Guidance for Industry Document for Veterinary Biologicals in India

1. Requirements for permission of New Drugs Approval
2. Post approval changes in biological products: Quality safety and Efficacy Documents
3. Stability Testing of Veterinary Biological Drug Substances and Drug Products
4. Import & Registration
5. Test Licence for import
6. Licence to manufacture vaccine under Form 28D
7. Field Trials.
8. Post Marketing Surveillance
9. Checklists (Marketing Authorization, Registration Certificate, Import Licence, Test Licence in Form 11, Post Approval Changes, Annual report form)

Version No.: -00

FOREWORD

The Central Drugs Standard Control Organization (CDSCO), being the apex regulatory authority for approval of drugs in India, is committed to ensure the safety, efficacy and quality of drugs. With the creation of separate Veterinary Division at CDSCO this Guidance Document has been developed for Veterinary Biological in conformity with the Drugs & Cosmetics Act 1940 and Rules 1945 there under and other functions of CDSCO wherever applicable.

These guidelines are intended for the guidance of the Market Authorization Holders (MAHs) i.e. manufacturers and importers of biological products for veterinary use. The procedure set out to facilitate the animal healthcare industry to submit the documents as per the requirements of Drugs and Cosmetics Act and Rules. This guideline applies to import or manufacture, registration and marketing approval of new drugs including new biological entity, new indication, new dosage forms, modified release form, new route of administration etc. under the Drugs & Cosmetics rules for veterinary biologicals.

This guideline indicates an appropriate format for submission of the data that have been acquired from Drugs & Cosmetics Act and Rules there under, defines the 'content requirements' for the specific type of submission and hence, this guidance document has to be read along with Drugs and Cosmetics Act 1940 and Rules made thereunder.

To maintain its consistency and enhanced transparency, this guidance documents may be amended from time to time as per requirements to reflect the updated practices of drug regulation.

Dr. S. Eswara Reddy
Drugs Controller General of India

Table of content

INTRODUCTION:

Regulation of Veterinary drugs follows the provisions of Drugs and Cosmetic Act 1940 and Rules 1945.
This document provides guidance on the information that must be provided to support applications for permission of manufacturing or import of new drugs and for registration of new veterinary biological products in India or for variations to existing registrations of veterinary biological products. The purpose of this guideline is to establish the regulation and control biological products for veterinary.

DEFINITIONS:

For the purpose of this guideline, the following definitions are established:

Licensing authority is entity responsible for the implementation of this Regulation, for its effective compliance by the sectors involved in the subject and activity which it comprises.

Veterinary biological product: means to products such as vaccines, serums and etc., prepared for creating active or passive immunity, measuring the state of immunity or diagnosing a disease or health disorder in animals.

Vaccine: This is an immunogen administered to stimulate the immune system in order to prevent, reduce, or provide therapy against a given disease or infection. Vaccines can be preparations of attenuated viruses, bacteria, or parasites; inactivated complete organisms from crude fractions or purified immunogens, including those derived from recombinant DNA in host cells, conjugates formed by covalent links of components, synthetic antigens, polynucleotides (e.g. plasmid DNA vaccines), living cells from vectors expressing specific heterologous immunogens, or immunogen-activated cells. There are also combinations of vaccines or immunogens produced from those mentioned above.

Marketing Authorization Holder: individual or legal entity legally authorized by the manufacturer or owner which has in its favour the registration of a product, for its commercialization and who is accountable to the competent authority.

Manufacturer: includes a manufacturer of drugs, who may be a Company or a unit or a body corporate or any other establishment in India or 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

New drug:

(a) a drug, as defined in the Act including bulk drugs substance 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.
(b) a drug already approved by the licensing authority mentioned in rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage forms (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 form (including sustained release dosage form) and route of administration.
(e) all vaccines and recombinant DNA (r-DNA) derived drugs shall be new drugs unless certified otherwise by the Licensing Authority under rule 21.
(d) a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval.

Registration:
This is the health procedure whereby the National Regulatory Authority grants authorization for the nationwide marketing and distribution of the product in question, based in the assessment of the evidence supporting its quality, efficacy and safety.

