Policy on Vaccine Approval

DRAFT GUIDANCE

This guidance document is for feedback purposes only. Comments suggestions, if any, may please be submitted to the office of Drugs Controller General India within thirty days

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION

DIRECTORATE GENERAL OF HEALTH SERVICES

MINISTRY OF HEALTH & FAMILY WELFARE

GOVT. OF INDIA

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1. Preamble

1.1 Introduction

Vaccines differ from therapeutic medicines first because of the biological, and thus inherently variable, nature of the products themselves, the raw materials used in their production, and the biological methods used to test them. Thus special expertise and procedures are needed for their manufacture, control, and regulation. Vaccines are unique in the fact that they are usually administered to very large numbers of healthy people; mostly infants, in national immunization programmes; thus safety and quality are paramount.

In recent years, the licensing and quality control for manufacturers and national regulatory authorities alike has become even more complex by the development of vaccine formulations containing an increased number of immunogens. Each new vaccine combination needs to be carefully tested clinically and testing and specifications may vary for each specific product.

In general, all vaccines manufactured / imported into the country are required to comply with the requirements and guidelines specified in the Drugs and Cosmetics Rules, 1945 & New Drugs and Clinical Trials Rules, 2019 and other applicable guidelines published by CDSCO form time to time in case of manufacturer r-DNA derived vaccines the requirements and guidelines prescribed by Department of Biotechnology are also required to be complied with. However, vaccines unlike chemical drugs are complex heterogeneous class of medical products, and hence specific consideration in respect of development of CMC data, non-clinical data, and clinical data will provide clear understanding of regulatory landscape for their development and approval in a scientific manner. Therefore, the following sections provide policy guidance to manufacture, import, conduct of clinical trial, post marketing assessment etc of vaccines in India.

1.2 Background

1.3 Scope

This document applies to the conduct of clinical trials, marketing approval, manufacture/ import/export, post marketing clinical assessment and post marketing approval requirements of vaccines in the country.

1.4 Purpose of this document

Vaccine Policy with respect to the regulatory requirements on various aspects is required to guide the importer/manufacturer/exporter in decision-making and developing a long-term plan from the regulatory perspective. This policy is limited to the regulatory aspects and does not intend to cover aspects of immunization policy of the country. Further, it is not a detailed guideline on specific vaccine. This Policy document intends to provide broader policy guidelines and framework to guide the importer/manufacturer/exporter in the research, development, clinical trial, manufacture, import, export, quality assessment and post approval requirements of vaccines in the country.

2. Policy on Administrative matter

2.1 Governing Act, Rules and Guidance:

Vaccine is a drug within the meaning of the Drugs and Cosmetics Act, 1940. The import, manufacture, sale distribution and conduct of the clinical trial are regulated under this Act. Vaccine is a “new drug” throughout its lifecycle. The requirements to assess the safety, immunogenicity and efficacy are provided under the New Drugs and Clinical Trials, 2019 (NDCT Rules). Further, the applications and approvals for obtaining permissions to import, manufacture and conduct of clinical trials are issued under these rules.

The Drugs and Cosmetics Rules, 1945 regulate the manufacture or import of vaccines once safety, immunogenicity and efficacy is established under the NDCT rules. Manufacture/import license is issued under these rules.

CDSCO also issued various guidance documents for the approval of vaccines, conduct of clinical trials etc. These guidance are revised from time to time. The current applicable guidance documents are available on the website of the CDSCO.

