S.R. 697(E) dated 26th October, 1995 (w.e.f. 26-10-1995).
103. Ins. By G.S.R. 697(E) dated 26th October, 1995 (w.e.f. 26-10-1995).
104. Subs. By G.S.R. 697(E) dated 26th October, 1995 (w.e.f. 26-10-1995).
105. The words "and cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier it was added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
106. Ins. by G.S.R. 103(E), dated 2nd February, 2017 (w.e.f. 2-2-2017).
107. Ins. by G.S.R. 59(E), dated 7th February, 1995 (w.e.f. 7-2-1995).
108. Subs, by G.S.R. 59(E), dated 7th February, 1995 (w.e.f. 7-2-1995).
109. Added by G.S.R. 984(E) dated 12th July, 1962 (w.e.f. 21-7-1962).
110. The words "and cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier it was inserted by G.S.R. 1140(E) dated 26th August, 1978 (w.e.f. 16-9-1978)
111. Subs. By G.S.R. 658(E) dated 19th October, 1993 (w.e.f. 19-10-1993)
112. Added by G.S.R. 552(E) dated 4th December, 1996 (w.e.f. 4-12-1996)
113. Ins. By G.S.R. 443(E) dated 12th April, 1989 (w.e.f. 12-4-1989).
114. Subs. By G.S.R. 532(E) dated 14th August, 1991 (w.e.f. 14-8-1991).
115. Subs. By S.O. 2139(E) dated 5th June 1972 (w.e.f. 12-8-1972)
116. Ins. By G.S.R. 443(E) dated 12th April, 1989 (w.e.f. 12-4-1989).
117. Subs. By G.S.R. 532(E) dated 14th August, 1991 (w.e.f. 14-8-1991).
118. Subs. By G.S.R. 700(E) dated 28th September, 2001 (w.e.f. 28-9-2001).
119. Subs. By G.S.R. 504(E) dated 18th July, 2002 (w.e.f. 18-7-2002)
120. The words "or cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
121. Subs. By G.S.R. 700(E) dated 28th September, 2001 (w.e.f. 28-9-2001).
122. Added by Notification No. F. 1-19/59-D, dated 13th June, 1961.(w.e.f. 24-6-1961)
123. The words "or cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier it was inserted by G.S.R. 850(E), dated 7th December, 1994 (w.e.f. 7-12-1994).
124. Subs. by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).
125. The words "cosmetic" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
126. The words "or cosmetic" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
127. Ins. By G.S.R. 89(E) dated 16th February, 1985 (w.e.f. 16-2-1985)
128. Ins. By G.S.R. 292(E) dated 29th May, 1997 (w.e.f 29-5-1997)
129. Subs. By S.O. 289, dated 20th December, 1972 (w.e.f. 3-2-1973).
130. Added Notification No. F. 1-9/62-D (G.S.R. 6), dated 26th December, 1964 (w.e.f. 2-1-1965)
131. Subs. by G.S.R. 59 (E), dated 7th February, 1995 (w.e.f. 7-2-1995).
132. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
133. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017)
134. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
135. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
136. Sub-rule (4) and the proviso omitted by G.S.R. 1337(E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier sub-rule (4) was amended by G.S.R. 788(E) dated 10th October, 1985 (w.e.f. 10-10-1985) and G.S.R. 601(E) dated 24th August, 2001 (w.e.f. 24-8-2001).
137. Subs. by Notification No. F. 1-16/57-D, dated 15th June, 1957.
138. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
139. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
140. Subs, by G.S.R. 487(E), dated 2nd July, 1984 (w.e.f. 2-7-1984).
141. Added by Notification No. F. 10-21/49-D, dated 10th March, 1953.
142. Added by Notification No. F. 1-9/60-D, dated 3rd July, 1961 (w.e.f. 8-7-1961).
143. Added by Notification No. F. 1-9/60-D, dated 3rd July, 1961 (w.e.f. 8-7-1961).
144. The words "or renew" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
145. Ins. By G.S.R. 42(E) dated 25th January, 1979 (w.e.f. 25-1-1979).
146. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017)
147. Subs. by G.S.R. 601(E), dated 24th August, 2001, for “a fee of rupees twenty” (w.e.f. 24-8-2001).
148. Proviso omitted by G.S.R. 1337(E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier proviso was amended by G.S.R. 601(E), dated 24th August, 2001, for “a fee of rupees twenty” (w.e.f. 24-8-2001).

149. Subs. by G.S.R. 601(E), dated 24th August, 2001, for “a fee of rupees twenty” (w.e.f. 24-8-2001).
150. Subs. by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier rule 63 was substituted by Notification No. F. 1-10/62-D, dated 10th April, 1964 and amended by S.O. 2139(E), dated 5th June, 1972 (w.e.f. 12-8-1972) and by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
151. Rule 63A omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier rule 63A was added by Notification No. F. 1-10/62-D, dated 10th April, 1964 and amended by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
152. Rule 63B omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier rule 63B was inserted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
153. Amended by Notification No. F. 1-16/57-D, dated 15th June, 1957 and Notification No. F. 1-19/59-D, dated 13th June, 1961.
154. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
155. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier these words were inserted by G.S.R. 681(E) dated 6th June, 1988 (w.e.f. 6-6-1988).
156. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
157. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
158. The words "or renewing" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier these words were inserted by G.S.R. 681(E) dated 6th June, 1988 (w.e.f. 6-6-1988).
159. Subs. By Notification No. F. 1-19/59-D, dated 13th June, 1961.
160. The words "or renew" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
161. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier these words were inserted by G.S.R. 681(E) dated 6th June, 1988 (w.e.f. 6-6-1988).
162. Ins. By G.S.R. 681(E) dated 5th December , 1980 (w.e.f. 5-12-1980)
163. Subs. By G.S.R. 351(E) dated 26th April, 2000(w.e.f. 26-4-2000)
164. Ins. By G.S.R. 91(E) dated 25th February, 1997 (w.e.f. 25-2-1997)
165. Subs. by Notification No. F. 1-9/60-D (S.O. 1588), dated 3rd July, 1961 (w.e.f. 8-7-1961).
166. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
167. Subs. By G.S.R. 676(E), dated 6th September, 1994 (w.e.f. 6-9-1994).
168. Certain words omitted by G.S.R. 462(E) dated 22nd June, 1982 (w.e.f. 22-6-1982)
169. Subs. By S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
170. Subs. by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).
171. Subs. by G.S.R. 588(E) dated 30th August, 2013, for Schedule H" (w.e.f. 27-2-2014).
172. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
173. Subs. by G.S.R. 588(E) dated 30th August, 2013, for Schedule H" (w.e.f. 27-2-2014).
174. Ins. by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014).
175. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
176. Added by Notification No. 1-63/61-D, dated 17th July, 1963.
177. Certain words omitted by G.S.R. 462(E) dated 22nd June, 1982 (w.e.f. 22-6-1982)
178. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
179. Ins. By G.S.R. 245(E) dated 3rd February, 1976 (w.e.f. 21-2-1976) or (w.e.f.11-2-1976)
180. Item(b) re-numbered as item(c), by G.S.R. 245(E) dated 3rd February, 1976 (w.e.f. 21-2-1976)
181. Subs. By G.S.R. 1242(E) dated 17th September, 1976 (w.e.f. 6-10-1979).
182. Subs. By Notification No. F.1-63/62-D, dated 17th July, 1963.
183. Ins. By 496(E) dated 9th June, 1995 (w.e.f. 9-6-1995)
184. Subs. By G.S.R. 1242, dated 17th September, 1979 (w.e.f. 6-10-1979).
185. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
186. Subs. by G.S.R. 588(E) dated 30th August, 2013, for Schedule H" (w.e.f. 27-2-2014).
187. Subs. by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).
188. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
189. Added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
190. Clauses (13) and (14) omitted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
191. Subs, by Notification No. F. 1-16/57-D, dated 15th June, 1957.
192. Subs. by G.S.R. 676(E), dated 6th September, 1994 (w.e.f. 6-9-1994).
193. Subs. by Notification No. F. 1-14/68-D (S.O. 3868), dated 26th October, 1968 (w.e.f. 2-11-1968).

194. Added by Notification No. F. 1-55/61-D, dated 22nd August, 1964 (w.e.f. 5-9-1964).
195. Added by S.O. 903, dated 10th February, 1976 (w.e.f. 28-2-1976)
196. Added by Notification No. F. 1-113/60-D (S.O. 23), dated 23rd December, 1969 (w.e.f. 3-1-1970).
197. Subs. by G.S.R. 676(E), dated 6th September, 1994 (w.e.f. 6-9-1994).
198. Subs. By 496(E) dated 9th June, 1995 (w.e.f. 9-6-1995)
199. Ins. By G.S.R. 352(E) dated 26th April, 2000 (w.e.f. 26-4-2000)
200. Added by G.S.R. 444, dated 31st March, 1973 (w.e.f. 28-4-1973).
201. Subs. by G.S.R. 676(E), dated 6th September, 1994 (w.e.f. 6-9-1994).
202. Added by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).
203. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
204. Added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
205. Ins. by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
206. Subs. By G.S.R. 73(E) dated 31st January, 2003, for Part XVIA (w.e.f. 31-1-2003). Ed.-Though in G.S.R. 73(E), it is stated that it is to be inserted but in fact it has been substituted. Earlier Part XVIA was inserted by G.S.R. 701(E) dated 27th September, 2001 (w.e.f. 28-9-2001).
207. Ins. By G.S.R. 716(E) dated 1st October, 2021 (w.e.f. 4-10-2021)
Ed.- As per G.S.R. 674(E) dated 10th November, 2005 (w.e.f. 10-11-2005) in rule 160B, in sub-rule (2), in clause (ii) sub-clause(b) is to be substituted as the substituted text is not in consonance with the original text, hence it is reproduced below:

208. In Rule 160B in sub-rule (2), in clause (ii), for sub-clause (b), the following shall be substituted for testing and analysis of Ayurveda, Siddha & Unani drugs namely:-
"(i) Expert in Ayurveda or Siddha or Unani medicine who possess a degree qualification recognized under Schedule II of Indian Medicine Central Council Act, 1970;
(ii) Chemist, who shall possess at least Bachelor Degree in Science or Pharmacy (Ayurveda) awarded by a recognized University ; and
(iii) Botanist (Pharmacologist), who shall possess at least Bachelor Degree in Science (Medical or Pharmacy) or Pharmacy (Ayurveda) awarded by a recognized University."
209. Added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
210. Subs. by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).
211. Ins. By G.S.R. 1242, dated 17th September, 1979 (w.e.f. 6-10-1979).
212. Rule 67 omitted by S.O. 289, dated 20th December, 1972 (w.e.f. 3-2-1973)
213. Part VIA (containing rules 67A to 67E, 67F, 67G and 67H) added by Notification No. F. 1-35/64-D, dated 18th August, 1964 (w.e.f. 22-8-1964)
214. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
215. Subs. by G.S.R. 601(E), dated 24th August, 2001, for certain words (w.e.f. 24-8-2001).Earlier these words were substituted by G.S.R. 779(E) dated 18th July, 1980(w.e.f. 26-7-1980)
216. Subs. By S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
217. Added by G.S.R.665(E) dated 6th May , 1977(w.e.f. 28-5-1977)
218. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
219. Ins. By G.S.R. 1380(E) dated 10th November, 2017 (w.e.f. 10-11-2017)
220. Added by Notification no. F.1-14/67-D, dated 3rd February, 1969.
221. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
222. Subs. By G.S.R. 1380(E) dated 10th November, 2017, for "who is in opinion of the licensing authority competent to deal in Homeopathic medicines." (w.e.f. 10-11-2017)
223. Subs by G.S.R. 1380(E), dated 10th November, 2017, for proviso (w.e.f. 10-11-2017). Earlier proviso was inserted by G.S.R. 680(E) dated 5th December, 1980 (w.e.f. 5-12-1980). Proviso, before substitution , stood as under:
"Provided that no registered Homeopathic medical practitioner who is practising Homeopathy in the premises where Homeopathic medicines are sold shall deal in Homeopathic medicines."
224. Subs by G.S.R. 1380(E), dated 10th November, 2017, for proviso (w.e.f. 10-11-2017). Clause (2), before substitution, stood as under:
"(2) The sale of Homeopathic medicines shall be conducted under the supervision of a person, competent to deal in Homeopathic medicines."
225. Added by Notification No. F. 1-59/68-D (S.O. 4816), dated 19th November , 1969 (w.e.f. 6-12-1969)
226. Ins. By G.S.R. 331(E) dated 8th May, 1984 (w.e.f.8-5-1984)

227. Added by S.O. 2139, dated 5th June , 1972(w.e.f. 1-8-1972)
228. Added by S.O. 2139, dated 5th June , 1972(w.e.f. 1-8-1972)
229. Subs. by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).
230. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
231. Ins. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992).
232. The words "or Renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
233. The words "or renewed, as the case may be" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
234. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
235. Clause (iii) omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Clause (iii), before omission stood as under:
"(iii) in case the application is for the renewal of licence, call for the information(s) of the past performance of the licensee.".
236. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
237. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
238. The words "or renew" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
239. Ins. by G.S.R. 89(E), dated 14th February, 1996 (w.e.f. 14-2-1996).
240. Subs. By notification No. F. 1-22/59-D, dated 9th April, 1960.
241. Subs, by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
242. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
243. Subs, by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
244. Subs, by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
245. The words "or for the purpose of renewal of licences" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
246. Subs. By. G.S.R. 640(E) dated 29th June, 2016, for "categorised in Schedule M and Schedule M-III" (w.e.f. 29-62016)
247. Sub-rule (3) omitted by G.S.R. 1337 (E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier sub-rule (3) was amended by G.S.R. 601(E) dated 24th August, 2001(w.e.f. 24-8-2001). Sub-rule (3), before omission, stood as under:
" (3) If a person applies for the renewal of a licence after the expiry thereof but within six months of such expiry the fee payable for the renewal of such licence shall be—
(i) in the case of Form 24B a licence fee of rupees five hundred plus an additional fee at the rate of rupees two hundred and fifty per month or part thereof in addition to an inspection fee of rupees two hundred;
(ii) in the case of Form 24F a licence fee of rupees six thousand plus an additional fee at the rate of rupees one thousand per month or part thereof in addition to an inspection fee of rupees one thousand;
(iii) in the case of Form 24 a licence fee of rupees six thousand plus an additional fee at the rate of rupees one thousand per month or part thereof in addition to an inspection fee of rupees one thousand and five hundred."
248. Subs, by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
249. Subs, by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).
250. Subs. By. G.S.R. 640(E) dated 29th June, 2016, for "categorised in Schedule M and Schedule M-III" (w.e.f. 29-62016)
251. Ins. By G.S.R. 311(E) dated 1st May, 2002 (w.e.f. 1-5-2002).
252. Amended by Notification No. F.1-16/57-D, dated 15th June, 1957.
253. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
254. Proviso omitted by G.S.R. 1337(E) dated 27th October, 2017 (w.e.f. 27-10-2017). Proviso , before omission , stood as under:
"Provided that if the applicant applies for the renewal of a licence after its expiry but within six months of such expiry, the fee payable for renewal of such licence shall be accompanied by a licence fee of rupees six thousand and an inspection fee of rupees one thousand and five hundred plus an additional fee at the rate of rupees one thousand per month or part thereof."
255. Subs. by G.S.R. 724(E), dated 7th November, 2013 (w.e.f. 7-11-2013). For *Explanation* (w.e.f. 7-11-2013). *Explanation*, before substitution, stood as under:
"Explanation.- For the purpose of this rule a loan licence means a licence which the Licensing Authority may issue to an applicant who does not have his own arrangements for manufacture but who intends to avail himself of the manufacturing facilities owned by a licensee in Form 25."
256. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).

Subs. By. G.S.R. 640(E) dated 29th June, 2016, for "categorised in Schedule M and Schedule M-III" (w.e.f. 29-62016)

257. Added by Notification no. F.1-20/64-D, dated 26th October, 1968 (w.e.f. 2-11-1968).

258. Subs. by G.S.R. 601(E), dated 24th August, 2001, for certain words (w.e.f. 24-8-2001).Earlier it was substituted by G.S.R. 779(E) dated 18th July, 1980(w.e.f. 26-7-1980)

259. Rule 69B omitted by G.S.R. 944(E) dated 21st September, 1988 (w.e.f. 21-9-1988). Earlier rule 69B was inserted by Notification No. F.1-19/59-D, dated 13th June , 1961

260. Subs, by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

261. Added by Notification No.F.1-16/57-D, dated 15th June, 1957 and Notification No. F. 1-22/59-D, dated 9th April, 1960.

262. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).