Raw material: substance, whatever its origin, active or inactive, used as component, active ingredient or excipient which is used for the manufacture of Veterinary medicinal products and related products, whether it remains unaltered or suffering modification

Efficacy:
Extent to which medicine treatment produces a beneficial result measured in the context of controlled clinical trial. This result should be measured not only on surrogate variables (such as decreased blood pressure, HbA1c glycaemia, increased density) but also in clinically relevant variables such as rate of myocardial infarction, stroke, kidney disease, decreased risk of fractures, etc.

Excipient:
A substance or mixture of substances, in concentrations present in a pharmaceutical form, with no pharmacological activity and whose function is to ensure stability, bioavailability, acceptability and feasibility of administration of the active pharmaceutical ingredient(s) of the medicine.

Final bulk product:
Every product that has gone through all stages of processing, including dosage form, except final packaging.

Finished product:
This is the final dosage form that has gone through all manufacturing stages, including packaging into the container and final packaging.

Combined vaccines: Consist of two or more monovalent vaccines of different diseases, or antigens combined by the manufacturer at the final formulation stage. Such vaccines are intended to protect against either more than one disease, or against one disease caused by different strains or serotypes of the same organism.

Certificate of analysis: document issued by the laboratory quality control

Labelling: means any information that adheres, print or record on the container and packaging Commercial presentation of a veterinary medicinal product or related product.

Product insert: printed instructions accompanying each commercial presentation of a veterinary medicinal product or related product as appropriate, complying with the provisions of this Regulation.

Container or packaging: is any container or wrapping intended to preserve the quality and
Safety of the veterinary medicinal product or related product, facilitating its handling.

Primary packaging container: the container into which is placed directly veterinary medicinal product or related product in its finished pharmaceutical form

Secondary packaging container: the container in which the container is placed containing the veterinary medicinal product or related product in its pharmaceutical form finished, for distribution and commercialization.

Validation: This involves a series of documented procedures or actions based on the principles of the Good Manufacturing Practices, which demonstrate that the processes, equipment, materials, activities, or systems meet predetermined specifications and quality requirements.

Guidance for
New Drug Approval (Veterinary Biologicals)

Objective
The purpose of this document is to achieve greater harmonization in the information submitted in the application for Market Authorization for Veterinary Biologicals. Since the same information will be requested and submitted in various countries, the licensing process and ultimately the availability of vaccines will be facilitated. It is expected that having a common document will also by making more efficient use of technical and financial resources.

Scope
Applies to all Biologicals to be registered for veterinary use, regardless of where they are manufactured, whether they are licenced in the country of origin or not, and considering the current requirements of Drugs and Cosmetic Act and Rules 1945
The manufacturer / sponsor has to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945

Covering Letter– The covering letter is an important part of the application and should clearly specify the intent of the application. The list of documents that are being submitted as well as any other important and relevant information may be provided in the covering letter. The covering letter should be duly signed and stamped by the authorized signatory, indicating the name & designation of the authorized signatory along with the name and address of the firm. Any exemption to the submission requirement be clearly specified in the covering letter on the firm/company letter head and justified in the submissions.

Form 44 is an application for grant of permission to import or manufacture a new drug or to undertake Field trial the Central Drugs Standard Control Organization prescribes information to be submitted for New Drugs Approval (Market Authorization) of Veterinary Biologicals in the specified format to simplify the submission requirements.
(Annexure 1)

Technical Dossier
The requirements in respect of Chemistry and Pharmaceutical information has been elaborated while requirement for non-clinical and Clinical trial requirements remains the same as per Schedule Y of Drugs and Cosmetic Rules 1945 except submissions as prescribed in this document.
The documents need to be submitted as per CTD format (Common Technical Document) and has Five Modules (Annexure 2)

Module I: Administrative/Legal Information
Module II: Summaries
Module III: Quality Information (Chemical, Pharmaceutical and Biological)
Module IV: Non-Clinical Information
Module V: Field Trial if applicable
NOTE: Submit two hard copies and two soft copies

Bharatkosh Online Payment:
Applicable fees as per Drugs and Cosmetics Act, 1945 and Rules thereunder shall be paid through Bharatkosh Online payment system.

