CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
DIRECTORATE GENERAL OF HEALTH SERVICES
MINISTRY OF HEALTH AND FAMILY WELFARE
GOVERMENT OF INDIA

GUIDANCE DOCUMENT FOR APPROVAL OF BA/BE NOC FOR EXPORT PURPOSE AS PER SCHEDULE Y & TEST LICENCE IN FORM 11 OF DRUGS AND COSMETICS RULES, 1945

BA/BE NOC FOR EXPORT DIVISION

DRAFT GUIDANCE DOCUMENT FOR APPLICATION/ APPROVAL OF BA/BE NOC FOR EXPORT PURPOSE AS PER SCHEDULE Y AND TEST LICENCE IN FORM 11 OF THE DRUGS AND COSMETICS RULES, 1945.

A large number of applications are being filed to the office of DCG (I) at CDSCO (HQ) by Pharmaceutical companies, both manufacturers and CRO's on behalf of them, requesting for the approval to carry out Bioequivalence studies on Indian subjects for export purpose.

In view of the above, for easy processing of such applications and to bring uniformity in decision making the office of DCGI would like to ensure the uniformity of documents to be submitted to the Directorate for review and approval of BE-NOC's to meet the requirement of guideline.

In this regard the concerned stakeholders of the aforementioned activities are hereby requested to submit their comments/suggestions, if any, on or before 5th March, 2018 through mail babe4export@gmail.com.

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A. INTRODUCTION

The office of Drugs Controller General (India) at CDSCO (HQ) FDA Bhawan, New Delhi has been receiving applications on behalf of Pharmaceutical companies, both Sponsors as well as CRO's, requesting for the approval to carry out BA/BE studies with various pharmaceutical dosage formulations on Indian subjects. The office of DCG(I) would like to ensure the demonstration of the safety and tolerability of generics against corresponding innovator drugs; to ensure they are comparable and safe for consumption by human subjects. An Assessment of "interchangeability" between the investigational and the innovator product is carried out by a study of "in vivo equivalence" or "bioequivalence" (BE). In view of the above, the office of DCGI would like to ensure the uniformity of documents to be submitted to this Directorate for review and approval of BE-NOC for export to meet tenets of Schedule Y of Drugs and Cosmetics Act 1940 & Rules 1945 and also Indian Good Clinical Practices (GCP) guidelines.

Purpose: To harmonize the submission of documents for applications seeking for licence to import drug products to conduct bioequivalence study for export purpose. This will also facilitate the examiners/reviewers to take uniform decisions and thereby shorten the application processing time.

Scope: Bioavailability and Bioequivalence studies are required by regulations to ensure therapeutic equivalence between a pharmaceutical equivalent test product and a reference product. The focus of this guidance document is to import of drug products, if required and to conduct bioequivalence study in human subjects for export purpose.

Bioavailability: Bioavailability refers to the relative amount of drug from an administered dosage from which enters the systemic circulation and the rate at which the drug appears in the systemic circulation.

Bioequivalence: Bioequivalence of a drug product is achieved if its extent and rate of absorption are not statistically significantly different from those of the reference product when administered at the same molar dose.

Good Clinical Practice Guidelines: Good Clinical Practice Guideline issued by the Directorate General of Health Service, Ministry of Health & Family Welfare, Government of India.

Modified Release Dosage Forms: Modified release dosage forms are those for which the drug-release characteristics of time course and/or drug release location are chosen to accomplish such therapeutic or convenience objectives that are not offered by immediate (conventional) release dosage forms.

Form-11 Licence: Form-11 is a license to import of drugs for examination, test or analysis. In case of BE studies, Form-11 Licence is issued against the Form-12 submitted by the firm to import of drug products to conduct BE study in human subject.

BE-NOC: BE-NOC means the No Objection Certificate issued by this directorate to conduct bioequivalence study in human subjects. If the firm wants to conduct BE studies, then firm should submit detailed study protocol, EC registration, BA/BE Centre approval copy, Form- 44, Form-12 and other relevant documents as per applicable checklist.

B. CURRENT PRACTICES

All BE-NOC applications shall be accompanied with the following documents in respective column of online application checklist.