2.2 Role of CDSCO and the State Drug Authorities

Vaccine is a drug within the meaning of the Drugs and Cosmetics Act, 1940 (herein after referred as Act). Import or manufacture for sale of vaccines are regulated under the Act, Drugs& cosmetics Rules, 1945 and New Drugs and Clinical Trials Rules, 2019. The powers to regulate vaccines are shared between the CDSCO and the State Drug Licensing Authorities (herein after referred as SLA. The details are as follows:

2.2.1 Role of Central Drug Standard Control Organization (CDSCO):

1) It is the National Regulatory Authority (NRA). The functions of CDSCO with respect to the vaccines include the following:
2) Grant of permission to manufacture or import vaccine for test and analysis
3) Regulate all aspects of clinical trials including grant of permission, clinical site monitoring, verification of Good Clinical Practices compliance, Ethics Committee registration, Serious Adverse Event monitoring and compensation etc.
4) Grant of marketing approval for vaccines imported and manufactured in the country
5) Post approval changes
6) Grant of Central Licensing Approval Authority (CLAA) approval for manufacturing
7) Lot release of vaccines
8) Inspection of the manufacturing facilities
9) Pharmacovigilance
10) Regulatory control as various designated ports

2.2.2 Role of State Licensing Authority (SLA):

1) Inspection of the manufacturing facilities
2) Generation of the manufacturing license for CLAA approval
3) Export certification
4) Quality monitoring through sampling from the market/institutions

2.2.3 Research and Development

Manufacture, Import, Sale Distribution and conduct of clinical trial are regulated under the provisions of the Act and rules made there under. Research on vaccines for academic and scientific purpose is not regulated under the Act, however, approvals have to be obtained to conduct clinical trial or to manufacture vaccine for developmental purpose provided the data be submitted to CDSCO or any other regulatory agency.

2.3 WHO NRA assessment

WHO assesses the NRA from time to time in respect of regulatory control over the vaccines manufactured in the country. Major parameters for assessment were related to Institutional Development Plan (IDP), quality system, independency of regulatory authorities, recall systems, adequacy of staff,

dossier review and system for providing feedback on adverse event following immunisation (AEFI) from National to State levels and vice versa. For strengthening and imparting necessary skills, CDSCO has an IDP to strengthen the Indian Drug regulatory mechanism.

The IDP is with the following objectives:

1) To improve the quality of regulatory process as per the current policy
2) To mitigate the risk, identified and assessed with respect to internal and external factors which can affect the routine regulatory procedures
3) To increase the staff and infrastructure to meet increasing workload and regulatory practices
4) Quality of regulatory process is being improved by:
    i. Training of the staff for assigned job functions
    ii. Developing SOP's for critical job functions
    iii. Developing guidance documents
    iv. Developing various checklist and reporting formats

2.4 RCGM and GEAC

RCGM and GEAC are statutory committees set up as per provisions of Rules, 1989.

Review Committee on Genetic Manipulation (RCGM) under the Department of Biotechnology is responsible for overseeing the development and preclinical evaluation of recombinant DNA derived products. It is responsible for authorizing the conduct of research and development, exchange of genetically engineered cell banks for the purpose of research and development and review of data up to preclinical evaluation.

GEAC functions under the Ministry of Environment and Forests (MoEF) as statutory body for review of applications and approval of activities where final drug product contains genetically modified organisms/ living modified organisms.

The relevant approvals are required at various stages of drug development including before conduct of clinical trial.

2.5 Role and responsibilities of the importer, manufacturer and sponsor of clinical trial

2.5.1 Vaccine Importer/Manufacturer role and responsibilities include the following:

1) The safety, immunogenicity and efficacy of a vaccine is the responsibility of the manufacturer and the import permission holder. Therefore, the manufacture/importer should obtain marketing permission before manufacture or import of the vaccine.
2) If the same vaccine is imported by different persons separate marketing approval should be obtained by each of the importer. In case of manufacture, each manufacturing site should obtain separate manufacturing license.
3) The importer or manufacture should have risk management plan for every vaccine.
4) The marketing approval holder shall address all the new safety concerns during the lifecycle of the vaccine.

2.5.2 Vaccine Clinical Trial Sponsor Role and responsibilities include the following:

1) The applicant seeking permission to conduct clinical trial is deemed to be the sponsor of the clinical trial and is responsible to ensure compensation and medical management in case of Serious Adverse Event of trial subjects.
2) If a clinical research organisation (CRO) or any other person makes an application for the grant of permission to conduct a clinical trial on behalf any other person, the CRO is the sponsor of the clinical trial.