263. Subs. By Notification No. F.1-16/57-D, dated 15th June, 1957.

264. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

265. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

266. Subs. by G.S.R. 71(E), dated 30th January, 1987 (w.e.f. 30-1-1987).

267. Added by Notification No. F.1-19/59-D (S.O. 1449), dated 13th June , 1961 (w.e.f. 24-06-1961)

268. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

269. Subs. by G.S.R. 93(E), dated 24th February, 1995 (w.e.f. 24-2-1995).

270. Added by Notification No. F. 1-14/68-D, dated 26th October, 1968.

271. Subs. by G.S.R. 93(E), dated 24th February, 1995 (w.e.f. 24-2-1995).

272. Subs, by G.S.R. 926(E), dated 24th June, 1977 (w.e.f. 16-7-1977).

273. These rules came into force on 28th May, 1977 vide G.S.R. 665, dated 6th May, 1977 (w.e.f. 28-5-1977).

274. Ins. by G.S.R. 1172 (E), dated 23rd August, 1977.

275. Ins. By G.S.R. 681(E) dated 5th December , 1980 (w.e.f. 5-12-1980)

276. Added by G.S.R. 515(E), dated 24th March , 1976 (w.e.f. 10-4-1976)

277. Subs, by G.S.R. 360(E), dated 10th April, 2018 for "patent or proprietary medicines" (w.e.f. 10-4-2018).

278. Ins. By G.S.R. 311(E) dated 1st May, 2002 (w.e.f. 1-5-2002).

279. Ins. By G.S.R. 735(E) dated 24th June, 1988 (w.e.f. 24-6-1988).

280. Ins. by G.S.R. 570(E), dated 7th August, 2014 (w.e.f. 7-8-2014).

281. Ins. by G.S.R. 828(E) dated 6th November, 2019 (w.e.f. 6-11-2019)

282. Added by Notification No. F. 1-22/59-D, dated 9th April, 1960.

283. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

284. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

285. Subs. by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).

286. Subs. by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).

287. The rules came into force on 16th July, 1977 vide G.S.R. 926(E) dated 24th June, 1977 (w.e.f. 16-7-1977)

288. Ins. by G.S.R. 1172 (E), dated 23rd August, 1977.

289. Added by G.S.R. 515(E), dated 24th March , 1976 (w.e.f. 10-4-1976)

290. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

291. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

292. Subs, by G.S.R. 360(E), dated 10th April, 2018 for "patent or proprietary medicines" (w.e.f. 10-4-2018).

293. Ins. by G.S.R. 828(E) dated 6th November, 2019 (w.e.f. 6-11-2019)

294. Ins. by G.S.R. 570(E), dated 7th August, 2014 (w.e.f. 7-8-2014).

295. Subs. By G.S.R. 1337(E) dated 27th October, 2017, for rule 72 (w.e.f.. 27-10-2017). Earlier rule 72 was amended by Notification No. F.1-10/62-D (S.O. 1326 (E)), dated 10th April, 1964 (w.e.f. 11-4-1964), by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972), by G.S.R. 462(E), dated 22nd June, 1982(w.e.f. 22-6-1982) and by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).

296. Rule 73 omitted by G.S.R. 1337(E) dated 27th October, 2017, (w.e.f.. 27-10-2017).Earlier it was amended by G.S.R. 462(E) dated 22nd June, 1982 (w.e.f. 22-6-1982).

297. Rule 73A omitted by G.S.R. 1337(E) dated 27th October, 2017, (w.e.f.. 27-10-2017). Earlier rule 73A was amended by Notification No. F.1-10/62-D (S.O. 1326(E), dated 10th April,1964, w.e.f. 11-4-1964.)

298. Subs. by G.S.R. 1337(E) dated 27th October, 2017, for rule 73AA (w.e.f.. 27-10-2017). Earlier rule 73AA was amended by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972) and by G.S.R. 601(E) dated 24th August, 2001 (w.e.f. 24-8-2001)

299. Ins. By G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

300. Rule 73B omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier rule 73B

301.

added by S.O. 1196(E) dated 6th May, 1960 (w.e.f. 14-5-1960).

302. Subs. By Notification No. F. 1-20/64-D (S.O. 3868(E) dated 26th October, 1968 (w.e.f. 2-11-1968))

303. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

304. Ins. by G.S.R. 1172 (E), dated 23rd August, 1977.

305. Subs. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)

306. Subs. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)

307. Subs. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)

308. Ins. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)

309. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

310. Ins. By G.S.R. 735(E) dated 24th June, 1988 (w.e.f. 24-6-1988).

311. Ins. by G.S.R 780(E), dated 10th November, 2008 (w.e.f. 1-11-2010).

312. Ins. by G.S.R 289(E), dated 15th April, 2015 (w.e.f. 15-4-2015).

313. Ins. By G.S.R. 327(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).

314. Added by S.O. 1196, dated 6th May, 1960 (w.e.f. 14-5-1960).

315. Ins. by G.S.R. 1172, dated 23rd August, 1977 (w.e.f. 10-9-1977).

316. Subs. By Notification No. F. 1-20/64-D (S.O. 3868(E) dated 26th October, 1968 (w.e.f. 2-11-1968))

317. Subs. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)

318. Subs. By Notification No. F. 1-20/64-D (S.O. 3868(E) dated 26th October, 1968 (w.e.f. 2-11-1968))

319. Added by Notification No. F. 1-20/64-D (S.O. 3868(E) dated 26th October, 1968 (w.e.f. 2-11-1968))

320. Added by G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973).

321. Ins. by G.S.R. 289(E), dated 15th April, 2015 (w.e.f. 15-4-2015).

322. Added by Notification No. F. 1-20/64-D (S.O. 3868(E) dated 26th October, 1968 (w.e.f. 2-11-1968))

323. Ins. by G.S.R. 1172, dated 23rd August, 1977 (w.e.f. 10-9-1977).

324. Ins. by G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973).

325. Ins. by G.S.R. 331(E), dated 8th May, 1984 (w.e.f. 8-5-1984).

326. Ins. by G.S.R. 289(E), dated 15th April, 2015 (w.e.f. 15-4-2015).

327. Ins. By G.S.R. 327(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).

328. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

329. Ins. by G.S.R. 28(E), dated 22nd January, 1993 (w.e.f. 22-1-1993).

330. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

331. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).

332. Subs. By. G.S.R. 640(E) dated 29th June, 2016, for "categorised in Schedule M and Schedule M-III" (w.e.f. 29-62016)

333. The words "or for the purpose of renewal of licences" omitted by G.S.R. 1337 (E) dated 27th October, 2017 (w.e.f. 27-10-2017).

334. Proviso omitted by G.S.R. 1337 (E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier proviso was amended by G.S.R. 601(E) dated 24th August, 2001(w.e.f. 24-8-2001)

335. Ins. by G.S.R. 119(E), dated 11th March, 1996 (w.e.f. 11-3-1996) as corrected by G.S.R. 513(E) dated 6th November, 1996.

336. Subs, by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).

337. Sub. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).

338. The words "or for the purpose of renewal of licences" omitted by G.S.R. 1337 (E) dated 27th October, 2017 (w.e.f. 27-10-2017).

339. Proviso omitted by G.S.R. 1337 (E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier proviso was amended by G.S.R. 601(E) dated 24th August, 2001(w.e.f. 24-8-2001)

340. Sub. by G.S.R. 601(E), dated 24th August, 2001, for sub-rules (4) and (5) (w.e.f. 24-8-2001). Earlier sub-rules (3) and (4) were re-numbered as sub-rules (4) and (5) respectively by G.S.R. 119(E) dated 11th March, 1996 (w.e.f. 11-3-1996)

341. Subs. By. G.S.R. 640(E) dated 29th June, 2016, for "categorised in Schedule M and Schedule M-III" (w.e.f. 29-62016)

342. Subs. By G.S.R. 654(E) dated 24-08-2022 (w.e.f. 24-08-2022). Earlier Ins. By G.S.R. 311(E) dated 1st May, 2002 (w.e.f. 1-5-2002). Before substitution clause (6) stood as under:
"[(6) Where an application under this rule is for the manufacture of drug formulations falling under the purview of new drug as defined in rule 122E, such application shall also be accompanied with approval, in writing, in favour of the applicant, from the licensing authority as defined in clause (b) or rule 21.]"

343. Added by Notification No. F.1-16/57-D, dated 15th June, 1957.

344. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

345. Subs, by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).

346. Subs. by G.S.R. 28(E), dated 22nd January, 1993 (w.e.f. 22-1-1993).

Proviso omitted by G.S.R. 1337 (E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier proviso was amended by S.O. 2139(E) dated 5th June, 1972 (w.e.f. 12-8-1972). Proviso, before omission, stood as under:

"Provided that if the applicant applies for the renewal of a licence after its expiry but within six months of such expiry the fee payable for renewal of the licence shall be rupees six thousand and an inspection of fee of rupees one thousand and five hundred plus an additional fee at the rate of rupees one thousand

347. per month or a part thereof."

Ins. by G.S.R. 724(E), dated 7th November, 2013 (w.e.f. 7-11-2013). *Explanation,* before substitution , stood as under:

"*Explanation.* − For the purpose of this rule a loan licence means a licence which a licensing authority may issue to an applicant who does not have his own arrangements for manufacture but who intends to

348. avail himself of the manufacturing facilities owned by another licensee in Form 28 and Form 28D."

349. Ins. by G.S.R. 574(E), dated 17th July, 2012, for "Form 28A" (w.e.f. 17-7-2012).

350. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

The words "or for the purpose of renewal of licences" omitted by G.S.R. 1337 (E) dated 27th October,

351. 2017 (w.e.f. 27-10-2017).

Proviso omitted by G.S.R. 1337 (E) dated 27th October, 2017 (w.e.f. 27-10-2017). Proviso, before omission, stood as under:

"Provided that if the application for the renewal of a licence is made after its expiry but within six months of such expiry, the fee payable for renewal of the licence shall be rupees six thousand plus an additional fee of one thousand rupees per month or a part thereof in addition to the inspection fee of

352. one thousand and five hundred rupees."

Proviso omitted by G.S.R. 574(E), dated 17th July, 2012, for "Form 28A" (w.e.f. 17-7-2012).Earlier it was inserted by G.S.R. 592(E) dated 13th August, 2008(w.e.f.13-8-2008). Proviso before omission, stood as under:

"Provided that if an item is a notified drug under rule 68A, the manufacturing unit undertaking manufacture on behalf of the loan licencee shall have a valid manufacturing licence approved by the

353. Licensing Authority and its manufacture on loan licence shall not affect the quality of the drug."

354. Subs, by G.S.R. 601(E), dated 24th August, 2001 (S.O. 1449(E)) (w.e.f. 24-8-2001).

Rules 75B omitted by G.S.R. 944(E), dated 21st September, 1988 (w.e.f. 21-9-1988). Earlier rule 75B

355. was added by Notification No. F.1-19/59-D (S.O. 1449), dated 13th June, 1961 (w.e.f. 24-6-1961).

356. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

357. Ins. by G.S.R. 28(E), dated 22nd January, 1993 (w.e.f. 22-1-1993).

358. The words "**or renewal**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

359. Subs, by G.S.R. 119(E), dated 11th March, 1996 (w.e.f. 11-3-1996).

360. Subs, by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).

361. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

362. Subs, by G.S.R. 71(E), dated 30th January, 1987 (w.e.f. 30-1-1987).

363. Ins. By G.S.R. 245(E) dated 3rd February, 1976 (w.e.f. 21-2-1976)

364. Subs. by G.S.R. 71(E), dated 30th January, 1987 (w.e.f. 30-1-1987).

365. Added by Notification No. F.1-19/59-D (S.O. 1449), dated 13th June , 1967 (w.e.f. 20-06-1967)

366. Added by Notification No. F. 1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 19-7-1969).

Subs. by G.S.R. 690(E), dated 25th September, 2014, for third proviso (w.e.f. 25-9-2014). Earlier third proviso was inserted by G.S.R. 109(E), dated 22nd February, 1994 (w.e.f. 22-2-1994). Third proviso, before substitution by G.S.R. 690(E) dated 25th September, 2014, stood as under:

"Provided further also that for the medical devices specified in Schedule C, the whole time employee under whose supervision the manufacture is conducted may be a Graduate in Science with Physics or Chemistry or Microbiology as one of the subjects; or graduate in Pharmacy; or Degree/Diploma holder in Mechanical or Chemical or Plastic Engineering of a University

367. recognized by the Central government for such purposes."

Conditions (2), (2A) and (3) subs, by G.S.R. 640(E), dated 29th June, 2016, for Conditions (2) and (3). Conditions (2) and (3), before substitution, stood as under:

"(2) The factory premises shall comply with the conditions prescribed in Schedule M and Schedule M III in the respect of Medical devices.

(3) The applicant shall provide adequate space, plant and equipment for any or all the manufacturing operations; the space, plant and equipment recommended for various operations are given in Schedule

368. M and Schedule M III."

369. Subs, by G.S.R. 926(E), dated 24th June, 1977 (w.e.f. 16-7-1977).

These rules came into force on 28th May, 1977 *vide* G.S.R. 665(E), dated 6th May, 1977 (w.e.f. 28-5-

370. 1977).

371. Ins. by G.S.R. 1172(E), dated 23rd August, 1977.
372. Ins. By G.S.R. 681(E) dated 5th December , 1980 (w.e.f. 5-12-1980)
373. Ins. by G.S.R. 444(E), dated 31st March, 1973 (w.e.f. 28-4-1973).
374. Added by G.S.R. 515(E), dated 24th March , 1976 (w.e.f. 10-4-1976)
375. Subs, by G.S.R. 360(E), dated 10th April, 2018 for "patent or proprietary medicines" (w.e.f. 10-4-2018).
376. Ins. By G.S.R. 311(E) dated 1st May, 2002 (w.e.f. 1-5-2002).
377. Subs. By G.S.R. 640(E) dated 29th June, 2016, for Condition (8) (w.e.f. 29-6-2016). Earlier condition (8) was inserted by G.S.R. 735(E) dated 24th June, 1988 (w.e.f. 24-6-1988). Condition (8), before substitution, stood as under:
"(8) The Licence shall comply, with the requirements of "Good Manufacturing Practices" as laid down in Schedule M."
378. Ins. by G.S.R. 570(E), dated 7th August, 2014 (w.e.f. 7-8-2014).
379. Ins. by G.S.R. 119(E), dated 11th March, 1996 (w.e.f. 11-3-1996)
380. Subs, by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).
381. Ins. by G.S.R. 327(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).
382. Ins. by G.S.R. 828(E) dated 6th November, 2019 (w.e.f. 6-11-2019)
383. Subs. By G.S.R. 574(E), dated 17th July, 2012, for " " (w.e.f. 17-7-2012).
384. The words "**or renewal**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
385. Subs, by G.S.R. 360(E), dated 10th April, 2018 for "patent or proprietary medicines" (w.e.f. 10-4-2018).
386. Ins. by G.S.R. 828(E) dated 6th November, 2019 (w.e.f. 6-11-2019)
387. Ins. by G.S.R. 570(E), dated 7th August, 2014 (w.e.f. 7-8-2014).
Ins. by G.S.R. 499(E), dated 17th July, 2019 (w.e.f. 17-7-2019). Earlier rule 77 was omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017) and earlier to that rule 77 was amended by Notification No. E.1-10/62-D (S.O. 1326(E)), dated 10th April, 1964 (w.e.f. 11-4-1964), by S.O. 2139(E) dated 5th June, 1972 (w.e.f. 12-8-1972), by G.S.R. 119(E), dated 11th March, 1996 (w.e.f. 11-3-1996) and by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
388. Subs. by Notification No. F. 1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 19-7-1969).
389. Subs. By G.S.R. 119(E), dated 11th March, 1996 (w.e.f. 11-3-1996).
390. Subs. by Notification No. F.1-16/57-D (S.O. 2136(E)), dated 15th June, 1957.
391. Subs. by Notification no. F.1-20/64-D (S.O. 3868(E)), dated 26th October, 1968 (w.e.f. 2-11-1968).
392. Ins. by G.S.R. 1172 (E), dated 23rd August, 1977.
393. Subs. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)
394. Subs. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)
395. Subs. by Notification No. F.1-16/57-D, dated 15th June, 1957.
396. Subs. By G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)
397. Subs. by Notification No. F. 1-14/68-D (S.O. 3868(E)), dated 26th October, 1968 (w.e.f. 2-11-1968).
398. Added by G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)
399. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
400. Ins. By G.S.R. 735(E) dated 24th June, 1988 (w.e.f. 24-6-1988).
401. Ins. by G.S.R 780(E), dated 10th November, 2008 (w.e.f. 1-11-2010).
402. Ins. by G.S.R 289(E), dated 15th April, 2015 (w.e.f. 15-4-2015).
403. Ins. By G.S.R. 327(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).
404. Added by Notification No. F. 1-14/68-D (S.O. 3868(E)), dated 26th October, 1968 (w.e.f. 2-11-1968).
405. Ins. by G.S.R. 574(E), dated 17th July, 2012, for "Form 28A" (w.e.f. 17-7-2012).
406. Subs. by G.S.R. 592(E), dated 13th August, 2008, for "Form 28" (w.e.f. 13-8-2008).
407. Subs. by G.S.R. 574(E), dated 17th July, 2012, for "Form 28" (w.e.f. 17-7-2012).
408. Added by G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973)
409. Subs. by G.S.R. 574(E), dated 17th July, 2012, for "Form 28" (w.e.f. 17-7-2012).
410. Ins. by G.S.R. 331(E), dated 8th May, 1984 (w.e.f. 8-5-1984).
411. Ins. by G.S.R 289(E), dated 15th April, 2015 (w.e.f. 15-4-2015).
412. Ins. By G.S.R. 327(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).
413. Subs. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992), as corrected by G.S.R. 373(E), dated 13th April, 1993.
414. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
415. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
416. Ins. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992)
417. Subs. By G.S.R. 119(E), dated 11th March, 1996 (w.e.f. 11-3-1996).
418. Subs. by Notification No. F.1-16/57-D, dated 15th June, 1957.
419.