NOC from Department of Animal Husbandry & Dairying (DAHD), Ministry of Agriculture & Farmer Welfare:
No objection certificate issued by DAHD, Ministry of Agriculture & Farmer Welfare for grant of permission to import or manufacture a new Veterinary biological or to undertake Field trial, if applicable in India to be submitted.

NOTE: There is no need of NOC from DAHD if vaccine containing same strain of same source is already approved in India.

IVRI Test Certificate:
Test reports of new veterinary vaccine duly certified from IVRI for at least 3 consecutive batches to be submitted for New Drugs Approval (Market Authorization) of Veterinary Biological.

NOTE: Submit two hard copies and two soft copies i.e. CD's (PDF format).

Hard copies: It must be well labelled with document number, name of the firm, date of submission etc. Number of volumes to be labelled as Volume No./ Total number of volumes e.g. if there are five volumes, volume three will be labelled as Volume: 3/5.

Soft Copies: They must be well labelled with document number, name of the firm, date of submission etc. Scanned copies of only signed document like test reports will be acceptable as soft copies. The table of content under each head should be linked to the files (s) or relevant document for easy tracking in CD's.

Manufacturer should preserve/maintain one hard copy and soft copy of submitted documents in his safe custody for any future reference, if required.

MODULE - 1

1.1	**Comprehensive table of contents (Modules 1 to 5)**
1.2	**Administrative information**
1.2.1	**Application in Form 44 and Fee receipt**
1.2.2	**Legal and statutory documents**
1.2.2.1	Licence and approvals: As applicable
	(a) Copy of Form 11 for imported drug product
	(b) Form-29 for indigenous drug
	(c) Field trial no objection letter / approval
	(d) GEAC clearance if applicable
1.2.2.2	Legal documents pertaining to application (to be notarized):
	a) A copy of plant registration / approval certificate issued by the Ministry of Health / National Regulatory Authority/ any other Competent Authority of the country of origin
	b) A copy of approval, if any, showing the drug is permitted for manufacturing and/or marketing in the country of origin
	c) A copy of Certificate of Pharmaceutical Product (COPP) as per WHO GMP certification scheme for imported drug products, if any
	d) A copy of Free Sale Certificate (FSC) from the country of origin for imported drug products
	e) Certificate of Good Manufacturing Practices of other manufacturers involved in the vaccine production process
	f) Batch release certificate issued by NRA/ Any other Competent Authority of country of origin for imported products
	g) Undertaking to declare summary of product characteristics (as per Annex. A)
1.2.2.3	A copy of Site Master File
1.2.2.4	Certificate of Analysis of three consecutive batches from Indian Veterinary Research Institute Izatnagar (U.P.)or Any other Notified Laboratory under D&C Act
1.2.3	**Coordinates related to the application**
1.2.3.1	Name, address, telephone, fax, e-mail of manufacturer of drug product
1.2.3.2	Name, address, telephone, fax, e-mail of the responsible official
1.2.3.3	Name, address, telephone, fax, e-mail of the authorized agent in India: (for imported drug products)
1.2.3.4	Name, designation, address, telephone, fax, e-mail of the official responsible for releasing batches of drug product
1.2.3.5	Name, address, telephone, fax, e-mail of the manufacturing premises holding Market Authorization of the drug product (for imported drug products)
1.2.3.6	Name, address, telephone, fax, e-mail of manufacturer of drug substance
1.2.3.7	Name, address, telephone, fax, e-mail of other manufacturer(s) involved in the production process
1.2.4	**General information on drug product**
1.2.4.1	Proprietary, commercial or trade name of drug product
1.2.4.2	Non-proprietary name or common name of drug product
1.2.4.3	Composition (as per label claim)
1.2.4.4	Dosage form
1.2.4.5	Strength per dosage unit
1.2.4.6	Route of administration
1.2.4.7	Commercial presentation
1.2.4.8	Conditions of storage