2.6 Post approval changes (PAC)

A vaccine is expected to be manufactured at the same site and the same procedure submitted at the time of approval. If there is any change in the manufacturing processes, manufacturing facility, site of manufacture, batch size, shelf life, presentation or any other change, which may affect its identity, strength, quality, purity, after granting permissions for manufacturing a vaccine or biological product as a new drug, the manufacturer has to submit application to the Central Licensing Authority duly supported with technical data

The PACs are categorised as follows:

1) Level-I- Supplements (Major quality changes)
2) Level- II- Notifiable Changes (moderate Quality changes)
3) Level- III Annual notification

The list of changes falling under each level is provided in the Guidance for Industry, post approval changes in Biological products: Quality,
Safety & Efficacy Documents

The applicant has to obtain prior approval for Level I and Level II changes and Level III changes are notified.

2.7 Vaccine Subject Expert Committee

CDSCO has constituted various Subject Expert Committee (SEC) to advise the Drugs Controller General (India) and to make recommendations on the proposals to conduct clinical trials, grant of marketing approvals, post approval changes, various aspects relating to safety, immunogenicity etc. The Committee comprises of experts from the fields of Medicine, Paediatrics, Pharmacology, Microbiology etc. Experts from relevant specialities are invited to the Committee as per need. The Committee after examination of the proposals give its recommendations. The recommendations of the Committee are advisory.

The applicant, if aggrieved with the recommendations of the SEC, may appeal for reconsideration, to the Technical Committee, headed by the Director General of Health Services (DGHS).

2.8 Stockpiling of unapproved vaccines for public health emergencies

As per the provisions of the Act and Rules, vaccine has to be manufactured only after obtaining marketing approval and manufacturing license. However, in case of emergencies the Government of India may by notification, permit manufacture for stockpiling of specified vaccine before grant of marketing approval subject to various conditions.

2.9 Mode of filing applications

All applications regarding conduct of clinical trials, marketing approvals and post approval changes have to be filed electronically on SUGAM portal. Those which are not supported by the portal can be filed with the CDSCO headquarter.

The approvals consequent to processing of the application on SUGAM portal are issued by way of digitally signed document by the competent authority and by hard copy in other cases.

3. Policy on Technical Matter

3.1 Requirements for grant of Marketing approval for import/manufacture of vaccines :

Vaccines are heterogeneous class of medical products; much of the considerations for their development should be given on a product-specific basis. Requirements may vary depending on the type of vaccine whether it is inactivated or live attenuated microorganisms based or antigen based which is extracted from pathogen or derived from r-DNA technology or by chemical synthesis, or a vaccine containing naked nucleic acid, including plasmids for expressing specific antigens or otherwise, it will also be dependent on manufacturing process, its mechanism of action and the nature of the disease to be prevented as well as target population.

The application is required to be made in the prescribed format along with the fees and information/data as per the checklist provided on the SUGAM portal. The application for the marketing approval shall be made only online. The data required for the grant of approval is as follows:

1) Chemical and pharmaceutical information;
2) Animal pharmacology data;
3) Animal toxicology data;
4) Human clinical pharmacology data as prescribed and as stated below:-

I. In general, the applicant has to generate safety, immunogenicity and efficacy data in Indian population unless it is exempted under Special situations where relaxation, abbreviations, omission or deferment of certain data may be considered.

II. for novel candidate vaccine discovered or developed in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as prescribed;

III. For novel candidate vaccines discovered or developed in countries other than India, Phase I data should be submitted along with the application. After submission of Phase I data generated outside India to the Central Licensing Authority, permission may be granted to repeat Phase I trials or to conduct Phase II trials and subsequently Phase III trial concurrently with other global trials for that drug.

IV. The data required will depend upon the type of vaccine proposed for approval. In case of vaccines already approved in other countries and is well established in respect to the safety, immunogenicity and efficacy the applicant should demonstrate that the proposed vaccine is non-inferior with the comparator in terms of Immune correlates of protection with already approved vaccine in the country.