420. Subs. by G.S.R. 601(E), dated 24th August, 2001, for " fee of rupees fifty" (w.e.f. 24-8-2001).
421. Ins. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992)
422. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
423. Ins. by G.S.R. 499(E), dated 17th July, 2019 (w.e.f. 17-7-2019). Earlier rule 83 was omitted by G.S.R. 1337(E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier to that rule 83 was amended by Notification No. F.1-16/57-D, dated 15th June, 1957.
Rule 83A omitted by G.S.R. 1337(E) dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier rule 83A was added by Notification No. F.1-16/57-D, dated 15th June, 1957 and amended by G.S.R. 574(E) dated 17th July, 2012 (w.e.f. 17-7-2012). Rule 83A, before omission , stood as under:
"*83A. Certificate of renewal of a loan licence.*−The certificate of renewal of a loan licence in Form
424. 28A or Form 28DA shall be issued in Form 26A or Form 26J respectively."
Rule 83AA omitted by G.S.R. 1337(E) dated 27th October, 2017 (w.e.f. 27-10-2017).Earlier rule 83AA was added by Notification No. F. 1-10/62-D (S.O. 1326(E)), dated 10th April, 1964 (w.e.f. 11-4-1964) and amended by S.O. 2139(E), dated 5th June, 1972 (w.e.f. 12-8-1972), by G.S.R. 601(E) dated 24th August, 2001 (w.e.f. 24-8-2001) and by G.S.R. 574(E), dated 17th July, 2012, (w.e.f. 17-7-2012). Rule 83AA, before omission , stood as under:
"*83-AA. Duration of loan licence.*−An original loan licence in Form 28A or Form 28DA or a renewed loan licence in Form 26A or Form 26J, unless sooner suspended or cancelled, shall be valid for a period of five years on and from the date on which it is granted or renewed:
Provided that if the application for the renewal of a licence is made before its expiry, or if the application is made within six months of its expiry, after payment of the additional fee, the licence shall continue to be in force until orders are passed on the application and the licence shall be deemed
425. to have expired if the application for its renewal is not made within six months of its expiry."
426. Added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
427. Subs. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992), as corrected by G.S.R. 373(E), dated 13th April, 1993.
428. The words "**or renewed**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
429. The words "or renew" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
430. Subs. By G.S.R. 119(E), dated 11th March, 1996 (w.e.f. 11-3-1996).
431. Added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
432. Ins. By G.S.R. 19(E) dated 10th January, 2019 (w.e.f. 10-1-2019).
433. Added by S.O. 2358(E) dated 21st June, 1972 (w.e.f. 26-8-1972).
434. Ins. By G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
435. Ins. by G.S.R. 101(E), dated 11th February, 2020 (w.e.f. 1-3-2021).
436. Ins. by G.S.R. 101(E), dated 11th February, 2020 (w.e.f. 1-3-2021).
437. Subs. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992), as corrected by G.S.R. 373(E), dated 13th April, 1993.
438. Ins. By G.S.R. 20(E) dated 11th January, 1996 (w.e.f. 11-1-1996).
439. Corrected *vide* Corrigendum G.S.R. 514(E), dated 5th November, 1996.
440. The words "or renewed" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
441. Ins. By G.S.R. 615(E) dated 9th August, 1994 (w.e.f. 9-8-1994), as corrected by G.S.R. 1185(E) dated 11th August, 1964 (w.e.f. 22-8-1964)
442. Part VIIA (containing rules 85A to 85E, 85F and 85-I) added by G.S.R. 1185(E) dated 11th August, 1964 (w.e.f. 22-8-1964)
443. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
444. Subs. By G.S.R. 245(E) dated 3rd February, 1976 (w.e.f. 21-2-1976) or (w.e.f. 11-2-1976)
445. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001). Earlier these words were substituted by G.S.R. 779(E) dated 18th July, 1980 (w.e.f. 26-7-1980).
446. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001). Earlier these words were substituted by G.S.R. 779(E) dated 18th July, 1980 (w.e.f. 26-7-1980).
447. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001). Earlier these words were substituted by G.S.R. 779(E) dated 18th July, 1980 (w.e.f. 26-7-1980).
448. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001). Earlier these words were substituted by G.S.R. 779(E) dated 18th July, 1980 (w.e.f. 26-7-1980).
449. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001). Earlier these words were substituted by G.S.R. 779(E) dated 18th July, 1980 (w.e.f. 26-7-1980).
450. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001). Earlier these words were substituted by G.S.R. 779(E) dated 18th July, 1980 (w.e.f. 26-7-1980).
451. Subs. By G.S.R. 779(E) dated 18th July, 1980 (w.e.f. 26-7-1980).
452. Subs. by G.S.R. 601(E), dated 24th August, 2001, for "rupees five" (w.e.f. 24-8-2001).

453. Ins. By G.S.R. 13(E) dated 7th January, 1983 (w.e.f. 7-1-1983)
454. Subs. by Notification No. F. 1-59/68-D (S.O. 4816), dated 19th November , 1969 (w.e.f. 6-12-1969).
455. Subs, by G.S.R. 812(E), dated 14th November, 1994 (w.e.f. 14-11-1994) as corrected by G.S.R. 517(E), dated 26th June, 1995.
456. Subs. by G.S.R. 570(E), dated 12th June, 1987 (w.e.f. 12-6-1987).
457. Ins. by G.S.R. 1380(E), dated 10th November, 2017 (w.e.f. 10-11-2017).
458. Ins. by G.S.R. 1172(E), dated 23rd August, 1977(w.e.f. 10-9-1977).
459. Ins. by Notification No. F. 1-59/68-D (S.O. 4816), dated 19th November , 1969 (w.e.f. 6-12-1969).
460. Ins. by G.S.R. 493(E), dated 9th June, 1995 (w.e.f. 9-6-1995), as corrected by G.S.R. 184(E), dated 12th April, 1996.
461. Ins. by G.S.R. 493(E), dated 9th June, 1995 (w.e.f. 9-6-1995), as corrected by G.S.R. 184(E), dated 12th April, 1996.
462. Ins. by G.S.R. 493(E), dated 9th June, 1995 (w.e.f. 9-6-1995), as corrected by G.S.R. 184(E), dated 12th April, 1996.
463. Ins. by G.S.R. 493(E), dated 9th June, 1995 (w.e.f. 9-6-1995), as corrected by G.S.R. 184(E), dated 12th April, 1996.
464. Ins. by G.S.R. 493(E), dated 9th June, 1995 (w.e.f. 9-6-1995), as corrected by G.S.R. 184(E), dated 12th April, 1996.
465. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
466. Subs. By S.O. 2139(E) dated 5th June 1972 (w.e.f. 12-8-1972).
467. Subs. by G.S.R. 444, dated 31st March, 1973 (w.e.f. 28-4-1973).
468. Subs. by Notification No. F. 1-14/68-D, dated 26th October, 1968 (w.e.f. 2-11-1968).
469. Ins. By G.S.R. 13(E) dated 7th January, 1983 (w.e.f. 7-1-1983)
470. Ins. by G.S.R. 680(E), dated 5th December, 1980 (w.e.f. 5-12-1980).
471. Added by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
472. Subs. by G.S.R. 926(E), dated 24th June, 1977 (w.e.f. 16-7-1977).
473. Added by Notification No. F.1-19/59-D (S.O. 1449), dated 13th June, 1961 (w.e.f. 24-6-1961).
474. Rule 90 re-numbered as sub-rule (1) thereof by S.O. 903, dated 10th February, 1976 (w.e.f. 28-2-1976).
475. Added by S.O. 903(E), dated 10th February, 1976 (w.e.f. 28-2-1976).
476. Subs. by G.S.R. 766(E), dated 27th October, 2021, for "Form 29" (w.e.f. 27-10-2021).
477. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
478. Ins. by G.S.R. 766(E), dated 27th October, 2021 (w.e.f. 27-10-2021).
479. Subs. by G.S.R. 103(E), dated 2nd February, 2017, for "one year from the date of issue" (w.e.f. 2-2-2017).
480. Subs. by G.S.R. 444, dated 31st March, 1973 (w.e.f. 28-4-1973).
481. Subs. By Notification No. F.1-10/68-D(S.O. 2482(E)) dated 17th June, 1969 (w.e.f. 28-6-1969).
482. Ins. By G.S.R. 676(E) dated 2nd June, 1988 (w.e.f. 2-6-1988).
483. Subs, by G.S.R. 592(E), dated 13th August, 2008, for "blood products, Narcotic and Psychotropic Substances" (w.e.f. 13-8-2008).
484. Ins. by G.S.R. 592(E), dated 13th August, 2008 (w.e.f. 13-8-2008).
485. Subs. by Notification No. F.1-19/59-D (S.O. 1449), dated 13th June , 1961 (w.e.f. 24-06-1961)
486. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
487. Ins. By G.S.R. 19(E) dated 15th December, 1977 (w.e.f. 7-1-1978).
488. Subs. By G.S.R. 222(E) dated 13th March, 2018, for certain words (w.e.f. 13-9-2018). Earlier these words were amended by G.S.R. 27(E) dated 17th January, 1981(w.e.f. 17-1-1981). The words before substitution, stood as under:
"(A) For this purpose, the proper name of the drug shall be printed or written in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name and shall be".
489. The words "in same font but" omitted by G.S.R. 1161(E) dated 3rd December, 2018 (w.e.f. 3-12-2018).
490. The words "in brackets" omitted by G.S.R. 205(E) dated 8th March, 2019 (w.e.f. 8-3-2019).
491. Sub-clause (E) omitted by G.S.R. 94(E) dated 8th February, 2000 (w.e.f. 8-2-2000). Earlier sub-clause (E) was inserted by G.S.R. 27(E) dated 17th January, 1981 (w.e.f. 17-1-1981)
492. Ins. by G.S.R. 1161(E) dated 3rd December, 2018 (w.e.f. 3-12-2018).
493. Certain words omitted by G.S.R. 285(E) dated 16th July, 1996 (w.e.f. 16-7-1996).
494. Ins. By G.S.R. 681(E) dated 5th December , 1980 (w.e.f. 5-12-1980).
495. Ins. by G.S.R. 285(E) dated 16th July, 1996 (w.e.f. 16-7-1996).
496. Subs. By G.S.R. 491(E) dated 25th July, 1991(w.e.f. 25-7-1991).
497. Subs. By G.S.R. 17(E) dated 7th January 1986 (w.e.f.7-1-1986).
498. Subs. By G.S.R. 17(E) dated 7th January 1986 (w.e.f.7-1-1986).

499. Ins. by G.S.R. 285(E) dated 16th July, 1996 (w.e.f. 16-7-1996).
500. Subs. by G.S.R. 592(E), dated 13th August, 2008 (w.e.f. 13-8-2008).
501. Subs. by G.S.R. 813(E), dated 27th July, 1988 (w.e.f. 27-7-1988).
502. Ins. by G.S.R. 426(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
503. Ins. by G.S.R. 597(E), dated 17th June, 1992 (w.e.f. 17-12-1992).

Subs. by G.S.R. 408(E), dated 26th April, 2018, for "In addition to the other particulars which are required to be printed or written under these rules, the label of innermost container of the following categories of drugs and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which should not be less than 1 mm in width and without disturbing the other conditions printed on the label under these rules, namely:—

Narcotic analgesics, hypnotics, sedatives, tranquillisers, corticosteriods, hormones, hypoglycemics, antimicrobials, antiepileptics, antidepressants, anticoagulants, anti-Cancer drugs and all other drugs
504. falling under Schedules G, H and X whether covered or not in the above list:" (w.e.f. 1-11-2018).
505. Subs. by G.S.R. 408(E), dated 26th April, 2018, for "Provided that" (w.e.f. 1-11-2018).
506. Ins.. by G.S.R. 592(E), dated 13th August, 2008 (w.e.f. 13-8-2008).
507. Ins. by G.S.R. 101(E), dated 11th February, 2020 (w.e.f. 1-3-2021).
508. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
Subs. by G.S.R. 408(E), dated 26th April, 2018, for clauses (a) to (e) (w.e.f. 1-11-2018).Earlier it was amended by G.S.R. 282(E), dated 16th july, 1996 (w.e.f. 16-7-1996), as corrected by G.S.R. 241(E),
509. dated 15th April, 1998, by G.S.R. 588(E), dated 30th August, 2013 (w.e.f. 27-2-2014).
510. Ins. by G.S.R. 850(E), dated 7th December, 1994 (w.e.f. 7-12-1994).
511. Subs. by Notification No. F. 1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 19-7-1969).
512. Ins. by G.S.R. 128(E), dated 17th January, 2012 (w.e.f. 17-1-2012).
Sub-rule (4) omitted and sub-rule (5) renumbered as sub-rule (4) by G.S.R. 462(E), dated 22nd June,
513. 1982 (w.e.f. 22-6-1982).
514. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
515. Ins. by G.S.R. 231(E), dated 20th March, 2019 (w.e.f. 20-3-2019).
516. Rules 98 to 101 omitted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
517. Subs. by Notification No. F. 1-3/51-D.S., dated 15th October, 1954.
518. Sub-rule (1) omitted by Notification No. F. 116/57-D (S.O. 2136), dated 15th June, 1957.
519. Subs. by Notification No. F-1-16/57-D (S.O. 2136), dated 15th June, 1957.
520. Subs. by G.S.R. 19, dated 15th December, 1977 (w.e.f. 7-1-1978).
521. Ins. by G.S.R. 1242(E) dated 17th September, 1976 (w.e.f. 6-10-1979).
522. Subs. by G.S.R. 796(E), dated 1st October, 1992 (w.e.f. 1-10-1993).
523. Subs. by G.S.R. 558(E), dated 17th July, 2015, for "Provided also that" (w.e.f. 17-7-2015).
524. Ins. by G.S.R. 242(E), dated 3rd April, 2001 (w.e.f. 3-4-2001).
525. Subs. by G.S.R. 558(E), dated 17th July, 2015, for "Provided further that" (w.e.f. 17-7-2015).
526. Ins. by G.S.R. 558(E), dated 17th July, 2015 (w.e.f. 17-7-2015).
527. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
528. Subs. by Notification No. F. 16-/52-DS (S.O. 2122), dated 22nd June, 1954.
529. Explanation omitted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
530. Part IXA Containing rules 106A ins. by G.S.R. 1185, dated 18th August, 1964 (w.e.f. 22-8-1964).
531. Subs, by G.S.R. 680(E), dated 5th December, 1980 (w.e.f. 5-12-1980).
532. Subs. by G.S.R. 466(E), dated 17th May, 1994 (w.e.f. 17-5-1994).
533. Subs. by Notification No. F. 1-59/68-D, dated 19th November, 1969.
534. Ins. by G.S.R. 263(E), dated 20th April, 2009 (w.e.f. 20-4-2009).
535. Subs. by G.S.R. 108(E), dated 22nd February, 1994 (w.e.f. 22-2-1994).
536. Added, by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).
537. Ins. by G.S.R. 108(E), dated 22nd February, 1994 (w.e.f. 22-2-1994).
538. Subs. by Notification No. F-1-5/47-D (S.O. 2889), dated 25th November, 1949.
539. Subs. by Notification No. F-1-6/62-D, dated 2nd July, 1969 (w.e.f. 02.07.1969).
540. Subs. by G.S.R. 647(E), dated 28th October, 1998 (w.e.f. 28-10-1998).
541. Subs. by G.S.R. 245(E) dated 3rd February, 1976 (w.e.f. 21-2-1976)
542. Ins. by S.O. 115(E), dated 4th January, 1961 (w.e.f. 14-1-1961).
543. Subs. by Notification No. F-1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 02.07.1969).
544. Subs. by Notification No. F-1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 02.07.1969).
545. Subs. by G.S.R. 19(E), dated 15th December, 1977 (w.e.f. 7-1-1978).

Subs. by G.S.R. 690(E), dated 25th September, 2014, for rule 109A (w.e.f. 25-9-2014). Earlier rule
546. 109A was inserted by G.S.R. 109(E), dated 22nd February, 1994 (w.e.f. 22-2-1994).
547. Ins. by G.S.R. 690(E), dated 25th September, 2014 (w.e.f. 25-9-2014).
548. Ins. by G.S.R. 690(E), dated 25th September, 2014 (w.e.f. 25-9-2014).
Rule 11A omitted by G.S.R. 1242, dated 17th September, 1979 (w.e.f. 6-10-1979). Earlier rule 11A
549. was inserted by Notification No. F. 1-5/53-DS, dated 17th January, 1955.
550. Subs. by Notification No. F-1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 02.07.1969).
551. Subs. by Notification No. F-1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 02.07.1969).
552. Ins. by G.S.R. 663(E), dated 3rd July, 1992 (w.e.f. 3-7-1992).
553. Rules 113 and 114 omitted by G.S.R. 663(E), dated 3rd July, 1992 (w.e.f. 3-7-1992).
554. Rules 116 and 118 omitted by G.S.R. 663(E), dated 3rd July, 1992 (w.e.f. 3-7-1992).
555. Subs. by G.S.R. 834(E), dated 29th December, 1999 (w.e.f. 30-12-1999).
Subs. by S.O. 1449, dated 13th June, 1961. Earlier it was inserted by Notification No. F. 1-27/56-D,
556. dated 18th December, 1956.
557. Ins. by G.S.R. 663(E), dated 3rd July, 1992 (w.e.f. 3-7-1992).
558. Clause (b) omitted by G.S.R. 19(E), dated 15th December, 1977 (w.e.f. 7-1-1978).
559. Ins. by G.S.R. 663(E), dated 3rd July, 1992 (w.e.f. 3-7-1992).
Part XA (containing rules 122A, 122B, 122C, 122D, 122E) ins. by G.S.R. 944(E), dated 21st
560. September, 1988 (w.e.f. 21-9-1988).
561. Subs. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).
562. Subs. by G.S.R. 1193(E), dated 12th December, 2018, for "fifty thousand rupees" (w.e.f. 12-12- 2018).
563. Subs. by G.S.R. 1193(E), dated 12th December, 2018, for "fifty thousand rupees" (w.e.f. 12-12- 2018).
Subs. by G.S.R. 1193(E), dated 12th December, 2018, for "fifteen thousand rupees" (w.e.f. 12-12-
564. 2018).
Subs. by G.S.R. 918(E), dated 30th November, 2015, for "Appendix I or Appendix IA" (w.e.f. 30-11-
565. 2015.)
566. Ins. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).
The word “Other than the Drugs Classifable under Schedule C and C(1)”omitted by G.S.R. 26(E),
567. dated 19th January, 2006 (w.e.f. 19-1-2006).
568. Subs. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).
569. Ins. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).
570. Ins. by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).
571. Subs. by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).
572. Rule 122C omitted by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).
573. Subs. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).
Subs. by G.S.R. 1193(E), dated 12th December, 2018, for "fifteen thousand rupees" (w.e.f. 12-12-
574. 2018).
575. Ins. by G.S.R. 313(E), dated 16th March, 2016 (w.e.f. 16-3-2016).
576. Ins. by G.S.R. 313(E), dated 16th March, 2016 (w.e.f. 16-3-2016).
577. Subs. by G.S.R. 826(E), dated 30th October, 2015 (w.e.f. 30-10-2015).
Rule 122DAA omitted by G.S.R. 826(E), dated 30th October, 2015 (w.e.f. 30-10-2015). Eralier rule
578. 122DAA was inserted by G.S.R. 32(E), dated 20th January, 2005 (w.e.f. 20-01-2005).
579. Ins. by G.S.R. 53(E), dated 30th January, 2013, (w.e.f. 30-1-2013).
580. Subs. by G.S.R. 889(E), dated 12th December, 2014, for sub-rule (1) (w.e.f. 12-6-2015).
581. Ins. by G.S.R. 889(E), dated 12th December, 2014, (w.e.f. 12-6-2015).
582. Ins. by G.S.R. 63(E), dated 1st February, 2013 (w.e.f. 1-2-2013).
583. Ins. by G.S.R. 72(E), dated 8th February, 2013 (w.e.f. 8-2-2013).
584. Subs. by G.S.R. 591(E), dated 17th August, 1999 (w.e.f. 17-8-1999).
585. Subs. by G.S.R. 918(E), dated 30th November, 2015 (w.e.f. 30-11-2015.)
586. Subs. by G.S.R. 45(E), dated 24th January, 2011 for item (i) (w.e.f. 24-1-2011)
The word “or its inclusion in the Indian Pharmacopoeia whichever is earlier”omitted by G.S.R. 724(E),
587. dated 7th November, 2013 (w.e.f. 7-11-2013).
Part XB (containing rules 122F to 122P) ins. by G.S.R. 28(E), dated 22nd January, 1993 (w.e.f. 22-1-
588. 1993).
589. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANKS" (w.e.f. 11-3-2020).
Subs. by G.S.R. 899(E), dated 27th December, 2011, for "AND MANUFACTURE OF BLOOD
590. PRODUCTS" (w.e.f. 27-12-2011).
591. Ins. by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
592. Subs. by G.S.R. 899(E), dated 27th December, 2011 for “and Part XIIC” (w.e.f. 27-12-2011).
593. Subs. by G.S.R. 166(E), dated 11th March, 2020, for clause (d) (w.e.f. 11-3-2020).

594. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
595. Ins. by G.S.R. 166(E), dated 11th March, 2020, (w.e.f. 11-3-2020).
596. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
597. Ins. by G.S.R. 166(E), dated 11th March, 2020, (w.e.f. 11-3-2020).
598. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANKS" (w.e.f. 11-3-2020).
599. Subs. by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
600. Subs. by G.S.R. 899(E), dated 27th December, 2011 for “or Form 27E” (w.e.f. 27-12-2011).
601. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
602. Subs. by G.S.R. 899(E), dated 27th December, 2011 for second proviso (w.e.f. 27-12-2011).
603. Explanation omitted by G.S.R. 733(E), dated 21st December, 2005 (w.e.f. 21-12-2005). Earlier Explanation was inserted by G.S.R. 89(E), dated 14th February, 1996 (w.e.f. 14-2-1996).
604. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
605. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
606. Ins. by G.S.R. 89(E), dated 14th February, 1996 (w.e.f. 14-2-1996).
607. Corrected vide corrigendum G.S.R. 447(E), dated 10th June, 1993 to G.S.R. 28(E), dated 22nd January, 1993.
608. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANKS" (w.e.f. 11-3-2020).
609. Subs. by G.S.R. 899(E), dated 27th December, 2011, for "MANUFACTURE OF BLOOD PRODUCTS" (w.e.f. 27-12-2011).
610. Rule 122G renumbered as sub-rule (1) by G.S.R. 733(E), dated 21st December, 2005 (w.e.f. 21-12-2005).
611. Subs. by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
612. Subs. by G.S.R. 899(E), dated 27th December, 2011, for "Form 26G or Form 26-I,as the case may be, before a licence in Form 28C or Form 26G or Form 26-I" (w.e.f. 27-12-2011).
613. Subs. by G.S.R. 166(E), dated 11th March, 2020, for condition (i) (w.e.f. 11-3-2020). Earlier condition (i) was substituted by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
614. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
615. Subs. by G.S.R. 166(E), dated 11th March, 2020, for sub-rule (2) and Explanation (w.e.f. 11-3-2020). Earlier sub-rule (2) and Explanation inserted by G.S.R. 733(E), dated 21st December, 2005 (w.e.f. 21-12-2005).
616. Subs. by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
617. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
618. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
619. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
620. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
621. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANKS" (w.e.f. 11-3-2020).
622. Corrected vide corrigendum G.S.R. 447(E), dated 10th June, 1993 to G.S.R. 28(E), dated 22nd January, 1993.
623. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
624. Subs. by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
625. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
626. Corrected vide corrigendum G.S.R. 447(E), dated 10th June, 1993 to G.S.R. 28(E), dated 22nd January, 1993.
627. Ins. by G.S.R. 20(E), dated 11th January, 1996 (w.e.f. 11-1-1996).
628. Corrected *vide* Corrigendum G.S.R. 514(E), dated 6th November, 1996.
629. Subs. by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
630. Subs. by G.S.R. 899(E), dated 27th December, 2011, for "Form 26G or Form 26-I shall be subject to the special conditions set out in Schedule F, Part XIIB and Part XIIC” (w.e.f. 27-12-2011).
631. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANKS" (w.e.f. 11-3-2020).
632. Corrected vide corrigendum G.S.R. 447(E), dated 10th June, 1993 to G.S.R. 28(E), dated 22nd January, 1993.
633. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
634. Corrected vide corrigendum G.S.R. 447(E), dated 10th June, 1993 to G.S.R. 28(E), dated 22nd January, 1993.
635. Corrected vide corrigendum G.S.R. 447(E), dated 10th June, 1993 to G.S.R. 28(E), dated 22nd January, 1993.
636. Published in the Gazette of India, Extra Pt. II, Sec.3(i), dated 22nd January, 1993 (w.e.f. 22-5-1993).
637. Ins. by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999).
638. Ins. by G.S.R. 328(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).
639. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANKS" (w.e.f. 11-3-2020).

640. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANKS" (w.e.f. 11-3-2020).
641. Subs. by G.S.R. 19(E), dated 15th December, 1977 (w.e.f. 7-1-1978).
Rule 124A omitted by G.S.R. 103(E), dated 2nd February, 2017 (w.e.f. 2-2-2017). Earlier rule 124A was inserted by S.O. 2889, dated 2nd July, 1969 (w.e.f. 19-7-1969) and amended by G.S.R. 647(E),
642. dated 28th October, 1998 (w.e.f. 28-10-1998).
643. Added by G.S.R 665(E), dated 6th May, 1977 (w.e.f. 28-5-1977).
644. Ins by G.S.R. 318(E), dated 1st May, 1984 (w.e.f. 1-5-1984).
645. Ins. by G.S.R. 1115(E), dated 30th September, 1986 (w.e.f. 30-9-1986).
646. Subs. by Notification No. F. 1-28/65-T) (S.O. 886), dated 8th March, 1966 (w.e.f. 26-3-1966).
647. Ins by G.S.R. 109(E), dated 22nd February, 1994 (w.e.f. 22-2-1994).
648. Subs. by Notification No. F. 1-20/60-D (S.O. 400), dated 24th January, 1964 (w.e.f. 1-2-1964).
Subs-heading "Insecticides" and the entry relating thereto omitted by G.S.R. 139, dated 8th January,
649. 1976 (w.e.f. 31-1-1976).
650. Added by Notification No. F. 1-13/60-D (S.O. 23), dated 23rd December, 1969 (w.e.f. 3-1-1970).
651. Ins. by G.S.R. 245(E), dated 17th June, 1996 (w.e.f. 17-6-1996).
652. Subs. By S.O. 289, dated 20th December, 1972 (w.e.f. 3-2-1973)
653. Ins. by G.S.R. 1074(E), dated 19th August, 1978.
654. Subs. By G.S.R. 370(E), dated 7th April, 1994 (w.e.f. 7-4-1994).
655. Ins. by G.S.R. 76(E), dated 8rd February, 2012 (w.e.f.8-2-2012).
656. Ins. by G.S.R. 681(E), dated 6th June, 1988 (w.e.f. 6-6-1988).
657. Ins. by G.S.R. 1074(E), dated 19th August, 1978.
658. Omitted by G.S.R. 753(E), dated 4th November, 1999 (w.e.f. 4-11-1999).
659. Subs. by G.S.R. 11(E), dated 7th January, 1991 (w.e.f. 7-11-1991).
660. Omitted by G.S.R. 753(E), dated 4th November, 1999 (w.e.f. 4-11-1999).
661. Ins. by G.S.R. 1074(E), dated 19th August, 1978.
662. Ins. by G.S.R. 1074(E), dated 19th August, 1978.
Ins. By G.S.R. 623(E) dated 10-08-2022 (w.e.f. 10-08-2022). Earlier this proviso was inserted by G.S.R. 76(E), dated 8rd February, 2012 (w.e.f.8-2-2012). Before substitution the proviso stood as:
"Provided that disinfectants mya also contain colours specified under Schdule Q, which are non-
663. staining."
664. Ins. by G.S.R. 1186(E), dated 7th December, 2018 (w.e.f. 7-12-2018).
665. Added by Notification No. F. 1-37/58-D, dated 21st July, 1958.
Part XIII (containing rules 129, 129A to 129H 130, 131, 132, 133, 134, 134A, 135, 135A, 135B, 136) omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Part XIII (containing rules 129, 129A, to 129H) inserted by Notification No. F. 1-36/64-D (G.S.R. 1183), dated 17th August, 1964 (w.e.f. 22-8-1964). Rule 129, Rules 129A to 129H subs. by G.S.R. 426(E), dated 19th May, 2010, read with corrigendum G.S.R. 263(E), dated 30th March, 2011, corrigendum G.S.R. 733(E), dated 29th September, 2011, corrigendum G.S.R. 270(E), dated 30th March, 2012 and
666. corrigendum G.S.R. 733(E), dated 29th September, 2012 for rule129 (w.e.f. 1-4-2013).
Part XIV (containing rules 137, 138, 138A, 139, 139A, 139AA, 139AB, 139AC, 139AD, 139AE, 139B, 140, 141, 141A, 141AA, 142, 142A, 142B, 143, 143A, 144, 144A, 145, 145A, 145AA, 145B,
667. 145BA, 145C, 145D)omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
Part XV (containing rules 145, 147, 148, 148A, 148B, 148C, 149, 149A, 150, 150A) omitted by G.S.R.
668. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
Part XV(A) (containing rules 150B to 150K) ins. by G.S.R. 1172, dated 23rd August, 1977 (w.e.f. 23-
669. 8-1977).
670. The words "cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
671. Ins. by G.S.R. 223(E), dated 18th March, 2019 (w.e.f. 19-3-2019).
672. The words "cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
The words "OR RENEWAL" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-
673. 2017).
674. The words "or cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
Ins. by G.S.R. 223(E), dated 18th March, 2019, for " for sale of drugs or cosmetics, shall be made in
675. Form 36" (w.e.f. 19-3-2019).
676. The words "and cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
Proviso omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier proviso was
677. substituted by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
678. Ins. by G.S.R. 510(E), dated 26th July, 1982 (w.e.f. 26-7-1982).
679. Subs. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
680. The words "cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).

681. The words "and cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
682 The words "or cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
683. Ins. by G.S.R. 223(E), dated 18th March, 2019 (w.e.f. 19-3-2019).
684. The words "OR RENEWAL" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
685. The words "or cosmetics as the case may be" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
686. The words "OR RENEWED" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
687. The words "or cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
688. The words "or cosmetics as the case may be" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
689. Subs. by G.S.R. 1337(E), dated 27th October, 2017 for rule 150D (w.e.f. 27-10-2017). Earlier rule 150D was inserted by G.S.R. 1172 (E), dated 23rd August, 1977 (w.e.f. 23-8-1977) and amended by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
690. Ins. by G.S.R 780(E), dated 10th November, 2008 (w.e.f. 1-11-2010).
691. The words "or cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
692. The words "OR RENEWAL" omitted by G.S.R. 499(E), dated 17th July, 2019 (w.e.f. 17-7-2019).
693. Subs. by G.S.R. 223(E), dated 18th March, 2019 for clause (f) (w.e.f. 19-3-2019).
694. The word "or a cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
695. Ins. by G.S.R. 93(E), dated 24th February, 1995 (w.e.f. 24-2-1995).
696. The words "or cosmetics as the case may be" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
697. The word "or cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
698. Sub. by G.S.R. 601(E), dated 24th August, 2001 (w.e.f. 24-8-2001).
699. Rule 150J omitted by G.S.R. 499(E), dated 17th July, 2019 (w.e.f. 17-7-2019).
700. The word "or items of cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
701. Part XVI (containing rules 151 to 153, 154 to 160) added by Notification No. F. 1-23/6 (S.O. 642(E)), dated 2nd February, 1970 (w.e.f. 21-2-1970).
702. Subs, by G.S.R. 716(E), dated 1st October, 2021, for "(Including Siddha)" (w.e.f. 1-10-2021).
703. Subs, by G.S.R. 716(E), dated 1st October, 2021, for "(Including Siddha)" (w.e.f. 1-10-2021).
704. Subs, by G.S.R. 716(E), dated 1st October, 2021, for rule 153 (w.e.f. 1-10-2021). Earlier rule 153was amended by G.S.R. 79(E), dated 14th February, 2005 (w.e.f. 14-2-2005).
705. Subs, by G.S.R. 716(E), dated 1st October, 2021, for rule 153A (w.e.f. 1-10-2021). Earlier rule 153A was added by G.S.R. 376(E), dated 20th July, 1978 (w.e.f. 20-7-1978) and amended by G.S.R. 79(E), dated 14th February, 2005 (w.e.f. 14-2-2005).
706. Subs, by G.S.R. 716(E), dated 1st October, 2021, for rule 154 (w.e.f. 1-10-2021).
707. Subs, by G.S.R. 716(E), dated 1st October, 2021, for rule 154A (w.e.f. 1-10-2021). Earlier rule 154A was added by G.S.R. 376(E), dated 20tih July, 1978 (w.e.f. 20-7-1978).
708. Rule 155 was omitted by G.S.R. 716(E), dated 1st October, 2021,(w.e.f. 1-10-2021).
709. Rule 155A was omitted by G.S.R. 716(E), dated 1st October, 2021,(w.e.f. 1-10-2021). Earlier rule 155A was added by G.S.R. 376(E), dated 20th July, 1978 (w.e.f. 20-7-1978).
710. Ins. by G.S.R. 198(E), dated 7th March, 2003 (w.e.f. 7-3-2003).
711. Rule 155B renumbered as sub-rule (1) thereof by G.S.R. 376(E), dated 3rd May, 2010 (w.e.f. 3-4-2010).
712. Subs, by G.S.R. 716(E), dated 1st October, 2021, for “for period of five years” (w.e.f. 1-10-2021). Earlier these words were inserted by G.S.R. 376(E), dated 3rd May, 2010 (w.e.f. 3-5-2010).
713. Sub-rule (2) was omitted by G.S.R. 716(E), dated 1st October, 2021,(w.e.f. 4-10-2021). Earlier sub-rule (2) was inserted by G.S.R. 376(E), dated 3rd May, 2010 (w.e.f. 3-4-2010).
714. Subs. by G.S.R. 716(E), dated 1st October, 2021, for rule 156 (w.e.f. 1-10-2021). Earlier rule 156 was amended by G.S.R. 79(E), dated 14th February, 2005 (w.e.f. 14-2-2005) and by G.S.R. 376(E), dated 3rd May, 2010 (w.e.f. 3-5-2010).
715. Subs. by G.S.R. 716(E), dated 1st October, 2021, for rule 156A (w.e.f. 1-10-2021). Earlier rule 156A was added by G.S.R. 376(E), dated 3rd May, 2010 (w.e.f. 3-5-2010) and amended by G.S.R. 79(E), dated 14th February, 2005 (w.e.f. 14-2-2005)
716. The words "OR RENEWAL" omitted by G.S.R. 716(E), dated 1st October, 2021 (w.e.f. 1-10-2021).
717. The words “or renewed in Form 26D” omitted by G.S.R. 716(E), dated 1st October, 2021 (w.e.f. 1-10-2021).
718. Subs, by G.S.R. 716(E), dated 1st October, 2021, for "(Including Siddha)" (w.e.f. 1-10-2021).