1.2.4.9	Summary of product characteristics (As per Annex A- Module I)
1.2.4.10	Product Labelling (should conform to the specifications under the Drugs and Cosmetics Rules 1945)
	a. Primary package label
	b. Secondary package label
	c. Package insert (in English)
1.2.4.11	Summary of the packaging procedures for Indian shipments (including box sizes, packing volumes).
1.2.5	**Summary protocol of batch production and control**
1.2.6	**List of countries where MA or import permission for the said drug product is pending and the date of pendency.**
1.2.7	**List of countries where the drug product has been licenced and summary of approval conditions.**
1.2.8	**List of countries where the drug product is patented.**
1.2.9	**Domestic price of the drug followed in the countries of origin in INR**
1.2.10	**A brief profile of the manufacturer's research activity**
1.2.11	**A brief profile of the manufacturer's business activity in domestic as well as global market**
1.2.12	**Information about the expert(s)/ Information regarding involvement of experts, if any**
1.2.13	**Environmental risk assessment.**
1.2.14	**IVRI Certification:** Samples of drug product with testing protocols and release specifications should be forwarded to Indian Veterinary Research Institute Izatnagar (U.P.) or any other Notified Laboratory under D&C Act for certification before Marketing in the country. In case of first time manufactured in the country, the initial first three batches along with its corresponding protocol is required to the submitted to the said laboratory.

MODULE - 2

2.1	**Table of contents of Module 2**
2.2	**Introduction**
2.3	**Quality overall summary**
2.3.S	Summary of Veterinary Biological drug substance
2.3.P	Summary of Veterinary Biological drug product
2.3.A	Appendices
2.4	**Overview of Pharmacology & Toxicology studies**
2.4.1	Pharmacology
2.4.2	Pharmacokinetics
2.4.3	Toxicology
2.5	**Pharmacology & Toxicology Summary**
2.5.1	Introduction
2.5.2	Summary of pharmacology
2.5.3	Summary of toxicology
2.6	**Overview of Field studies**
2.6.1	Introduction
2.6.2	Table of contents
2.6.3	Detailed discussion of product development
2.6.4	Overview of immunogenicity
2.6.5	Overview of efficacy
2.6.6	Overview of safety

2.6.7	Conclusions on risk-benefit balance
2.6.8	List of literature
2.7	**Field trial summary**
2.7.1	Introduction
2.7.2	Table of contents
2.7.3	Summary of studies of immunogenicity
2.7.4	Summary of studies of efficacy
2.7.5	Summary of studies of safety

MODULE - 3

Quality Information (Chemical, Pharmaceutical and Biological)

3.1	**Table of contents for Module 3**
3.2	**Quality contents**
3.2.S	**Veterinary Biological Drug substance(s): Information must be submitted for each drug substance in the product.**
3.2.S.1	**General information, starting materials and raw materials**
3.2.S.1.1	Trade and/or non-proprietary name (s) of drug substance
3.2.S.1.2	Structural formula, molecular formula and relative molecular weight (if applicable)
3.2.S.1.3	General description and history of starting material
3.2.S.1.4	Strain
3.2.S.1.4.1	System of seed/master/working banks
3.2.S.1.4.2	Embryonated eggs and other cell substrates
3.2.S.1.5	General description of raw materials
3.2.S.1.6	Analytical certificates signed by the manufacturer and the applicant for registration
3.2.S.2	**Manufacturing process for drug substance**
3.2.S.2.1	Manufacturer(s)
3.2.S.2.2	Description of manufacturing process
3.2.S.2.3	Flow diagram of manufacturing process
3.2.S.2.4	Control of critical steps in process and control
3.2.S.2.5	Validation of manufacturing process
3.2.S.2.6	Manufacturing process development
3.2.S.2.7	Description of inactivation or detoxification process
3.2.S.2.8	Description of purification process
3.2.S.2.9	Description of conjugation process
3.2.S.2.10	Stabilization of active ingredient
3.2.S.2.11	Reprocessing
3.2.S.2.12	Filling procedure for the active ingredient, in-process controls
3.2.S.2.13	Selection and justification of critical steps
3.2.S.2.14	Description of batch identification system
3.2.S.3	**Characterization of Veterinary Biological drug substance**
3.2.S.3.1	Physicochemical Characterization
3.2.S.3.2	Biological Characterization
3.2.S.4	**Quality control of Veterinary Biological drug substance**
3.2.S.4.1	Specifications
3.2.S.4.2	Analytical procedures
3.2.S.4.3	Validation of analytical procedures