B.1. Application for BA/BE NOC for Export purpose [New molecule (New Chemical entity) not approved in India but approved in other countries].

1. Application in Form-44 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization.
2. Treasury Challan (TR–6)/Bharatkosh receipt of Rs. 25000/- (Medical and Public Health Account: 0210).
3. Application in Form-12 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization, if required.

4. Treasury Challan (TR–6)/ Bharatkosh receipt of Rs. 100/- (Medical and Public Health Account: 0210), if required.
5. Undertaking by the Principal Investigator (PI) in original duly signed on a company letterhead as per appendix VII of Schedule "Y" of Drugs and Cosmetic Rules.
6. BA/BE Centre approval copy issued by DCG(I), New Delhi, along with details of number of beds provided at the centre (CRO) including ICU beds for effective handling of SAEs in emergency situations.
7. Sponsor's Authorization letter duly signed by the Authorized Signatory on company letterhead.
8. The study protocols, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per Schedule Y guidelines; & copy of approval of protocol from the IEC, if available.
9. Copy of registration of Independent/Institutional Ethics Committee (IEC) under Rule-122DD from the Office of Drugs Controller General (India), New Delhi.
10. The study synopsis.
11. Undertaking letter from the sponsor stating that you will provide complete medical care as well as compensation for the injury or Death and the same statement should be incorporated in the Informed Consent Form further in case of such injuries or Deaths, the details of compensation provided should be intimated to this Directorate as per Rule 122 DAB of D&C Act 1940 & Rules there under.
12. Non-clinical and clinical data as per Appendix I of Schedule "Y" of Drugs and Cosmetic Rules, 1945.
13. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects/patients demonstrating safety and tolerability of the molecule.
14. Regulatory approval status of the drug indicating the strength, dosage form and countries.

15. Names of the countries where the drug is currently being marketed (to be mentioned in the covering letter also).
16. Package insert/ prescribing information of the product.
17. Chemical and Pharmaceutical data including stability data.
18. Certificate of Analysis (COA) of representative batches (both Test & Reference formulations) to be used in the BE study along with dissolution profile in case Oral Solid dosage forms.
19. For multiple dose BE study adequate supporting safety data and PK/PD should be submitted covering the duration of period for which the study has to be conducted. If Regulatory Guidance is available, provide a copy of the same.
20. For all Injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days.
21. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Healthy Human subjects a Scientific justification with special emphasis on Safety of subjects with a proper Risk Evaluation and Mitigation Strategy should be submitted. If regulatory guidance is available, provide a copy of the same.
22. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Patients a Scientific justification with special emphasis on Safety with a proper Risk Evaluation and Mitigation Strategy should be submitted.
23. Report of any study related deaths during last 3 years at BA/BE centre. If yes, the copy of intimation should be submitted.
24. Address details of the IEC location and study site location.

B.2. Application for BA/BE NOC for Export purpose [New Drugs approved in India within period of 1 year].

1. Application in Form-44 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization.
2. Treasury Challan (TR–6)/Bharatkosh receipt of Rs. 25000/- (Medical and Public Health Account: 0210).

3. Application in Form-12 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization, if required.
4. Treasury Challan (TR–6)/Bharatkosh receipt of Rs. 100/- (Medical and Public Health Account: 0210), if required.
5. Undertaking by the Principal Investigator (PI) in original duly signed on a company letterhead as per appendix VII of Schedule "Y" of Drugs and Cosmetic Rules, 1945.
6. Regulatory status of the Drug in India indicating strength and dosage.
7. BA/BE Centre approval copy issued by DCG(I), New Delhi, along with details of number of beds provided at the centre (CRO) including ICU beds for effective handling of SAEs in emergency situations.
8. Sponsor's Authorization letter duly signed by the Authorized Signatory on company letterhead.
9. The study protocols, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per Schedule Y guidelines; & copy of approval of protocol from the IEC, if available.
10. Copy of registration of Independent/Institutional Ethics Committee (IEC) under Rule-122DD from the Office of Drugs Controller General (India), New Delhi.
11. The study synopsis.
12. Undertaking letter from the sponsor stating that you will provide complete medical care as well as compensation for the injury or Death and the same statement should be incorporated in the Informed Consent Form further in case of such injuries or Deaths the details of compensation provided should be intimated to this Directorate as per Rule 122 DAB of D&C Act 1940 & Rules there under.
13. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects/ patients demonstrating safety and tolerability of the molecule.
14. Package insert/ prescribing information of the product.