Subs, by G.S.R. 376(E), dated 3rd May, 2010, for clause (1A) (w.e.f. 4-5-2010). Earlier clause (1A)
719. was inserted by G.S.R. 198(E), dated 7th March, 2003 (w.e.f. 7-3-2003).
720. The words "OR RENEWAL" omitted by G.S.R. 716(E), dated 1st October, 2021 (w.e.f. 1-10-2021).
Subs. by G.S.R. 390(E), dated 18th May, 2015, for sub-rules (1B) and (1C) (w.e.f .18-5-2016). Earlier
721. sub-rules (1B) and (1C) was inserted by G.S.R704(E), dated 25th October, 2013 (w.e.f. 25-10-2013).
722. Subs. by G.S.R. 716(E), dated 1st October, 2021, for sub-rule (1D) (w.e.f. 1-10-2021).
723. Sub-rule (1E) omitted by G.S.R. 716(E), dated 1st October, 2021 (w.e.f. 1-10-2021).
724. Ins. by G.S.R. 512(E), dated 9th July, 2008 (w.e.f. 9-7-2008).
725. Ins. by G.S.R. 716(E), dated 1st October, 2021 (w.e.f. 1-10-2021).
Subs. by G.S.R. 716(E), dated 1st October, 2021, for sub-clause (c) (w.e.f. 1-10-2021). Earlier sub-
726. clause (c) was inserted by G.S.R. 331(E) dated 8th May, 1984 (w.e.f.8-5-1984).
727. Added by G.S.R. 376(E), dated 20th July, 1978 (w.e.f. 20-7-1978)
Subs. by G.S.R. 716(E), dated 1st October, 2021, for sub-clause (e) (w.e.f. 1-10-2021). Earlier sub-
728. clause (e) was inserted by G.S.R. 331(E) dated 8th May, 1984 (w.e.f.8-5-1984).
729. Ins. by G.S.R. 663(E), dated 10th August, 2010 (w.e.f. 10-8-2010).
730. Ins. by G.S.R. 153(E), dated 5th March, 2014 (w.e.f. 5-3-2014).
731. Ins. by G.S.R. 716(E), dated 1st October, 2021 (w.e.f. 1-10-2021).
732. Ins. by G.S.R. 716(E), dated 1st October, 2021 (w.e.f. 1-10-2021).
733. Part XVII (containing rule 161) added by Notification No. F. 1-23/6, dated 2nd Feburary, 1970.
734. Subs. by G.S.R. 904(E), dated 2nd November, 1992 (w.e.f. 2-11-1992).
735. Ins. by G.S.R. 844(E), dated 26th November, 2012 (w.e.f. 26-11-2013).
736. Subs. by G.S.R. 844(E), dated 26th November, 2012 (w.e.f. 26-11-2013).
737. Ins. by G.S.R. 904(E), dated 2nd November, 1992 (w.e.f. 2-11-1992).
738. Ins. by G.S.R. 787(E), dated 17th October, 2000 (w.e.f. 17-10-2000).
Subs. by G.S.R. 789(E), dated 12th August, 2016, for rule 161B (w.e.f. 12-8-2016). Earlier rule 161B
739. was inserted by G.S.R. 764(E), dated 15th October, 2009 (w.e.f. 15-10-2009).
740. Part XVIII (containing rule 162 to 167) added by Notification No. F. 1-23/6, dated 2nd Feburary, 1970.
741. Ins. by G.S.R. 76(E), dated 3rd February, 2003 (w.e.f. 3-2-2003).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for rule 163A (w.e.f. 23-3-2021). Earlier rule 163A
742. was inserted by G.S.R. 352(E), dated 1st June, 2006 (w.e.f. 8-6-2006).
743. Subs. by G.S.R. 202(E), dated 22nd March, 2021, for rule 163B (w.e.f. 23-3-2021).
744. Ins. by G.S.R. 202(E), dated 22nd March, 2021 (w.e.f. 23-3-2021).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for "Pharmacopoeial Laboratory for Indian
745. Medicine" (w.e.f. 23-3-2021).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for "Pharmacopoeial Laboratory for Indian
746. Medicine" (w.e.f. 23-3-2021).
747. Ins. by G.S.R. 202(E), dated 22nd March, 2021 (w.e.f. 23-3-2021).
748. Subs. by G.S.R. 202(E), dated 22nd March, 2021, for rule 164 (w.e.f. 23-3-2021).
749. Subs. by G.S.R. 202(E), dated 22nd March, 2021, for "Ayurveda, Siddha or Unani" (w.e.f. 23-3-2021).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for "and Boards of Indian Systems of Medicine"
750. (w.e.f. 23-3-2021).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for "Ayurvedic (including Siddha) or Unani" (w.e.f.
751. 23-3-2021).
752. The words "of Chapter VIA" omitted by G.S.R. 202(E), dated 22nd March, 2021 (w.e.f. 23-3-2021).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for rule 167 (w.e.f. 23-3-2021). Earlier rule 167 was
753. sub. by G.S.R. 376(E), dated 20th July, 1978 (w.e.f. 20-7-1978)
754. Part XIX (containing rule 168) inserted by G.S.R. 519(E), dated 26th June, 1995 (w.e.f. 26-6-1995).
755. Subs. by G.S.R. 422(E), dated 11th June, 2002 (w.e.f. 11-6-2002).
Subs. by G.S.R. 755(E), dated 23ed October, 2008, for rule 169 (w.e.f. 27-10-2008). Earlier rule 169
756. was added by G.S.R. 285(E) dated 11th May, 2005 (w.e.f. 12-5-2005).
757. Ins. by G.S.R. 1230(E), dated 21st December, 2018 (w.e.f. 24-12-2018).
758. Ins. by G.S.R. 352(E), dated 1st June, 2006 (w.e.f. 8-6-2006).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for heading "Memorandum to the Pharmocoposial
759. Laboratory for Indian Medicine (PLIM)" (w.e.f. 23-3-2021).
760. Ins. by G.S.R. 352(E), dated 1st June, 2006 (w.e.f. 8-6-2006).
Subs. by G.S.R. 202(E), dated 22nd March, 2021, for "Pharmacopoeial Laboratory for Indian
761. Medicine" (w.e.f. 23-3-2021).
762. Forms 3 to 7 omitted by Notification No. F. 1-16/57-D, dated 15th June, 1957.
763. Subs. by G.S.R. 604(E), dated 24th August, 2001, for Form 8 (w.e.f. 24-8-2001).
764. Subs. by G.S.R. 604(E), dated 24th August, 2001, for Form 8A (w.e.f. 24-8-2001). Earlier Form 8A

was inserted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
765. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
Subs. By G.S.R. 604(E), dated 24th August, 2001, for “signed by or on behalf of the manufacturer”
766. (w.e.f. 1-1-2003).
767. Subs. by G.S.R. 604(E), dated 24th August, 2001, for Form 10 (w.e.f. 24-8-2001).
Subs. by G.S.R. 604(E), dated 24th August, 2001, for Form 10A (w.e.f. 24-8-2001). Earlier Form 10A
768. was inserted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
769. Subs. by G.S.R. 103(E), dated 2nd February, 2017, for “one year” (w.e.f. 2-2-2017).
770. Ins. by G.S.R. 604(E), dated 24th August, 2001, (w.e.f. 24-8-2001).
Added by Notification No. F. 1-36/54-DS, dated 3rd March, 1955 and amended by G.S.R. 753(E),
771. dated 4th November, 1999 (w.e.f. 4-11-1999).
Subs. by G.S.R. 604(E), dated 24th August, 2001, for “A fee of rupees fifteen has been credited to Government under the Head of Account “ 0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines under the Drugs and Cosmetics Rules, 1945- Central” vide treasury receipt attached.”
772. (w.e.f. 24-8-2001).
773. Ins. by Notification No. F. 1-36/54-DS, dated 3rd March, 1955.
774. Ins. by G.S.R. 604(E), dated 24th August, 2001, (w.e.f. 24-8-2001).
775. Subs. by G.S.R. 753(E), dated 4th November, 1999 (w.e.f. 4-11-1999).
776. Subs. by G.S.R. 521(E), dated 1st June, 2018, for "for a period of six months" (w.e.f. 1-6-2018).
777. Subs, by G.S.R. 59 (E), dated 7th February, 1995 (w.e.f. 7-2-1995).
778. Added by Notification No. F. 1-23/67-D (S.O. 642(E)), dated 2nd February, 1970 (w.e.f. 21-2-1970).
779. Ins. by G.S.R. 376(E), dated 3rd May, 2010 (w.e.f. 3-5-2010).
780. Added by Notification No. 1-3/51-DS, dated 15th October, 1954.
781. Subs. by G.S.R. 1594, dated 28th October, 1976 (w.e.f. 13-11-1976).
782. The words “cosmetics” omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
783. Subs. by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).
784. The words “or cosmetics” omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
785. Subs. by S.O. 2139(E), dated 5th June, 1972 (w.e.f. 12-8-1972).
786. The words “cosmetics” omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
787. Ins. By G.S.R. 292(E) dated 29th May, 1997 (w.e.f.29-5-1997)
788. The words “or cosmetics” omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
789. Subs. by G.S.R. 592(E), dated 13th August, 2008, for the figure"19" (w.e.f. 13-8-2008).
790. Subs. By G.S.R. 370(E), dated 7th April, 1994 (w.e.f. 7-4-1994).
791. Added by Notification No. F. 1-23/67-D (S.O. 642(E)), dated 2nd February, 1970 (w.e.f. 21-2-1970).
792. Subs. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-
793. 2017).
The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-
794. 2017).
795. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
796. Omitted by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
797. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
798. Subs. by G.S.R. 487(E) dated 2nd July, 1984 (w.e.f. 2-7-1984).
799. Ins. by G.S.R. 42(E), dated, 25th January, 1979 (w.e.f. 25-1-1979).
800. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-
801. 2017).
802. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
803. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
804. Subs. by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
805. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
806. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
807. Certain words omitted by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
808. Subs. by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
809. Certain words omitted by G.S.R. 504(E) dated 18th July, 2002 (w.e.f. 18-7-2002)
810. Subs. by Notification No. 1-63/61-D, dated 17th July, 1963.
811. Ins. By S.O. 23 (E) dated 23rd December, 1969 (w.e.f. 3-1-1970).
Clause 4 omitted by S.O. 289(E) dated 20th December, 1992 (w.e.f. 3-2-1973). Earlier clause (4) added
812. by Notification No. F.1-113/69-D, dated 23rd December, 1969.
813. Ins. by G.S.R. 42(E), dated, 25th January, 1979 (w.e.f. 25-1-1979).

814. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
815. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 2 (w.e.f. 27-10-2017).
816. Added by Notification No. F. 1-35/64-D (G.S.R. 1185), dated 18th August, 1964 (w.e.f. 22-8-1964)
817. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
818. Added by Notification No. F. 1-59/68-D (S.O. 4816), dated 19th November , 1969 (w.e.f. 6-12-1969)
819. Added by G.S.R 665(E), dated 6th May, 1977 (w.e.f. 28-5-1977).
820. Added by Notification No. F. 1-35/64-D (G.S.R. 1185), dated 18th August, 1964 (w.e.f. 22-8-1964)
821. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
822. Added by G.S.R 665(E), dated 6th May, 1977 (w.e.f. 28-5-1977) (w.e.f. 28-5-1977).
823. Added by Notification no. F.1-14/67-D (G.S.R. 594), dated 3rd February, 1969.
824. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
825. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982) corrected vide corrigendum G.S.R. 373(E) dated 2nd May, 1983.
826. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 3 (w.e.f. 27-10-2017).
827. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982) corrected vide corrigendum G.S.R. 373(E) dated 2nd May, 1983.
828. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
829. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 3 (w.e.f. 27-10-2017).
830. Ins. By G.S.R. 370(E), dated 7th April, 1994 (w.e.f. 7-4-1994).
831. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
832. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
833. Subs. by S.O. 2139(E), dated 5th June, 1972 (w.e.f. 12-8-1972).
834. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 2 (w.e.f. 27-10-2017).
835. Condition No. 3 omitted by G.S.R. 17(E) dated 7th January 1986 (w.e.f.7-1-1986).
836. Added by Notification No. 1-63/61-D, dated 17th July, 1963.
837. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
838. Ins. by S.O. 1458(E), dated 27th April, 1965 (w.e.f. 8-5-1965).
839. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
840. Subs. by G.S.R. 487(E), dated 2nd July, 1984 (w.e.f. 2-7-1984).
841. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 2 (w.e.f. 27-10-2017).
842. SI. No. 4 omitted by G.S.R. 504(E) dated 18th July, 2002 (w.e.f. 18-7-2002)
843. Certain words omitted by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
844. Condition No. 2 omitted by G.S.R. 17(E) dated 7th January 1986 (w.e.f. 7-1-1986).
845. Ins. by S.O. 1458(E), dated 27th April, 1965 (w.e.f. 8-5-1965).
846. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
847. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
848. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 2 (w.e.f. 27-10-2017).
849. Ins. by G.S.R. 681(E), dated 6th June, 1988 (w.e.f. 6-6-1988).
850. Condition No. 2 omitted by G.S.R. 17(E) dated 7th January 1986 (w.e.f. 7-1-1986).
851. Added by Notification No. 1-63/61-D, dated 17th July, 1963.
852. Added by Notification No. F.1-113/69-D (S.O. 23), dated 23rd December, 1969 (w.e.f. 3-1-1970)
853. Ins. by S.O. 1458(E), dated 27th April, 1965 (w.e.f. 8-5-1965).
854. Ins. by G.S.R. 42(E), dated, 25th January, 1979 (w.e.f. 25-1-1979).
855. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 2 (w.e.f. 27-10-2017).
856. FORM 21C omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 21C was amended by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982) and by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
857. FORM 21CC omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 21CC was inserted by G.S.R. 42(E), dated 25th January, 1979 (w.e.f. 25-1-1979) and amended by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
858. FORMS 22 and 23 omitted by S.O. 289(E), dated 20th December, 1962.
859. The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
860. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
861. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
862. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for "grant/renewal" (w.e.f. 27-10-2017).
863. Ins. by S.O. 1196(E), dated 6th May, 1960 (w.e.f. 14-5-1960).
864. The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
865. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

866. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for "grant/renewal" (w.e.f. 27-10-2017).
867. Subs. by Notification No. F. 1-598-D (S.O. 4816) dated 19th November, 1969(w.e.f. 6-12-1969).
868. Ins. by G.S.R. 499(E), dated 17th July, 2019 (w.e.f. 17-7-2019). Earlier it was omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017)
869. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
870. Subs. By G.S.R. 13(E) dated 7th January, 1983 (w.e.f. 7-1-1983) corrected vide corrigendum G.S.R. 334(E) dated 11th May, 1983.
871. Subs. by G.S.R. 499(E), dated 17th July, 2019, for “grant” (w.e.f. 17-7-2019). Earlier the word “grant” was substituted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017)
872. Subs. by G.S.R. 716(E), dated 1st October, 2021, for Form 24D (w.e.f. 4-10-2021). Earlier Form 24D was inserted by Notification No. 1-23/6 (S.O. 642), dated 2nd February, 1970 (w.e.f. 21-2-1970).
873. Subs. by G.S.R. 716(E), dated 1st October, 2021, for Form 24E (w.e.f. 4-10-2021). Earlier Form 24E was added by G.S.R. 376(E) dated 20th July, 1978 (w.e.f. 20-7-1978).
874. Ins. by G.S.R. 716(E), dated 1st October, 2021, (w.e.f. 4-10-2021).
875. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
876. The words "**OR RENEWAL**” omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
877. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
878. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for "grant/renewal" (w.e.f. 27-10-2017).
879. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
880. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
881. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 3 (w.e.f. 27-10-2017).
882. Ins. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992).
883. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
884. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
885 Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
886. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
887. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
888. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 4 (w.e.f. 27-10-2017).
889. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
890. Added by Notification No. F. 1-22/59-D, dated 9th April, 1960.
891. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
892. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 2 (w.e.f. 27-10-2017).
893. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
894. Added by Notification No. F. 1-36/64-D, dated 18th august, 1964.
895. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
896. Subs. By G.S.R. 13(E) dated 7th January, 1983 (w.e.f. 7-1-1983)
897. Added by S.O. 903(E), dated 10th February, 1976 (w.e.f. 28-2-1976).
898. Subs. by G.S.R. 716(E), dated 1st October, 2021, for Form 25D (w.e.f. 4-10-2021). Earlier Form 25D was added by Notification No. 1-23/67-D (S.O. 642), dated 2nd February, 1970 (w.e.f. 21-2-1970).
899. Subs. by G.S.R. 716(E), dated 1st October, 2021, for Form 25E (w.e.f. 4-10-2021). Earlier Form 25E was added by G.S.R. 376(E) dated 20th July, 1978 (w.e.f. 20-7-1978).
900. Ins. By G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
901. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
902. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
903. Ins. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992).
904. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
905. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
906. Subs. by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
907. FORM 26 omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 26 was substituted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
908. FORM 26A omitted by G.S.R 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 26 was substituted by G.S.R 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
909. FORM 26B omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 26B was substituted by Notification No. F. 1-22/59-D, dated 9th April, 1964.
910. Subs. By G.S.R. 370(E), dated 7th April, 1994 (w.e.f. 7-4-1994).