V. 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 phases;

VI. Application has to be made as per the requirements under the NDCT rules.

VII. The applicant has to be submit evidence supported by data for all the claims made in the package inserts, promotional literature and patient education material with respect to the vaccine.

VIII. 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 Central Licensing Authority along with the application.

The data is required to be submitted in the CTD format consisting of five modules namely.

a) Module 1: Administrative information;
b) Module 2: Overviews and summaries of Modules 3–5;
c) Module 3: Quality (pharmaceutical documentation);
d) Module 4: Non-clinical reports (pharmacology/toxicology);
e) Module 5: Clinical study reports.

Administrative details

a) Summaries
b) Quality
c) mainly required is CMC, nonclinical and clinical development of any vaccine

3.2 Manufacturing license for vaccine:

1) A vaccine has to be manufactured for sale or distribution only after obtaining a valid manufacturing license under the provisions of the Act. The requirements to obtain a manufacturing license for a vaccine product include compliance with the requirements of GMP verified through inspection, marketing approval for the product and analytical report of the Central Drugs Laboratory that the vaccine is meeting the specifications.
2) The application for the grant of manufacturing license has to be made to the SLA with copies to the CDSCO. The SLA, if satisfied, forwards the license in prescribed format to the CLAA for approval. CLAA accords his approval if the applicant meets the prescribed requirements.
3) Requirements for obtaining manufacturing license for export. The requirements for obtaining a manufacturing license of a vaccine for export purpose are same as those mentioned for domestic purpose. However, in case the applicant is not holding marketing approval for a product and

intends to export the same, upon application CDSCO will issue a No objection certificate subject to various conditions including undertaking that the importing country has no objection to import of the vaccine, CDL lot release etc for specific quantity of the vaccine and the destination country.

3.3 Lot release by CDL

Each lot of imported Vaccine imported or manufactured shall be released by at Central Drugs Laboratory under the Ministry of Health and Family Welfare in the Central Government before sale or distributed in to the market

Lot release is key to the control of vaccines and similar biologicals, which are inherently variable due to the biological nature of starting materials, manufacturing process, and test methods. Therefore, post-licensing monitoring for vaccines and other biologicals involves, in addition to the above, lot-by-lot release, as each lot can be considered unique. Lot release is based, at minimum, on the review of Summary Lot Protocols which describe the production process in detail. Lot release function is a regulatory requirement for release into the market.

4. Promotion of Research and Development

4.1 Non-clinical Data Requirements

4.1.1 Toxicity and safety testing

Toxicity studies in animals may be considered for the assessment of the potential toxic effects of a vaccine in target organs, including the haematopoietic and immune systems as well as to assess systemic toxicity. Applicability of repeated dose toxicity tests depends on the vaccine dose regimen and the composition of the vaccine. Usually there is no chronic exposure of the subject to a vaccine through repeated administration.

Where different routes of administration are proposed, multiple safety and toxicity studies in a suitable animal model should be considered. These should address the specific safety concerns associated with administration of the vaccine by each of the proposed routes.

4.1.2 Immunogenicity:

Data obtained from the immunization of animals with candidate vaccine preparations shall provide valuable information to support a clinical indication.

Preclinical studies should be designed to assess the relevant immune responses, e.g. seroconversion rates, geometric mean antibody titres, or cell-mediated immunity in vaccinated animals. Immunogenicity studies may include the characterization of antibody class, avidity, affinity, half-life, memory, and potential induction of cell-mediated immunity as well as release of soluble mediators affecting the immune system, as appropriate.

Animal toxicity data generated in other countries may be accepted and may not be asked to be repeated or duplicated in India on a case to case basis depending upon the quality of data and the credentials of the laboratory where such data has been generated.

4.2 Clinical Development

In general, the applicant should conduct Phase-I, II followed by III clinical studies in the country to demonstrate the safety, immunogenicity and efficacy of the vaccine.
However, if the vaccine is already approved for marketing in other countries or in India, the requirement to conduct Phase-I and/or II may be omitted or abbreviated on case by case basis.
In case of imported vaccines, the importer should generate safety and immunogenicity data through a bridging study in India.
The applicant has to generate immunogenicity data in the target age groups.