15. Chemical and Pharmaceutical data including stability data.
16. Certificate of Analysis (COA) of representative batches (both Test & Reference formulations) to be used in the BE study along with dissolution profile in case Oral Solid dosage forms.
17. For Multiple dose BE study adequate supporting safety data & PK/PD data should be submitted covering the duration of period for which the study has to be conducted. If Regulatory Guidance is available provide a copy of the same
18. For all Injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days.
19. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Healthy Human subjects a Scientific justification with special emphasis on Safety of subjects with a proper Risk Evaluation and Mitigation Strategy should be submitted. If regulatory guidance is available provide the copy of the same.
20. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Patients a Scientific justification with special emphasis on Safety with a proper Risk Evaluation and Mitigation Strategy should be submitted.
21. Report of any study related deaths during last 3 years at BA/BE centre. If yes, the copy of intimation should be submitted.
22. Address details of the IEC Location and study site location.

B.3. Application for BA/BE NOC for Export purpose [New Drugs approved within period of more than 1 year & less than 4 years].

1. Application in Form-44 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization.
2. Treasury Challan (TR–6)/Bharatkosh receipt of Rs. 15000/- (Medical and Public Health Account: 0210).
3. Application in Form-12 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization, if required.

4. Treasury Challan (TR–6)/Bharatkosh receipt of Rs. 100/- (Medical and Public Health Account: 0210), if required.
5. Undertaking by the Principal Investigator (PI) in original duly signed on a company letterhead as per appendix VII of Schedule "Y" of Drugs and Cosmetic Rules.
6. Regulatory status of the Drug in India indicating strength and dosage.
7. BA/BE Centre approval copy issued by DCG(I), New Delhi, along with details of number of beds provided at the centre (CRO) including ICU beds for effective handling of SAEs in emergency situations.
8. Sponsor's Authorization letter duly signed by the Authorized Signatory on company letterhead.
9. The study protocols, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per Schedule Y guidelines; & copy of approval of protocol from the IEC, if available.
10. Copy of registration of Independent/Institutional Ethics Committee (IEC) under Rule-122DD from the Office of Drugs Controller General (India), New Delhi.
11. The study synopsis.
12. Undertaking letter from the sponsor stating that you will provide complete medical care as well as compensation for the injury or Death and the same statement should be incorporated in the Informed Consent Form further in case of such injuries or Deaths the details of compensation provided should be intimated to this Directorate as per Rule 122 DAB of D&C Act 1940 & Rules there under.
13. Chemical and Pharmaceutical data including stability data.
14. Certificate of Analysis (COA) of representative batches (both Test & Reference formulations) to be used in the BE study along with dissolution profile in case Oral Solid dosage forms.
15. For Multiple dose BE study adequate supporting safety data (PK/PD) should be submitted covering the duration of period for which the study has to be conducted. If Regulatory Guidance is available provide a copy of the same

16. For all Injectables, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days.
17. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Healthy Human subjects a Scientific justification with special emphasis on Safety of subjects with a proper Risk Evaluation and Mitigation Strategy should be submitted. If regulatory guidance is available provide the copy of the same.
18. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Patients a Scientific justification with special emphasis on Safety with a proper Risk Evaluation and Mitigation Strategy should be submitted.
19. Report of any study related deaths during last 3 years at BA/BE centre. If yes, the copy of intimation should be submitted.
20. Address details of the IEC Location and study site location.

B.4. Application for BA/BE NOC for Export purpose [A drug product in modified release form irrespective of their approval status].

1. Application in Form-44 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization.
2. Treasury Challan (TR–6)/Bharatkosh receipt of Rs. 15000/- (Medical and Public Health Account: 0210) for approved in India or TR-6/Bharatkosh receipt of Rs. 25000/- in case of drugs not approved in India (new chemical entity).
3. Application in Form-12 duly signed, by the Authorized signatory with details of name and designation along with relevant drugs details and utilization, if required.
4. Treasury Challan (TR–6)/Bharatkosh receipt of Rs. 100/- (Medical and Public Health Account: 0210), if required.
5. Undertaking by the Principal Investigator (PI) in original duly signed on a company letterhead as per appendix VII of Schedule “Y” of Drugs and Cosmetic Rules.