911. Added by Notification No. 1-23/67-D (S.O. 642(E)) dated 2nd February, 1970 (w.e.f. 21-2-1970).
912. Added by G.S.R. 376(E), dated 20th July, 1978 (w.e.f. 20-7-1978).
913. Added by G.S.R. 376(E), dated 20th July, 1978 (w.e.f. 20-7-1978).
914. Ins. By G.S.R. 198(E) dated 7th March, 2003 (w.e.f. 7-3-2003).
915. Subs. by G.S.R. 376(E), dated 3rd May, 2010, for "period of two years" (w.e.f. 4-5-2010).
916. Subs. by G.S.R. 716(E), dated 1st October, 202, for Form 26E2-I (w.e.f. 4-10-2021). Earlier Form 26E2-I was inserted by G.S.R. 153(E) dated 5th March, 2014 (w.e.f. 5-3-2014).
917. Subs. by G.S.R. 716(E), dated 1st October, 202, for Form 26E2-II (w.e.f. 4-10-2021). Earlier Form 26E2-II was inserted by G.S.R. 153(E) dated 5th March, 2014 (w.e.f. 5-3-2014).
918. Subs. by G.S.R. 716(E), dated 1st October, 202, for Form 26E3 (w.e.f. 4-10-2021). Earlier Form 26E3 was inserted by G.S.R. 153(E) dated 5th March, 2014 (w.e.f. 5-3-2014).
919. Ins. By G.S.R. 1230(E) dated 21st December, 2018 (w.e.f. 24-12-2018).
920. Ins. By G.S.R. 1230(E) dated 21st December, 2018 (w.e.f. 24-12-2018).
921. FORM 26F omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 26F was inserted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982) and amended by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14.12.1992), by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
922. Subs. By G.S.R 245(E) dated 5th April, 1999, for Form 26G (w.e.f. 5-4-1999). Earlier Form 26G was inserted by G.S.R. 28(E) dated 22nd January, 1993 (w.e.f. 22-1-1993).
923. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANK" (w.e.f. 11-3-2020).
924. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "Blood Bank" (w.e.f. 11-3-2020).
925. FORM 26H omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).Earlier FORM 26H was inserted by G.S.R. 119(E) dated 11th March , 1996 (w.e.f.11-3-1996) and corrected vide corrigendum G.S.R. 513(E) dated 5th November, 1996 and by G.S.R. 26(E) dated 19th January, 2006 (w.e.f. 19-1-2006).
926. Ins. By G.S.R 245(E) dated 5th April, 1999 (w.e.f. 5-4-1999).
927. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
928. Form 26J omitted by G.S.R. 499(E), dated 17th July, 2019 (w.e.f. 17-7-2019). Earlier Form 26J was inserted by G.S.R. 574(E), dated 17th July, 2012 (w.e.f. 17-7-2012).
929. The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
930. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
931. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
932. Ins. by G.S.R. 28(E), dated 22nd January, 1993 (w.e.f. 22-1-1993).
933. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for "grant/renewal" (w.e.f. 27-10-2017).
934. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
935. The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
936. Subs. by G.S.R. 788(E), dated 10th October, 1985, for FORM 21C (w.e.f. 10-10-1985).
937. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for "grant/renewal" (w.e.f. 27-10-2017).
938. Subs. By G.S.R 245(E) dated 5th April, 1999, for Form 27C(w.e.f. 5-4-1999). Earlier Form 27C was inserted by G.S.R. 28(E) dated 22nd January, 1993 (w.e.f. 22-1-1993)
939. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANK" (w.e.f. 11-3-2020).
940. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "Blood Bank" (w.e.f. 11-3-2020).
941. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "Blood Bank" (w.e.f. 11-3-2020).
942. Ins. by G.S.R. 119(E) dated 11th March, 1996 (w.e.f.11-3-1996) corrected vide corrigendum G.S.R. 513(E) dated 5th November, 1996
943. The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
944. Subs. by G.S.R. 26(E) dated 19th January, 2006 (w.e.f. 19-1-2006).
945. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for "grant/renewal" (w.e.f. 27-10-2017).
946. Ins. by G.S.R. 574(E), dated 17th July, 2012 (w.e.f. 17-7-2012).
947. The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
948. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for "grant/renewal" (w.e.f. 27-10-2017).
949. Ins. By G.S.R 245(E) dated 5th April, 1999 (w.e.f. 5-4-1999).
950. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
951. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
952. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
953. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).

954. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 4 (w.e.f. 27-10-2017).
955. Ins. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992).
956. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
957. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
958. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
959. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
960. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
961. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
962. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).
963. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 3A (w.e.f. 27-10-2017). Earlier paragraph 3A was inserted by Notification No. F. 1-10/62-D dated 10th April, 1964.
964. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
965. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
966. Subs. by G.S.R. 788(E), dated 10th October, 1985 (w.e.f. 10-10-1985).
967. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 4 (w.e.f. 27-10-2017).
968. Ins. by G.S.R. 923(E), dated 14th December, 1992 (w.e.f. 14-12-1992).
969. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
970. Subs. by G.S.R. 245(E), dated 5th April, 1999, for Form 28C (w.e.f. 5-4-1999). Earlier Form 28C was inserted by G.S.R. 28(E) dated 22nd November, 1993.
971. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "BLOOD BANK" (w.e.f. 11-3-2020).
972. Ins. by G.S.R. 119(E) dated 11th March, 1996 (w.e.f.11-3-1996) corrected vide corrigendum G.S.R. 513(E) dated 5th November, 1996
973. Subs. by G.S.R. 26(E) dated 19th January, 2006 (w.e.f. 19-1-2006).
974. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 5 (w.e.f. 27-10-2017).
975. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
976. Ins. by G.S.R. 574(E), dated 17th July, 2012 (w.e.f. 17-7-2012).
977. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 3 (w.e.f. 27-10-2017).
978. The words "and any certificate of renewal in force" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
979. Ins. By G.S.R 245(E) dated 5th April, 1999 (w.e.f. 5-4-1999).
980. Ins. by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
981. Subs. by G.S.R. 103(E), dated 2nd February, 2017, for "one year" (w.e.f. 2-2-2017).
982. FORM 31 omitted By G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Form 31 was added by Notification No. F. 1-36/64-D (G.S.R. 1183 (E)), dated 17th August 1964 (w.e.f. 22-8-1964) and amended by G.S.R. 788(E) dated 10th October, 1985 (w.e.f. 10-10-1985), by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
983. FORM 31A omitted By G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Form 31A was added by G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973) and amended by G.S.R. 788(E) dated 10th October, 1985 (w.e.f. 10-10-1985), by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
984. FORM 32 omitted By G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Form 32 was added by Notification No. F. 1-36/64-D dated 17th August 1964 (w.e.f. 22-8-1964) and amended by S.O. 903(E) dated 10th February, 1976 (w.e.f. 28-2-1976), by G.S.R. 788(E) dated 10th October, 1985 (w.e.f. 10-10-1985) and by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
985. FORM 32A omitted By G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Form 32A was added by Notification No. F. 1-36/64-D dated 17th August 1964 (w.e.f. 22-8-1964) and amended by S.O. 903(E) dated 10th February, 1976 (w.e.f. 28-2-1976), by G.S.R. 788(E) dated 10th October, 1985 (w.e.f. 10-10-1985) and by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).
986. FORM 33 omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 33 was added by Notification No. F. 1-36/64-D (G.S.R. 1183(E)) dated 17th August 1964 (w.e.f. 22-8-1964).
987. FORM 33A omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 33A was added by G.S.R. 444(E) dated 31st March, 1973 (w.e.f. 28-4-1973).
988. FORM 34 omitted By G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Form

34 was added by Notification No. F. 1-36/64-D (S.O. 1183(E)) dated 17th August 1964 (w.e.f. 22-8-1964) and amended by G.S.R. 59(E) dated 7th February, 1995 (w.e.f. 7-2-1995), by G.S.R. 510(E) dated 26th July, 1982 (w.e.f. 26-7-1982) and corrected by corrigendum G.S.R. 61(E), dated 11th February, 1982.

989. Added by Notification No. F. 1-14/68-D (G.S.R. 3869) dated 26th October, 1968 (w.e.f. 2-11-1968)

990. Subs. by G.S.R. 592(E), dated 13th August, 2008, (w.e.f. 13-8-2008).

991. Ins. by G.S.R. 1172(E), dated 23rd August, 1977 (w.e.f. 10-9-1977)

The words "**OR RENEWAL**" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

992. The word "COSMETICS" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020)

993. Ins. by G.S.R. 223(E), dated 18th March, 2019 (w.e.f. 19-3-2019).

994. The words "or renewal" omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017).

995. The words "items of cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f 15-12-2020).

996. The word "Cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).

997. Ins. by G.S.R. 1172(E), dated 23rd August, 1977.

998. Ins. by G.S.R. 223(E), dated 18th March, 2019 (w.e.f. 19-3-2019).

999. Subs. by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).

1000. The words "items of cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f 15-12-2020).

1001. Subs. by G.S.R. 1337(E), dated 27th October, 2017, for paragraph 3 (w.e.f. 27-10-2017).

1002. The words "and any certificate of renewal in Form 38" omitted by G.S.R. 499(E), dated 17th July, 2019 (w.e.f. 17-7-2019).

1003. The words "or items of cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-1-2020).

1004. Subs. by G.S.R. 681(E), dated 5th December, 1980 (w.e.f. 5-12-1980)

1005. FORM 38 omitted by G.S.R. 1337(E), dated 27th October, 2017 (w.e.f. 27-10-2017). Earlier FORM 38 was inserted by G.S.R. 1172, dated 23rd August, 1977 and amended by G.S.R. 231(E), dated 4th June, 1996 (w.e.f. 4-6-1996).

1006. Ins. by G.S.R. 1172(E), dated 23rd August, 1977.

1007. The word "cosmetic" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).

1008. Subs. by G.S.R. 681(E), dated 6th June 1988 (w.e.f. 6-6-1988).

1009. Ins. by G.S.R. 223(E), dated 18th March, 2019 (w.e.f. 19-3-2019).

1010. Ins. by G.S.R. 604(E), dated 24th August, 2001 (w.e.f. 1-2-2003).

1011. Figures "(1), (2) and (3)" omitted by G.S.R. 35(E), dated 20th January, 2005 (w.e.f. 20-1-2005).

1012. Ins. by G.S.R. 604(E), dated 24th August, 2001 (w.e.f. 1-2-2003).

1013. Figures "(1), (2) and (3)" omitted by G.S.R. 35(E), dated 20th January, 2005 (w.e.f. 20-1-2005).

1014. FORM 42 omitted By G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Form 42 was added by G.S.R. 426(E) dated 19th May, 2010, read with corrigendum G.S.R. 263(E), dated 30th March, 2011, corrigendum G.S.R. 733(E), dated 29th September, 2011, corrigendum G.S.R. 270(E), dated 30th March, 2012 and corrigendum G.S.R. 733(E), dated 29th March, 2012 (w.e.f. 1-4-2013).

1015. FORM 43 omitted By G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Form 43 was added by G.S.R. 426(E) dated 19th May, 2010, read with corrigendum G.S.R. 263(E), dated 30th March, 2011, corrigendum G.S.R. 733(E), dated 29th September, 2011, corrigendum G.S.R. 270(E), dated 30th March, 2012 and corrigendum G.S.R. 733(E), dated 29th March, 2012 (w.e.f. 1-4-2013).

1016. Subs. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).

1017. Item (8) and their entries relating thereto omitted by G.S.R. 329(E) dated 3rd April, 2017 (w.e.f. 3-4-2017)

1018. Subs. by G.S.R. 826(E), dated 30th October, 2015 (w.e.f. 30-10-2015).

1019. Subs. by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).

1020. Subs. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).

1021. Subs. By G.S.R. 317(E) dated 18th April, 2019, for paragraph (2) (w.e.f. 22-4-2019).

1022. Subs. By G.S.R. 317(E) dated 18th April, 2019, for "conspicuous red and vertical line on the left side running throughout the body of the label which shall not be less than 1mm in width and" (w.e.f. 22-4-2019).

1023. Ins. by G.S.R. 101(E) dated 18th February, 2011 (w.e.f. 18-2-2011).

1024. Ins. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).

1025. Ins. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).

1026.

1027. Subs. By G.S.R. 317(E) dated 18th April, 2019, for paragraph (2) (w.e.f. 22-4-2019).
1028. Subs. By G.S.R. 317(E) dated 18th April, 2019, for "conspicuous red and vertical line on the left side running throughout the body of the label which shall not be less than 1mm in width and" (w.e.f. 22-4-2019).
1029. Ins. by G.S.R. 101(E) dated 18th February, 2011 (w.e.f. 18-2-2011).
1030. Ins. by G.S.R. 900(E), dated 12th December, 2001 (w.e.f. 12-12-2001).
1031. Ins. By G.S.R. 73(E) dated 31st January, 2003 (w.e.f. 31-1-2003).
1032. Ins. By G.S.R. 73(E) dated 31st January, 2003 (w.e.f. 31-1-2003).
1033. Ins. By G.S.R. 73(E) dated 31st January, 2003 (w.e.f. 31-1-2003).
1034. Ins. By G.S.R. 73(E) dated 31st January, 2003 (w.e.f. 31-1-2003).
1035. Ins. by G.S.R. 828(E) dated 6th November, 2019 (w.e.f. 6-11-2019)
1036. Subs. By G.S.R. 478(E) dated 7th August, 1998 (w.e.f. 7-8-1998).
1037. The words "III. Cosmetics Rupees 400-1500 (The exact amount of the fee shall be determined by the Director of Laboratory or the Government analyst, as the case may be .)" omitted by G.S.R. 763(E), Dated 15th December, 2020 (w.e.f. 15-12-2020).
1038. Item "V" relating to "Homeopathic Medicines" and the entries relating thereto omitted by G.S.R. 202(E), dated 22nd March, 2021 (w.e.f. 23-3-2021).
1039. Clause (2) omitted by G.S.R. 202(E), dated 22nd March, 2021 (w.e.f. 23-3-2021).
1040. Subs. by G.S.R. 202(E), dated 22nd March, 2021, for Schedule B(1) (w.e.f. 23-3-2021).
1041. Subs. by Notification No. F. 1-30/47-A, dated 5th January, 1950.
1042. Subs. by Notification No. F.1-8/60-D, dated 31st August, 1960.
1043. Subs. by G.S.R. 487(E) dated 2nd July, 1984 (w.e.f. 2-7-1984).
1044. Subs. by Notification No. F. 1-14/68-D (S.O. 3869), dated 26th October, 1968 (w.e.f. 2-11-1988)
1045. Subs. by Notification No. F.1-8/60-D, dated 31st August, 1960.
1046. Ins. By G.S.R. 1242(E) dated 17th September, 1976 (w.e.f. 6-10-1979).
1047. Ins. by G.S.R. 109(E), dated 22nd February, 1994 (w.e.f. 22-2-1994).
1048. Amended by Notification No. F. 1-22/59-D, dated 9th April, 1960.
1049. Subs, by G.S.R. 487(E), dated 2nd July, 1984 (w.e.f. 2-7-1984).
1050. Ins. By G.S.R. 600(E) dated 27th August, 2002 (w.e.f. 1-9-2002).
1051. Subs, by G.S.R. 360(E), dated 10th April, 2018 for entry under item 1 "Substances not intended for medical use" (w.e.f. 10-4-2018).
1052. Ins. by G.S.R. 724(E), dated 7th November, 2013 (w.e.f. 7-11-2013).
1053. Serial Nos. 2 and 3 omitted by Notification No. F. 1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 19-7-1969).
1054. Serial No. 4 Omitted by G.S.R. 604(E), dated 24th August, 2001 (w.e.f. 1-1-2003).
1055. Amended by Notification No. F. 1-53/55-D, dated 7th January, 1957.
1056. Amended by G.S.R. 19, dated 15th December, 1977 (w.e.f. 7-1-1978).
1057. Ins. by G.S.R. 528(E), dated 8th July, 2003 (w.e.f. 8-7-2003).
1058. The words "cosmetics" omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020).
1059. Ins. by G.S.R. 690(E), dated 25th September, 2014 (w.e.f. 25-9-2014).
1060. Ins. by G.S.R. 604(E), dated 24th August, 2001 (w.e.f. 1-1-2003).
1061. Subs. by G.S.R. 897(E), dated 21st September, 2016, for sub-item 2.3 (w.e.f. 21-9-2016).
1062. Ins. by G.S.R. 35(E), dated 20th January, 2005 (w.e.f. 20-1-2005)
1063. Subs. by G.S.R. 897(E), dated 21st September, 2016, for sub-item 2.3 (w.e.f. 21-9-2016).
1064. Ins. by G.S.R. 35(E), dated 20th January, 2005 (w.e.f. 20-1-2005)
1065. Schedule D (III) omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier it was inserted by G.S.R. 426(E), dated 19th May, 2010, read with corrigendum G.S.R. 263(E), dated 30th March, 2011, corrigendum G.S.R. 733(E), dated 29th September, 2011, corrigendum G.S.R. 270(E), dated 30th March, 2012 and corrigendum G.S.R. 733(E), dated 29th September, 2012 (w.e.f. 1-4-2013).
1066. Schedule E omitted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
1067. Subs. by G.S.R. 683(E), dated 19th August, 2010, for *SCHEDULE E(1)* (w.e.f. 19-*8-2010).*
1068. Part I to Part XIIA omitted by G.S.R. 663(E), dated 3rd July, 1992 (w.e.f. 3-7-1992) corrected vide corrigendum G.S.R. 27(E), dated 22nd January, 1993.
1069. Part XIIB and Part XIIC subs, by G.S.R. 245(E), dated 5th April, 1999 (w.e.f. 5-4-1999), previously Part XIIB and Part XIIC, were substituted for Part XIIB by G.S.R. 28(E), dated 22nd January, 1992 (w.e.f.22-1-1992) and before that Part XIIB was added by Notification No. F 1-17/67-D, 24th June, 1967.
1070. Note: 2nd Amendment Rules, 1999 (w.e.f. 5-4-1999).
1071. Ins. by G.S.R. 101(E) dated 18th February, 2011 (w.e.f. 18-2-2011).