4.2.1 Phase-III

Phase III trials involve a larger number of subjects than were included in the earlier phases of development and, thus, provide expanded safety assessments.
The duration of follow-up should be determined taking into account the type of vaccine and other relevant factors (e.g. disease incidence, characteristics of immune response to vaccine, and anticipated and safety profile of the vaccine.)

4.2.2 Post Marketing Clinical Evaluation

To ensure the vaccine safety and effectiveness of marketed vaccine, post-marketing assessment may be carried out through the following ways:

1) Phase IV (Post Marketing Trial)
2) Post Marketing Surveillance or observational or non-interventional study for active surveillance
3) Post Marketing Surveillance including assessment of Adverse Events Following Immunization (AEFI) and Adverse Events of Special Interest (AESI).

Such studies are required in cases where the safety data is limited at the time of consideration of approval or to monitor any specific safety issue.

4.2.3 Clinical Study Principles

Clinical trial should be planned, designed, conducted, analysed and reported according to sound scientific and ethical principles. Following important principles should be followed:

1) The primary objective of any clinical trial should be clearly and explicitly stated which may include exploratory or confirmatory characterisation of safety, efficacy, assessment of pharmacokinetic and pharmacodynamics parameters;
2) The clinical trial should be designed appropriately so that it provides the desired information;
3) Appropriate comparator may be utilised to achieve the objective with respect to primary and secondary end points. Comparison may be made with placebo, no treatment, active controls or of different doses of the new drug or investigational new drug;
4) The number of subjects to be included in the clinical trial should be adequate depending on the nature and objective of the clinical trial.

4.2.4 Lot to Lot consistency

A well-defined manufacturing process with its associated process controls assures that an acceptable product is produced on consistent basis in accordance with Good Manufacturing Practice (GMP). In general, the firm should generate lot to lot consistency data before the grant of marketing approval

4.3 Special considerations with respect to Vaccines:

4.3.1 Adjuvant:

Compatibility of the adjuvant(s) with all the antigenic components of the vaccine should be demonstrated. Where relevant, adsorption of all the antigenic components present in the vaccine, should be shown to be consistent on a lot-to-lot basis. Possible desorption of antigen during the shelf-life of the product should be evaluated, reported and specifications set. If a new adjuvant is proposed for use in a vaccine formulation, appropriate preclinical studies are necessary.

Preclinical animal studies to determine the safety profile of the combination of adjuvant and vaccine should also be undertaken.

Preclinical studies should evaluate the combination of adjuvant and antigen as formulated for clinical use.

4.3.2 Excipients and Preservatives

If a new additive such as a preservative or excipient is to be used, its safety should be investigated and documented. If a new preservative is used, its safety as well as efficacy or appropriateness for use in a particular product must be documented. The safety of new additives can be evaluated using vaccine formulations without antigen. However, the compatibility of a new additive with all vaccine antigens should be documented as well as the toxicological profile of the particular combination of antigen(s) and additive in animal models.

4.3.3 Other Types of Product Requiring Special Considerations

Some types of data and testing are specific for certain types of product, such as genetic stability of vaccines based on GMOs, data concerning the inactivation and attenuation methods, demonstration of comparability of combination vaccines, contribution of adjutants and safety/toxicity studies for particular vaccines.

4.3.4 Molecular Biology Considerations

The details regarding host cell cultures (including viral clearance), vectors, gene sequences, promoters etc. used in the production should be provided with appropriate drawings/figures.

4.3.5 Combination vaccines

New combinations of antigens or serotypes should be studied for appropriate immunogenicity in an animal model, if available, before initiation

of clinical trials in humans. The response and the quality of response to each of the antigens in the vaccine should be assessed. It is preferable to study a new combination in comparison with the individual antigens in animals to determine whether augmentation or diminution of response occurs. Interference between live vaccine strains may also be studied in animal immunogenicity tests.