6. Regulatory status of the Drug in India/other Countries indicating strength and dosage form.
7. BA/BE Centre approval copy issued by DCG(I), New Delhi, along with details of number of beds provided at the centre (CRO) including ICU beds for effective handling of SAEs in emergency situations.
8. Sponsor's Authorization letter duly signed by the Authorized Signatory on company letterhead.
9. The study protocols, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per Schedule Y guidelines; & copy of approval of protocol from the IEC, if available.
10. Copy of registration of Independent/Institutional Ethics Committee (IEC) under Rule-122DD from the Office of Drugs Controller General (India), New Delhi.
11. The study synopsis
12. Undertaking letter from the sponsor stating that you will provide complete medical care as well as compensation for the injury or Death and the same statement should be incorporated in the Informed Consent Form further in case of such injuries or Deaths the details of compensation provided should be intimated to this Directorate as per Rule 122 DAB of D&C Act 1940 & Rules there under.
13. Chemical and Pharmaceutical data including stability data.
14. Certificate of Analysis (COA) of representative batches (both Test & Reference formulations) to be used in the BE study along with dissolution profile in case Oral Solid dosage forms.
15. For Multiple dose BE study adequate supporting safety data & PK/PD data should be submitted covering the duration of period for which the study has to be conducted. If Regulatory Guidance is available provide a copy of the same.
16. For all Injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days.
17. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Healthy Human subjects a Scientific justification with special

emphasis on Safety of subjects with a proper Risk Evaluation and Mitigation Strategy should be submitted. If regulatory guidance is available provide the copy of the same.

18. For Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances etc in Patients a Scientific justification with special emphasis on Safety with a proper Risk Evaluation and Mitigation Strategy should be submitted.
19. Report of any study related deaths during last 3 years at BA/BE centre. If yes, the copy of intimation should be submitted.
20. Address details of the IEC Location and study site location.
21. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects/ patients demonstrating safety and tolerability of the molecule.
22. Package insert/prescribing information of the product.

B.5. Application for Test license (Form11) for BA/BE study of old drugs [Drugs approved for more than 4 years].

1. Covering letter of the firm.
2. Regulatory status of the Drug in India indicating strength & dosage form.
3. Form-12 application along with relevant Treasury Challan (TR-6)/Bharatkosh receipt.
4. The study protocols, Investigator undertaking, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per Schedule Y guidelines; & copy of approval of protocol from the IEC, if available.
5. The study synopsis.

If the study to be conducted with old drugs in healthy subject then application shall be submitted to respective Zonal Offices.

If the study to be conducted with old drugs in patients then application shall be submitted to CDSCO (HQ).

NOTE: Firm shall submit separate application for each protocol along with requisite fee.

All above requirements are general in nature, however depending on the nature of the drug, disease and studies further specific information may also be required to be furnished by the firm.

C. FORM-12:

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. The format of the form 12 is shown below:

FORM 12

(*See* rule 34)

Application for licence to import drugs for purpose of examination, test or analysis

I,… ……..resident of ……. by occupation……. hereby apply for a licence to import the drugs specified below for the purposes of examination, test or analysis at.....from.....and I undertake to comply with the conditions applicable to the licence.

1[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 and *classes of drugs:* *Quantities:*

Date…….. *Signature…*

T.R 6 Challan/ Bharatkosh receipt:-

Requisite Amount should be paid in T.R 6 Challan (duly signed and stamped by the Bank Officer)/ Bharatkosh receipt alongwith the application. A challan of Rs 100/- for first product and Rs 50/- for of each additional product (irrespective of strength dosage form and pack size) must be submitted along with the Application. A format of the T.R 6 Challan is shown below:-