1072. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1073. Subs. by G.S.R. 733(E), dated 21st December, 2005, for "ELISA or RPHA test kits for Hepatitis and HIV I & II." (w.e.f. 21-12-2005).
1074. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1075. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1076. Ins. by G.S.R. 328(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).
1077. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1078. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1079. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1080. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1081. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1082. Subs. by G.S.R. 40(E), dated 29th January, 2001 (w.e.f. 1-6-2001).
1083. Part XIID inserted by G.S.R. 899(E), dated 27th December, 2011 (w.e.f. 27-12-2011).
1084. Renumbered by Notification No. F. 18-1/46, dated 18th June, 1948.
1085. Subs. by G.S.R. 19, dated 15th December, 1977 (w.e.f. 7-1-1978).
1086. Added by Notification No. F. 1-6/62-D (S.O. 2889), dated 2nd July, 1969 (w.e.f. 19-7-1969).
1087. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1088. Subs. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1089. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1090. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1091. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1092. Subs. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1093. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1094. Subs. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1095. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1096. Certain words omitted by G.S.R. 659(E), dated 31st August, 1994 (w.e.f 31-8-1994).
1097. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1098. Subs. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1099. Ins. by G.S.R. 659(E), dated 31st August, 1994 (w.e.f. 31-8-1994).
1100. Subs. by G.S.R. 647(E), dated 28th October, 1998 (w.e.f. 28-10-1998).
1101. Ins. by G.S.R. 318(E), dated 1st May, 1985 (w.e.f. 1-5-1985).
1102. Ins. by G.S.R. 1115(E), dated 30th September, 1986 (w.e.f. 30-9-1986).
1103. Added by Notification No. F. 1-13/60-D (S.O. 23), dated 23rd December, 1969 (w.e.f. 3-1-1970).
1104. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
1105. Ins. By G.S.R. 626(E) dated 2nd July, 1987 (w.e.f. 2-7-1987).
1106. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
1107. Subs. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
1108. Subs. by G.S.R 160(E) dated 16th March, 2006 (w.e.f. 16-3-2006).
1109. Entry No. 15 (relating to Alprazolam) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014)
1110. Entries No. 92 to 98 (relating to Cefdinir, Cefepime Hydrochloride, Cefetamet Pivoxil, Cefpirome, Cefodoxime Proxetil, Ceftazidime Pentahydrate, Cefitzoxime Sodium) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014).
1111. Entries No. 105 and 147 (relating to Chlordiazepoxide and Diazepam) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014).
1112. Entries No. 107 (relating to Chlorpheniramine Maleate) and 145 (relating to Dextromethorphan Hydrobromide) omitted by G.S.R. 602(E) dated 19th July, 2010 (w.e.f. 19-7-2010).
1113. Entries No. 123 and 132 (relating to Clofazimine and Codeine) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014).
1114. Entry No. 156 (relating to Diphenoxylate, its Salts) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014)
1115. Entries No. 184, 187 and 287 (relating to Ethambutol Hydrochloride, Ethionamide and Levofloxacin) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014).
1116. Serial No. 269 (Ketamine Hrydrochloride) omitted by G.S.R. 724(E) dated 7th November, 2013 (w.e.f. 7-11-2013).
1117. Entries No. 311, 324, 339, 360, 392 and 418 (relating to Meropenam, Midazolam, Moxifloxacin, Nitrazepam, Pentazocine and Pyrazinamide) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014)
1118. Entry No. 382 (relating to Oxytocin) omitted by G.S.R. 795(E) dated 21st August, 2018 (w.e.f. 1-9-2018).

Entries No. 466, 493, 507 and 534 (relating to Sparfloxacin, Thiacetazone, Tramadol Hydrochloride and Zolpidem) omitted by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014).

1119. Ins. By G.S.R. 303(E) dated 30th March, 2017 (w.e.f. 30-3-2017).

1120. Ins. By G.S.R. 277(E) dated 23rd March, 2018 (w.e.f.23-3-2018).

1121. Ins. By G.S.R. 408(E) dated 26th April, 2018 (w.e.f.1-11-2018).

1122. Subs. by G.S.R. 186(E) dated 6th March, 2019, for "steroids" (w.e.f.1-4-2019).

1123. Ins. By G.S.R. 153(E) dated 26th February, 2019 (w.e.f. 26-2-2019).

1124. Ins. by G.S.R. 588(E) dated 30th August, 2013 (w.e.f. 27-2-2014)

1125. Ins. by G.S.R. 795(E) dated 21st August, 2018 (w.e.f. 1-9-2018).

1126. Ins. By G.S.R. 258(E) dated 7th April, 2021 (w.e.f. 1-11-2021).

1127. Schedule I omitted by G.S.R. 462(E) dated 22nd June, 1982 (w.e.f. 22-6-1982).

1128. Subs. by G.S.R. 21(E) dated 11th January, 1996 (w.e.f. 11-1-1996).

1129. Item 2 omitted by Notification No. F. 1-56/47-D dated 16th January, 1950.

1130. Added by Notification No. F.1-2/47-D dated 13th February, 1950.

1131. Subs. by Notification No. F.1-22/59-D, dated 9th April, 1960.

1132. Items 3 and 4 omitted by Notification No. F. 1-6/62-d (S.O. 2889) dated 2nd July, 1960 (w.e.f. 19-7-1969).

1133. Subs. by G.S.R. 1074(E), dated 19th August, 1978.

1134. Subs. by G.S.R. 462(E) dated 22nd June, 1982 (w.e.f. 22-6-1982).

1135. Certain words omitted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

1136. Ins. By G.S.R. 460(E), dated 20th June, 1984 (w.e.f. 20-6-1984).

1137. Ins. by G.S.R. 592(E), dated 13th August, 2008 (w.e.f. 13-8-2008).

1138. Added by Notification No. F. 1-22/59-D, dated 9th April, 1960.

1139. Certain words omitted by G.S.R. 812(E), dated 14th November, 1994 (w.e.f.14-11-1994).

1140. Ins. by G.S.R. 648(E), dated 16th September, 2002 (w.e.f. 1-10-2002).

1141. Ins. by G.S.R. 592(E), dated 13th August, 2008 (w.e.f. 13-8-2008).

1142. Ins. By G.S.R. 909(E) dated 20th December, 2001 (w.e.f. 20-12-2001).

1143. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "Blood Bank" (w.e.f. 11-3-2020).

1144. Condition (2) omitted by G.S.R. 328(E), dated 3rd April, 2017 (w.e.f. 3-4-2017).

1145. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "Blood Bank" (w.e.f. 11-3-2020).

1146. Item 6 omitted by G.S.R. 681(E), dated 5th December, 1980 (w.e.f. 5-12-1980).

1147. Item 8 omitted by G.S.R. 1185(E) dated 18th August, 1964 (w.e.f. 22-8-1964)

1148. Added by Notification No. F. 1-19/50-D.S., dated 30th March, 1953.

1149. Added by Notification No. DR/Sch. Ddk/F. 1-40/54-D.S., dated 27th January, 1955.

1150. Omitted by G.S.R. 665(E), dated 6th May, 1977 (w.e.f. 28-5-1977).

1151. Subs, by G.S.R. 19(E), dated 15th December, 1977 (w.e.f. 7-1-1978).

1152. Item 11 omitted by Notification No. F. 1-36/64-D (G.S.R. 1188(E)), dated 17th August, 1964 (w.e.f. 22-8-1964).

1153. Amended by Notification No. F. 1-20/60-D (S.O. 400(E)), dated 24th January, 1964 (w.e.f. 2-1-1964).

1154. Added by G.S.R. 926(E), dated 24th June, 1977 (w.e.f. 16-7-1977).

1155. Added by Notification No, F.1-19/59-D, dated 13th June, 1961.

1156. Subs. by S.O. 2139(E), dated 5th June, 1972 (w.e.f. 12-8-1972).

1157. Subs, by G.S.R. 1060(E), 5th September, 1986, (w.e.f. 5-9-1986).

1158. Subs, by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

1159. Added by Notification No. 1-39/61-D (S.O. 1057), dated 23rd March, 1964 (w.e.f. 28-3-1964).

1160. Added by G.S.R. 926(E), dated 24th June, 1977 (w.e.f. 16-7-1977).

1161. Ins. G.S.R. 784(E), dated 28th August, 1989 (w.e.f. 28-8-1989).

1162. Subs, by G.S.R. 730(E), dated 10th December, 1991 (w.e.f. 10-12-1991) corrected *vide* corrigendum G.S.R. 63(E), dated 20th January, 1992.

1163. Ins. by G.S.R. 648(E), dated 16th September, 2002 (w.e.f. 1-10-2002).

1164. The words "16. Cosmetics—The provisions of Chapter IV of the Act and the rules made thereunder, which require them to be covered by a licence for sale provided that the cosmetics sold, if of Indian origin, are manufactured by licensed manufacturers." omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier it was added by Notification No. F. 1-36/64-D (G.S.R. 1183(E)), dated 17th August, 1964 (w.e.f. 22-8-1964).

1165. Added by Notification No. 1-21/63-D (G.S.R. 70(E)), dated 4th January, 1965 (w.e.f. 9-1-1965).

1166. Item 18 omitted by G.S.R. 1594(E), dated 28th October, 1976 (w.e.f. 13-11-1976).

1167. Added by S.O. 2139(E), dated 5th June, 1972 (w.e.f. 12-8-1972).

1168. Added by G.S.R. 926, dated 24th June, 1977 (w.e.f. 16-7-1977).

1169. Added by G.S.R. 697(E), dated 11th November, 1977 (w.e.f. 11-11-1977).

1170.

1171. Ins. by G.S.R. 1241, dated 15th September, 1979 (w.e.f. 6-10-1979).
1172. Ins. by G.S.R. 540(E), dated 22nd September, 1980 (w.e.f. 22-9-1980).
1173. Subs. by G.S.R. 140(E), dated 26-2-2021 for "and (iv) Anganwadi Workers" (w.e.f. 26-2-2021).
1174. Ins. by G.S.R. 680(E), dated 5th December, 1980 (w.e.f. 5-12-1980).
1175. Subs, by G.S.R. 1060(E), 5th September, 1989, (w.e.f. 5-9-1989).
1176. Ins. by G.S.R. 371(E) dated 24th March, 1988 (w.e.f. 24-3-1988).
1177. Ins. By G.S.R. 677(E) dated 2nd June, 1988 (w.e.f. 2-6-1988).
Subs. by G.S.R. 408(E), dated 27th April, 2018, for entries under column (1) of Serial No. 27 (w.e.f. 1-11-2018). Entries under column (1), before substitution, stood as under:
"Oral Rehydration Salts (Manufactured as per the following formula):—
- Sodium Chloride 3.5 g/litre:
- Trisodium citrate dihydrate 2.9 g/litre.
- Potassium Chloride 1.5 g/litre.

May be replaced by Sodium bicarbonate (Sodium hydrogen Carbonate) 2.5 g/litre, when citrate salt is
1178. not available.".
1179. Ins. by G.S.R. 753(E), dated 4th November, 1999 (w.e.f. 4-11-1999).
1180. Ins. by G.S.R. 6(E), dated 4th January, 2001 (w.e.f. 4-1-2001).
1181. Subs. by G.S.R. 166(E), dated 11th March, 2020, for "Blood Bank" (w.e.f. 11-3-2020).
1182. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for Serial No. 31 (w.e.f. 10-11-2017).
1183. Ins. by G.S.R. 648(E) dated 16th September, 2002 (w.e.f. 1-10-2002).
1184. Ins. by G.S.R. 549(E) dated 16th July, 2003 (w.e.f. 16-7-2003).
1185. Ins. By G.S.R. 101(E) dated 18th February, 2011 (w.e.f. 18-2-2011).
Subs, by G.S.R. 385(E), dated 19th April, 2018, for Serial No. 34 (w.e.f. 19-4-2018). Earlier it was
1186. inserted by G.S.R. 734(E), dated 21st December, 2005 (w.e.f. 21-12-2005).
Subs. by G.S.R. 76(E), dated 31st January, 2017, for Serial No. 35 and 35 and entries relating thereto (w.e.f. 31-1-2017). Earlier Serial No. 35 and 35 were inserted by G.S.R. 917(E), dated 22nd December, 2009 (w.e.f. 22-12-2009) and G.S.R. 690(E), dated 25th September, 2014 (w.e.f. 25-9-2014)
1187. respectively and amended by G.S.R. 107(E), dated 17th February, 2015 (w.e.f. 17-2-2015).
1188. Ins. by G.S.R 47(E), dated 25th January, 2019 (w.e.f. 25-1-2019).
1189. Schedule L omitted by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).
1190. Ins. by G.S.R 780(E), dated 10th November, 2008 (w.e.f. 1-11-2010).
1191. Subs. by G.S.R 922(E) dated 28.12.2023(w.e.f. 28.12.2023).
Subs. by G.S.R. 431(E), dated 30th June, 2005, for "and no other manufacturing activity shall be
1192. undertaken therein" (w.e.f. 30-6-2005).
1193. Subs. by G.S.R. 431(E), dated 30th June, 2005, for "creation of recesses" (w.e.f. 30-6-2005).
1194. Subs, by G.S.R. 431(E), dated 30th June, 2005, for "clean towels, hand dryers" (w.e.f. 30-6-2005).
Subs. by G.S.R. 431(E), dated 30th June, 2005, for "The effective segregation of these areas shall be
1195. demonstrated with adequate records of maintenance and services" (w.e.f. 30-6-2005).
Subs, by G.S.R. 431(E), dated 30th June, 2005, for "There shall be segregated enclosed areas, secured for recalled or rejected material and for such material which are to be processed or recovered" (w.e.f.
1196. 30-6-2005).
Subs. by G.S.R. 431(E), dated 30th June, 2005, for "such that finished batch of a drug can be traced to
1197. the retail level" (w.e.f. 30-6-2005).
Subs. by G.S.R. 431(E), dated 30th June, 2005, for "Grade C background and if necessary, under
1198. Laminar Air Flow work station" (w.e.f. 30-6-2005).
Subs. by G.S.R. 431(E), dated 30th June, 2005, for "shall not exceed 27 degree centigrade and relative
1199. humidity 55% respectively" (w.e.f. 30-6-2005).
1200. Subs. by G.S.R. 431(E), dated 30th June, 2005, for "TABLE I" (w.e.f. 30-6-2005).
Subs. by G.S.R. 431(E), dated 30th June, 2005, for "Grade A corresponds with Class 100 or M 3.5 or
1201. ISO class 5; Grade B with class 1000 or M 4.5 or ISO Class 6" (w.e.f. 30-6-2005).
1202. Subs. by G.S.R. 431(E), dated 30th June, 2005, for "usually at risk" (w.e.f. 30-6-2005).
Subs, by G.S.R. 431(E), dated 30th June, 2005, for "Where alcohol or Isopropyl alcohol is used for dilution of disinfectants for use as hand sprays, the preparation of the same shall be done in the bulk preparation area and the diluted solution membrane-filtered into suitable sterile containers held in
1203. aseptic area" (w.e.f. 30-6-2005).
Sub-paragraph "8.9 Steam coming in contact with the product, primary containers and other product contact surfaces hall be sterile and pyrogen free. The steam condensate shall meet microbiological specification of not more than 10 cfu per 100 ml. The condensate shall also meet IP specification for Water for Injection and shall have an endotoxin level of not more than 0.25 EU/ml. There shall be a
1204. suitable schedule for the monitoring of steam quality." omitted by G.S.R. 431(E), dated 30th June,

2005 (w.e.f. 30-6-2005).

1205. Subs. by G.S.R. 431(E), dated 30th June, 2005, for "Where the facilities are designed to provide special environmental conditions of pressure differentials between rooms, these conditions shall be regularly monitored and any specification results brought to the immediate attention of the Production and Quality Assurance departments which shall be immediately attended to" (w.e.f. 30-6-2005).

1206. Subs. by G.S.R. 431(E), dated 30th June, 2005, (w.e.f. 30-6-2005).

1207. Ins. by G.S.R. 431(E), dated 30th June, 2005, (w.e.f. 30-6-2005).

1208. Subs, by G.S.R. 431(E), dated 30th June, 2005, for "Manufacturing personnel shall wear non-fiber shedding clothing to prevent contamination of the products" (w.e.f. 30-6-2005).

1209. The words "Area shall be ventilated." omitted by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1210. Subs, by G.S.R. 431(E), dated 30th June, 2005, for "No rags or dusters" (w.e.f. 30-6-2005).

1211. Subs, by G.S.R. 431(E), dated 30th June, 2005, for "Mixing and storage tanks (Stainless steel)" (w.e.f. 30-6-2005).

1212. Subs, by G.S.R. 431(E), dated 30th June, 2005, for "Jacketted Kettle" (w.e.f. 30-6-2005).

1213. The words "(Electrically operated)" omitted by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005)

1214. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1215. Subs, by G.S.R. 431(E), dated 30th June, 2005, for "Mixing and storage tanks (Stainless steel)" (w.e.f. 30-6-2005).

1216. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1217. Subs. by G.S.R. 431(E), dated 30th June, 2005, for "tablet machine" (w.e.f. 30-6-2005).

1218. Subs. by G.S.R. 431(E), dated 30th June, 2005, for "Granulator" (w.e.f. 30-6-2005).

1219. Subs. by G.S.R. 431(E), dated 30th June, 2005, for "Dissolution test apparatus" (w.e.f. 30-6-2005).

1220. Ins. by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1221. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1222. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1223. The words "/ dispersible" omitted by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005)

1224. The words "(electrically operated)" omitted by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005)

1225. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1226. The words "(preferably semi automatic or automatic filling machines)" omitted by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1227. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1228. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1229. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1230. Added by G.S.R. 431(E), dated 30th June, 2005 (w.e.f. 30-6-2005).

1231. Subs. by G.S.R. 678(E) dated 31st October, 2006, for Schedule MI (w.e.f. 31-10-2006). Earlier Schedule MI was inserted by G.S.R. 507(E) dated 12th June, 1987 (w.e.f.12-6-1987)

1232. The words "or outside" omitted by G.S.R. 1380(E), dated 10th November, 2017 (w.e.f. 10-11-2017).

1233. Subs by G.S.R. 1380(E), dated 10th November, 2017, for "origins" (w.e.f. 10-11-2017).

1234. Subs by G.S.R. 1380(E), dated 10th November, 2017, for "stainless steel of grade 304" (w.e.f. 10-11-2017).

1235. Subs by G.S.R. 1380(E), dated 10th November, 2017, for "shall be separate and shall be 55 square meters for each for basic installations" (w.e.f. 10-11-2017).

1236. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for "neutral glass" (w.e.f. 10-11-2017).

1237. Ins. by G.S.R. 1380(E), dated 10th November, 2017 (w.e.f. 10-11-2017).

1238. Ins. by G.S.R. 1380(E), dated 10th November, 2017 (w.e.f. 10-11-2017).

1239. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for item "(ii) Dissecting microscope" (w.e.f. 10-11-2017).