4.3.6 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 or efficacy. The shelf life of the vaccine has to be assigned based on the real time stability reports

4.3.7 Special situations for vaccine where Relaxation, Abbreviation, Omission or Deferment of Data may be considered

1) Depending on categories and nature of the vaccine to be imported or manufactured for sale or clinical trial to be undertaken requirements of chemical and pharmaceutical information, animal pharmacology and toxicology data, clinical data may differ. The requirements may also differ depending on the specific phase of clinical trial proposed to be conducted as well as clinical parameters related to the specific study drug.
2) For vaccines intended to be used in the diseases of special relevance to Indian scenario or unmet medical need in India, following mechanism may be followed to expedite the development of vaccine and approval process.

3) Accelerated Approval Process

Accelerated approval process may be allowed to a new preventive vaccine for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of treatments. In such case, the approval of the vaccine may be based on data generated in clinical trial where immune correlates of protection shall be considered rather than using standard outcome measures such as survival or breakthrough

cases, which are reasonably likely to predict clinical benefit, or a clinical end point.

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After granting accelerated approval for such vaccine, the post marketing trials shall be required to validate the anticipated clinical benefit. Accelerated approval may also be granted to a vaccine if it is intended for the prevention of a serious or life threatening condition or disease of special relevance to the country, and addresses unmet medical needs If the remarkable efficacy is observed in the clinical trials of a new candidate vaccine for the unmet medical needs of serious and life threatening diseases in the country, it may be considered for grant of marketing approval and in such cases additional post licensure studies may be required to be conducted after approval to generate the data on larger population

4) Situations where quick or expeditious review process can be sought for approval of a new drug after clinical development

In situation where the evidence for clinical safety and efficacy have been established even if the vaccine has not completed the all or normal clinical trial phases, the sponsor or applicant may apply to the licensing authority for expedited review process wherein the licensing authority will examine and satisfy the following conditions. –

1) It is for a drug that is intended to treat a serious or life threatening or rare disease or condition;
2) If approved, the vaccine would provide a significant advantage in terms of safety or efficacy;
3) There is substantial reduction of a treatment-limiting adverse reaction and enhancement of patient compliance that is expected to lead to an improvement in serious outcomes;
4) the sponsor or applicant may also apply to the licensing authority for expedited review process for the vaccine

5. Safety Monitoring in Post Market scenario

5.1 Periodic safety update report

The marketing approval holder should submit the Periodic Safety Update Report as per the frequency mentioned under the NDCT rules

5.2 AEFI surveillance system

Vaccines are not entirely without risk and adverse reactions may occur. Being a large consumer, leading manufacturer and exporter of vaccines, India is expected to have a well-developed Adverse Event Following Immunisation (AEFI) Surveillance system. AEFI surveillance program demonstrates the country's intent of delivering quality immunization services with safe vaccines and ensure vaccine confidence. The AEFI surveillance system has been put in place in the country. The national AEFI guidelines are issued and revised from time to time. The guidelines provide information to health care providers and programme managers at national, state, district, block and primary health care levels for establishing a sensitive AEFI surveillance system. The national AEFI guidelines provide complete guidance and other details for reporting, investigating and conducting the causality assessment of cases reported as AEFIs.

a. Post marketing studies

6. Vaccine Quality monitoring

The Vaccine quality monitoring is mainly based on the following principles:

a. Compliance with the principles of the GMP carried out from time to time
b. Lot release protocol assessment
c. Investigation of Market complaints
d. Surveillance of the quality of products by analysing samples taken from manufacturers and the distribution chain, either randomly or because they are suspected of being substandard.
   Monitoring is conducted by both, CDSCO as well as the SLA.

7. References

1. India Vaccine Policy
2. Drugs and Cosmetics Act, 1940
3. Drugs and Cosmetics Rules, 1945
4. New Drugs and Clinical Trial Rules, 2019
5. Regulation of vaccines: building on existing drug regulatory authorities WHO