T.R-6(See Rule 92)	**Bank Receipt No.**

Receipt of cash paid into Bank of Baroda, K.G. Marg, New Delhi-110001

To be filled by the remitter					**To be filled by the Department Officer or the Treasury**		
By whom Tendered	**Name (designation) and address of the person on whose behalf money is paid**	**Full particular of the remittance and/of authority (If any)**	**Amount**		**Head of Account**	**Accounts Officer by whom adjustable**	**Order to the Bank**
			Rs.	**P.**			
					0210-Medical + Public Health, 04-Public Health, 104-Fee and Fines	**Pay and Accounts Offices, DGHS,New Delhi**	**Date Correct, Receive and grant receipt (Signature and full Designation of the Officer ordering the money to be paid in).**
Signature		**Total**					
(in words) Rupees_____					**To be used only in the case of remittance to the Bank through Departmental officer or the Treasury Officer.**		

Received payment (in words) rupees…….. ……..Bank Officer

Cashier **Account** **Date**

D. FORM-44 :-

Application for permission to import or manufacture new drugs for sale or to undertake clinical trials/Bioavailability/Bioequivalence (BA-BE) studies shall be made in Form 44. For any BE-NOC application firm shall submit the Form 44. In Form 44 drug name, strength & dosage form should be mentioned in appropriate manner at specified places with the signature of authorized person. The format of Form 44 is given below:

FORM 44

[See rules 122A, 122B, 122D and 122-DA]

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 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 / date 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) Indications for which proposed to be used

(7) Manufacturer of the raw material (bulk drug substances)

(8) Patent status of the drug

(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

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 peer-reviewed journals/text books)

(2) Data on pharmacokinetics / pharmacodynamics combination

(3) Any other data generated by the applicant 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, efficacy and 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)

Date: ..... Signature: .....

Designation: .....

Note - Delete whichever is not applicable.

T.R 6 Challan/ Bharatkosh receipt:-

Requisite Amount should be paid in T.R 6 Challan (duly signed and stamped by the Bank Officer)/Bharatkosh receipt along with the application. A challan of Rs 25000/- for new drugs not approved in India but approved in other countries or new drugs approved in India within period of 1 year and a challan of Rs 15000/- for the drug approved in India in of more than 1 year for must be submitted along with the Application. A format of the T.R 6 Challan is shown below:-

T.R-6(See Rule 92)	**Bank Receipt No.**

Receipt of cash paid into Bank of Baroda, K.G. Marg, New Delhi-110001

To be filled by the remitter					**To be filled by the Department Officer or the Treasury**		
By whom Tendered	**Name (designation) and address of the person on whose behalf money is paid**	**Full particular of the remittance and/of authority (If any)**	**Amount**		**Head of Account**	**Accounts Officer by whom adjustable**	**Order to the Bank**
			Rs.	**P.**			
					0210-Medical + Public Health, 04-Public Health, 104-Fee and Fines	**Pay and Accounts Offices, DGHS, New Delhi**	**Date Correct, Receive and grant receipt (Signature and full Designation of the Officer ordering the money to be paid in).**
Signature		**Total**					
(in words) Rupees_____					**To be used only in the case of remittance to the Bank through Departmental officer or the Treasury Officer.**		

Received payment (in words) rupees…….. …….....Bank Officer		
Cashier	**Account**	**Date**

E. UTILIZATION/JUSTIFICATION OF THE QUANTITY REQUIRED TO IMPORT FOR BA/BE STUDY

Quantities of drugs required to import under form 11 licence should be justified. Utilization/justification should be duly signed by the Authorized Signatory. The detailed utilization break up for quantity of drug product mentioned in Form-12, shall be submitted.

F. REPLIES IN RESPONSE TO QUERIES

Upon review of submitted online application, the query will be issued with respect to deficiency. In response to the query, firm shall submit reply in proper manner as per the query issued by this Directorate.

G. APPLICATION FOR POST APPROVAL CHANGES (AMENDMENT) IN ALREADY ISSUED BE-NOC

Applicant shall apply for amendment if there is any change in proposed study, for which BE NOC has already been issued by the directorate. The criteria for post approval changes/ amendments are as follows:

(1) Major changes (For amendments)

(i) Site change/ Site transfer

(ii) Protocol Version changes (Change in Study design, Increase in number of subject)

(iii) Renewal of Test License

(iv) Changes in Principal Investigator

(v) Change in Bioanalytical site

(2) Minor Changes (For notification)

(i) Any administrative changes without affecting subject safety

(ii) Decrease in number of Subjects

(iii) Typographical Error

Documents required for submission of amendments:

(i) Copy of earlier issued BE-NOC,

(ii) Revised protocol/ ICF, if applicable,

(iii) Requisite Challan, if applicable,

(iv) Other relevant document on case to case basis.