1240. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for item "(iv) the materials shall be free of inorganic or organic foreign matter;" (w.e.f. 10-11-2017).

1241. The words "and should not be more than six months old" omitted by G.S.R. 1380(E), dated 10th November, 2017 (w.e.f. 10-11-2017).

1242. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for item "(i) a small twig of the plant with leaves shall be available if the part used is bark of the plant;" (w.e.f. 10-11-2017).

1243. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for item "(vi) the materials shall be in open mesh bags or in suitable material which permits the passage of air inside;" (w.e.f. 10-11-2017).

1244. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for item "(vii) each consignment of the material shall be accompanied by a statement of the supplier's name; name of the plant with description of the

part supplied; the pharmacopeial reference, place of collection/ harvest, date and time of collection and packaging and weight." (w.e.f. 10-11-2017).

1245. Sub-paragraph 6.4 omitted by G.S.R. 1380(E) dated 10th November, 2017 (w.e.f. 10-11-2017).

1246. Subs. by G.S.R. 1380(E), dated 10th November, 2017, for "date of manufacture" (w.e.f. 10-11-2017).

1247. Schedule M-II omitted by G.S.R. 763(E) dated 15th December, 2020 (w.e.f.15-12-2020). Earlier it was inserted by G.S.R. 723(E) dated 11th August, 1992 (w.e.f. 11-8-1992).

1248. Subs. By. G.S.R. 640(E) dated 29th June, 2016, (w.e.f. 29-62016). Earlier Schedule M-III was inserted by G.S.R. 109(E) dated 22nd February, 1994 (w.e.f.22-2-1994).

1249. Subs. by S.O. 2139, dated 5th June, 1972 (w.e.f. 12-8-1972).

1250. Subs. by G.S.R. 1243, dated 19th September, 1979, for Schedule O (w.e.f. 6-10-1979). Earlier Schedule O was added by Notification No. F. 1-20/60-D, dated 24th January, 1964.

1251. Subs. by G.S.R. 735(E), dated 21st December, 2005, for Part I (w.e.f. 21-12-2005).

1252. Subs. By G.S.R. 17(E) dated 7th January 1986, for Schedule P (w.e.f.7-1-1986) corrected vide corrigendum G.S.R. 1059(E) dated 5th September, 1986. Earlier Schedule P was added by Notification no. 1-7/62-D, dated 11th May, 1964.

1253. Subs. By G.S.R. 250(E) dated 4th April, 2002 (w.e.f. 4-4-2002).

1254. Subs. by G.S.R. 626(E), dated 14th October, 1991 (w.e.f. 14-10-1991).

1255. Ins. By G.S.R. 215(E) dated 19th March, 1999 (w.e.f. 19-3-1999).

1256. Subs. by G.S.R. 626(E), dated 14th October, 1991 (w.e.f. 14-10-1991).

1257. Subs. by G.S.R. 26(E), dated 19th January, 2006 (w.e.f. 19-1-2006).

1258. Subs. by G.S.R. 174(E), dated 16th March, 2005, for serial No. "2. BCG Vaccine 14 in cold place" (w.e.f. 16-3-2005).

1259. Ins. By G.S.R. 215(E) dated 19th March, 1999 (w.e.f. 19-3-1999).

1260. Subs. by G.S.R. 174(E), dated 16th March, 2005, for serial No. "1. Adrenaline for Injection 12 In cold place" (w.e.f. 16-3-2005).

1261. Ins. by G.S.R. 796(E), dated 1st October, 1992 (w.e.f. 1-10-1993).

1262. Ins. by G.S.R. 753(E), dated 4th November, 1999 (w.e.f. 4-11-1999).

1263. Schedule Q omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Schedule Q was added by Notification No. F. 1-36/64-D (G.S.R. 1183(E)), dated 17th August, 1964 (w.e.f. 22-8-1964) and amended by G.S.R. 11(E), dated 7th January, 1991 (w.e.f. 7-11-1991) , by G.S.R. 811(E), dated 14th November, 1994 (w.e.f. 14-11-1994) and by G.S.R. 203(E), dated 18th March, 2015 (w.e.f. 18-3-2015).

1264. Added by Notification no. 1-28/65-D, dated 8th March, 1966 and subs. by G.S.R. 495(E) dated 9th June, 1995 (w.e.f. 9-6-1995).

1265. Subs. by G.S.R. 353(E) dated 26th April, 2000 (w.e.f. 26-4-2000).

1266. Subs. by G.S.R. 353(E) dated 26th April, 2000 (w.e.f. 26-4-2000).

1267. Subs. by G.S.R. 690(E), dated 25th September, 2014 (w.e.f. 25-9-2014). Earlier SCHEDULE R1 was inserted by G.S.R. 109(E) dated 22nd February, 1994 (w.e.f. 22-2-1994).

1268. Schedule S omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier Schedule S was inserted by G.S.R. 510(E) dated 26th July, 1982 (w.e.f. 26-7-1982) and omitted by G.S.R. 1098(E) dated 9th July, 1976 (w.e.f. 24-7-1976) and amended by G.S.R. 731(E) dated 23rd August , 1990 (w.e.f. 23-8-1990), by G.S.R. 673(E) dated 27th October, 1993 (w.e.f.27-10-1993), by G.S.R. 553(E) dated 20th July, 1995 (w.e.f. 20-7-1995), by G.S.R. 592(E) dated 13th August, 2008 (w.e.f. 13-8-2008), by G.S.R. 724(E) dated 7th November, 2013 (w.e.f. 7-11-2013) and by G.S.R. 203(E) dated 18th March, 2015 (w.e.f. 18-3-2015).

1269. Subs. by G.S.R. 560(E) dated 7th March, 2003 (w.e.f. 7-3-2003). Earlier Schedule T was added by Notification No. 1-23/67-D, dated 2nd February, 1970.

1270. Subs. by G.S.R. 463(E) dated 8th July, 2005 and corrected vide corrigendum G.S.R. 705(E) dated 29-11-2005.

1271. Ins. By G.S.R. 157(E) dated 4th March, 2009 read with corrigendum G.S.R. 338(E) dated 15th April, 2010 (w.e.f. 9-3-2009)

1272. Subs. by corrigendum G.S.R. 338(E) dated 15th April, 2010, for "may be".

1273. Subs. by corrigendum G.S.R. 338(E) dated 15th April, 2010, for "or e-mail or".

1274. Subs. by corrigendum G.S.R. 338(E) dated 15th April, 2010, for "may be".

1275. Subs. by G.S.R. 463(E) dated 8th July, 2005 and corrected vide corrigendum G.S.R. 705(E) dated 29-11-2005.

1276. Ins. By G.S.R. 512(E) dated 9th July, 2008 (w.e.f. 9-7-2008).

1277. Subs. by G.S.R. 735(E) dated 24th June, 1988, for Schedule O (w.e.f. 26-6-1988). Earlier Schedule O was added by Notification No. X. 20.64-D, dated 26th October, 1968.

1278. Schedule U (1) omitted by G.S.R. 763(E), dated 15th December, 2020 (w.e.f. 15-12-2020). Earlier

Schedule U (1) was added by G.S.R. 1594, dated 28th October, 1976, (w.e.f. 13-11-1976).

1279. Added by G.S.R. 665, dated 6th May, 1977 (w.e.f. 28-5-1977).

Omitted by G.S.R. 56 (E), dated 22nd January, 1992 (w.e.f. 22-1-1992). Earlier Paragraphs 1 and 3

1280. were inserted by G.S.R. 331(E), dated 8th May, 1984 (w.e.f. 8-5-1984).

1281. Added by G.S.R. 930, dated 13th July, 1978 (w.e.f. 2-7-1978).

1282. Ins. by G.S.R. 792 (E), dated 17th September, 1987 (w.e.f. 17-9-1987).

1283. Subs, by G.S.R. 917(E), dated 22nd December, 2009, for "mg" (w.e.f. 22-12-2009).

1284. Certain words omitted by G.S.R. 59(E) dated 22nd January, 1992 (w.e.f. 22-1-1992)

Schedule W omitted by G.S.R. 94(E) dated 8th May, 2000 (w.e.f. 8-5-2000). Earlier Schedule W was

1285. inserted by G.S.R. 27(E) dated 17th January, 1981 (w.e.f 1-8-1981).

1286. Ins. by G.S.R. 462(E), dated 22nd June, 1982 (w.e.f. 22-6-1982).

1287. Ins. by G.S.R. 724(E), dated 7th November, 2013 (w.e.f. 7-11-2013).

1288. Certain words omitted by G.S.R. 647(E), dated 28th October, 1998 (w.e.f. 28-10-1998).

1289. Certain words omitted by G.S.R. 673(E), dated 27th October, 1993 (w.e.f. 27-10-1993).

1290. Subs. by G.S.R. 32(E), dated 20th January, 2005, for Schedule Y (w.e.f. 20-01-2005).

Subs, by G.S.R. 889(E), dated 12th December, 2014, for clause (iv) (w.e.f. 12-6-2015). Earlier clause (iv) was inserted by G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013). Clause (iv), before substitution, stood as under:

"(iv) In case of serious adverse event of death occurring to the clinical trial subject, the Ethics Committee shall forward it's report on the serious adverse event of death/after due analysis, along with its opinion on the financial compensation, ii any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial, to the Chairman of the Expert Committee constituted by the Licensing Authority under Appendix XII with a copy of the report to the Licensing Authority within twenty one calendar days of the occurrence of the serious adverse event of death. In case of serious adverse event, other than death occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event after due analysis along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, to the Licensing Authority within twenty one

1291. calendar days or the occurrence of the serious adverse event."

1292. Ins. by G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

1293. Ins. by G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

Sub-para (3) renumbered as sub-para, (3)(i) thereof by G.S.R. 53(E) dated 30th January, 2013 (w.e.f.

1294. 30-1-2013)

1295. Certain words substituted by G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

Subs, by G.S.R. 889(E), dated 12th December, 2014, for "The report of the serious adverse event of death, after due analysis shall be forwarded by the Investigator to Chairman of the Ethics Committee and Chairman of the Expert Committee constituted by the Licensing Authority under Appendix XII with a copy of the report to the Licensing Authority and the head of the Institution where the trial nas been conducted within ten calendar days of occurrence of the serious adverse event of death. The report of the serious adverse event 'other than death, after due analysis shall be forwarded to the Licensing Authority, Chairman of the Ethics Committee and the head of the Institution where the trial has been conducted within ten calendar days of occurrence of the serious adverse event." (w.e.f. 12-6-

1296. 2015).

1297. Ins. By G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

1298. Ins. by G.S.R. 611(E), dated 31st July, 2015 (w.e.f. 31-7-2015).

Subs, by G.S.R. 889(E), dated 12th December, 2014, for clause (iv) (w.e.f. 12-6-2015). Earlier clause (iv) was inserted by G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013). Clause (iv), before substitution, stood as under:

"(iv) In case of serious adverse event of death occurring to the clinical trial subject, the Ethics Committee shall forward it's report on the serious adverse event of death/after due analysis, along with its opinion on the financial compensation, ii any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial, to the Chairman of the Expert Committee constituted by the Licensing Authority under Appendix XII with a copy of the report to the Licensing Authority within twenty one calendar days of the occurrence of the serious adverse event of death. In case of serious adverse event, other than death occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event after due analysis along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the

1299. Licensing Authority for conducting the clinical trial, to the Licensing Authority within twenty one

calendar days or the occurrence of the serious adverse event.

1300. Ins. By G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

1301. The words "and unexpected" omitted by G.S.R. 889(E), dated 12th December, 2014 (w.e.f. 12-6-2015).

1302. Ins. by G.S.R. 889(E), dated 12th December, 2014 (w.e.f. 12-6-2015).

Subs. by G.S.R. 287(E) dated 8th March, 2016, for clause (i) (w.e.f. 8-3-2016). Paragraph (4) and clause (i) relating thereto, before substitution, stood as under:

"(4) *Post Marketing Surveillance*.- (i) Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The applicants shall furnish Periodic Safety Update Reports (PSURs) in order to-

(a) report all the relevant new information from appropriate sources;

(b) relate these data to patient exposure ;

(c) summarize the market authorization status in different countries and any significant variations related to safety; and

(d) indicate whether changes should be made to product information in order to optimize the use of the

1303. product."

1304. Ins. by G.S.R. 313(E), dated 16th March, 2016 (w.e.f. 16-3-2016).

1305. Ins. by G.S.R. 826(E), dated 30th October, 2015 (w.e.f. 30-10-2015).

1306. Ins. by G.S.R. 918(E), dated 30th November, 2015 (w.e.f. 30-11-2015).

Subs. by G.S.R. 1041(E) dated 4th November, 2016, for "Daily topical (dermal) application of test

1307. substance in its clinical dosage form should be done." (w.e.f. 4-11-2016)

1308. Ins. by G.S.R. 1041(E) dated 4th November, 2016 (w.e.f. 4-11-2016)

Subs. by G.S.R. 287(E) dated 8th March, 2016, for entries under sub-heading "Oral or Parenteral or

1309. Transdermal" (w.e.f. 8-3-2016)

Subs. by G.S.R. 287(E) dated 8th March, 2016, for "phase I, II, III in male volunteers/patients" (w.e.f.

1310. 8-3-2016).

1311. Subs. By G.S.R. 53(E), dated 30th January, 2013, or item no. 9 (w.e.f. 30-1-2013).

Subs, by G.S.R. 889(E), dated 12th December, 2014, for clause (a) (w.e.f. 12-6-2015). Clause (a), before substitution, stood as under:

"(a) In the event of an injury occurring to the clinical trial subject, such subject shall be provided free

1312. medical management as long as required.".

1313. Ins. by G.S.R. 611(E), dated 31st July, 2015 (w.e.f. 31-7-2015).

1314. Ins. By G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

1315. Ins. By G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

1316. Subs. by G.S.R. 72(E), dated 8th February, 2013, for paragraph 1 (w.e.f. 8-2-2013).

Subs. by G.S.R. 72(E), dated 8th February, 2013, for "2. Format for Approval of Ethics Committee"

1317. (w.e.f. 8-2-2013).

1318. Ins. By G.S.R. 53(E), dated 30th January, 2013 (w.e.f. 30-1-2013).

Subs, by G.S.R. 889(E), dated 12th December, 2014, for clause (a) (w.e.f. 12-6-2015). Clause (a), before substitution, stood as under:

"(a) In the event of an injury occurring to the clinical trial subject, such subject shall be provided free

1319. medical management as long as required.".

1320. Ins. by G.S.R. 889(E), dated 12th December, 2014 (w.e.f. 12-6-2015)

1321. The words "and unexpected" omitted by G.S.R. 889(E), dated 12th December, 2014 (w.e.f. 12-6-2015).

1322. Ins. by G.S.R. 889(E), dated 12th December, 2014 (w.e.f. 12-6-2015)

1323. The words "Chairman of the Expert Committee with a copy of the report to" omitted by G.S.R. 889(E) dated 12th December, 2014 (w.e.f. 12-6-2015).

1324. Subs, by G.S.R. 889(E), dated 12th December 2014, for "ten calendar days" (w.e.f. 12-6-2015).

1325. The words "to the Chairman of the Expert Committee with a copy of the report" omitted by G.S.R. 889(E) dated 12th December, 2014 (w.e.f. 12-6-2015).

1326. Subs, by G.S.R. 889(E), dated 12th December, 2014, for "twenty one calendar days" (w.e.f. 12-6-2015).

1327. Ins. by G.S.R. 889(E), dated 12th December, 2014 (w.e.f. 12-6-2015)

1328. Subs, by G.S.R. 889(E), dated 12th December, 2014, for "thirty days of receiving the report from the Ethics Committee" (w.e.f. 12-6-2015).

1329. Subs, by G.S.R. 889(E), dated 12th December, 2014, for "three months of receiving the report of the serious adverse event" (w.e.f. 12-6-2015).

1330. Subs, by G.S.R. 889(E), dated 12th December 2014, for "ten calendar days" (w.e.f. 12-6-2015).

1331. Subs, by G.S.R. 889(E), dated 12th December, 2014, for "twenty one calendar days" (w.e.f. 12-6-

2015).

1332. Subs, by G.S.R. 889(E), dated 12th December, 2014, for "three months of receiving the report of the serious adverse event" (w.e.f. 12-6-2015).

1333. Ins. By G.S.R. 20(E) dated 18-01-2022 (w.e.f. 01.01.2023)

1334. Ins. By G.S.R. 30(E) dated 20-01-2022 (w.e.f. 20-01-2022)

1335. Ins. By G.S.R. 158(E) dated 24-02-2022 (w.e.f. 24-02-2022)

1336. Ins. By G.S.R. 357(E) dated 18-05-2022 (w.e.f. 01-11-2022)

1337. Ins. By G.S.R. 502(E) dated 30-06-2022 (w.e.f. 30-06-2022)

1338. Ins. By G.S.R. 654(E) dated 24-08-2022 (w.e.f. 24-08-2022)

1339. Ins. By G.S.R. 823(E) dated 17-11-2022 (w.e.f. 01-08-2023)

1340. Subs. by G.S.R 410(E) dated 02.06.2023 (w.e.f. 02.06.2023).

1341. Ins. By G.S.R 95(E) dated 05.02.2024 (w.e.f. 05.02.2024).

1342. G.S.R 216(E) dated 18.03.2024 (w.e.f. 18.03.2024).

1343. Subs. by G.S.R 341(E) dated 24.04.2023.

Error! Reference source not found.1344. Omitted by G.S.R 293(E) dated 04.04.2022 (w.e.f. 04.04.2022).

1345. Omitted by G.S.R 360(E) dated 01.07.2024 (w.e.f. 01.07.2024).