Notification: Conditions which are mentioned in the received BE NOC to be notified before initiation of the study –

(i) Approval of EC for the subject study shall be submitted to CDSCO (HQ) before initiation of the study

(ii) ICF and patient Information sheet in regional language approved by Ethics Committee should be submitted before recruitment of the subjects.

(iii) Complete stability data with study condition sufficient to cover storage, shipment and uses of Investigational product should be submitted before initiation of the study

(iv) Other relevant conditions if any.

H. DRUGS & COSMETICS RULES, 1945 APPLICABLE TO BENOC

Drug and Cosmetics Rule 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 Drugs and Cosmetics Act and rules, 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 authorise;

(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 Chapter III of the Act and of which the licensing authority has given to him not less than one month's notice.

Drug and Cosmetics Rule 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.

(3) Every application in Form 12 shall be accompanied by a fee of one hundred rupees for a single drug and an additional fee of fifty 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 credited under the Head of Account 0210-Medical and Public Health, 04- Public Health, 104-Fees and Fines.]

Drug and Cosmetics Rule 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.

Drug and Cosmetics Rule 122-A -

122-A. Application for permission to import new drug.- [(1) (a) No new drug 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 the grant of permission to import a new drug shall be made in Form 44 to the Licensing Authority, accompanied by a fee of fifty thousand rupees:

Provided 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 fifteen thousand 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 fifteen thousand rupees and such information and data as required by Appendix I or Appendix IA of Schedule Y, as the case may be].

(2) The importer of a new drug when applying for permission under sub-rule (1), shall submit data as given in Appendix I 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 of 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.

[(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 45- A, 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.]

Drug and Cosmetics Rule 122-B -

122-B. Application for approval to manufacture new drug- [(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 the 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 the new claims, is made, the fee to accompany such subsequent application shall be fifteen thousand rupees: Provided 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 and such information and data as required by Appendix 1 or Appendix 1-A 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 Appendix 1 to Schedule Y including the results of clinical trials carried out in the country in accordance with the guideline specified in Schedule Y and submit the report of such clinical trials in the same format given in Appendix II to the said Schedule.

[(2-A) The Licensing authority as defined in clause (b) of rule 21 after being satisfied that the drug if approved to be manufactured 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 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 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 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 Carnicogenicity 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.

Drug and Cosmetics Rule 122-D -

122-D. 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 122-E shall be made to the Licensing Authority as defined in clause (b) of Rule 21 in Form 44, accompanied by a fee of fifteen thousand rupees 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.

Drug and Cosmetics Rule 122-DA -

122-DA. 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 the Licensing 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 shall be required to be paid along with application for import/manufacture of a new drug based on successful completion of phases clinical trials by the applicant: Provided further that no fee shall be required to be paid along with 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 46-A, 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 applicant 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 before permission could be considered.

I. VALIDITY OF FORM-11 LICENCE

The validity of test licence in form 11 is three years from the date of issue.

J. REJECTION

Application for grant of BE-NOC for export purpose may not be considered in following cases:

(i) Inadequate safety data available in healthy subjects/ patients as applicable,

(ii) Drug (molecule) falling under Narcotic Drugs and Psychotropic Substances (NDPS) not approved in India,

(iii) Single dose and multi dose study in a single application,

(iv) More than one protocol in one application with the same study design.

(v) Inadequate documents w.r.t. applicable checklist,

ABBREVIATIONS:

BA: Bioavailability

BE: Bioequivalence

NOC: No Objection Certificate

TL: Test Licence

PI: Principal Investigator

IEC: Independent/Institutional Ethics committee

ICF: Informed Consent Form

PIS: Patient Information Sheet

GCP: Good Clinical Practices

CoA: Certificate of Analysis

CRO: Contract Research Organization

PK/PD: Pharmacokinetics/Pharmacodynamics