3.2.S.4.4	Consistency and analysis of batches
3.2.S.4.5	Justification of Specifications
3.2.S.5	**Reference standards**
3.2.S.6	**Container closure system**
3.2.S.6.1	Specifications of packaging materials (primary and secondary packaging)
3.2.S.6.2	Tests and evaluation of packaging materials
3.2.S.7	**Stability of Biological Drug substance**
3.2.S.7.1	Protocol of stability study, results and conclusions
3.2.S.7.2	Post-approval stability programme
3.2.S.7.3	Storage and shipping conditions
3.2.P	**Veterinary Biological Drug product**
3.2.P.1	**Description and composition of drug product**
3.2.P.2	**Pharmaceutical development**
3.2.P.2.1	Drug substance (s)
3.2.P.2.2	Drug product
3.2.P.2.3	Justification of final qualitative/quantitative formula
3.2.P.2.4	Manufacturing process
3.2.P.2.5	Container closure system, compatibility
3.2.P.3	**Manufacture of drug product**
3.2.P.3.1	Manufacturer(s)
3.2.P.3.2	Batch formula
3.2.P.3.3	Description of manufacturing process
3.2.P.3.4	Control of critical and intermediate steps
3.2.P.3.5	Validation and/or evaluation of the process
3.2.P.3.6	Description of batch identification system
3.2.P.4	**Control of excipients (adjuvant, preservative, stabilizers and others)**
3.2.P.4.1	Specifications
3.2.P.4.2	Analytical procedures
3.2.P.4.3	Validation of analytical procedures
3.2.P.4.4	Justification of specifications
3.2.P.4.5	Substances of human or animal origin
3.2.P.4.6	Use of new adjuvants, preservatives, stabilizers and excipients
3.2.P.5	**Control of drug product**
3.2.P.5.1	Specifications
3.2.P.5.2	Analytical procedures
3.2.P.5.3	Analytical certificates signed by the manufacturer and the applicant for registration
3.2.P.5.4	Validation of analytical procedures
3.2.P.5.5	Consistency and analysis of batches
3.2.P.5.6	Justification of specifications
3.2.P.6	**Reference standards of materials**
3.2.P.7	**Container closure system**
3.2.P.7.1	Specifications of packaging materials (primary and secondary packaging)
3.2.P.7.2	Tests and evaluation of packaging materials
3.2.P.8	**Stability of drug product**
3.2.P.8.1	Protocol of stability study, results and conclusions
3.2.P.8.2	Freeze dried products: stability testing of freeze dried materials, diluent and re-constituted product, thermal stability, where applicable

3.2.P.8.3	Post-approval stability program
3.2.P.8.4	Description of procedures to guarantee cold chain
3.2.A	**Appendix**
3.2.A.1	**Details of equipment and facilities for production of drug product: master formula, batch record and set release documentation in respect of consistency batches**
3.2.A.2	**Safety evaluation of adventitious agents**
3.3	**Bibliographic Reference**

MODULE - 4

4.1	**Table of contents of the Module**
4.2	**Reports on studies**
4.2.1	**Pharmacology**
4.2.1.1	**Pharmacodynamics studies (immunogenicity of product)**
4.2.1.2	**Pharmacodynamics studies of adjuvant (if applicable)**
4.2.2	**Pharmacokinetics**
4.2.2.1	**Pharmacokinetic studies (in case of new adjuvant, new modes of administration)**
4.2.3	**Toxicology**
4.2.3.1	General toxicology - information:
4.2.3.2	Special toxicology (for products to which it applies)
4.2.3.3	Toxicity of new substances used in formulation (new adjuvant, stabilizers, additives)
4.2.4	**Special considerations**
4.2.4.1	For attenuated vaccines, evaluation of possible "shedding" (excretion) of micro-organism
4.2.4.2	Toxicity of new substances used in formulation (new adjuvant, stabilizers, additives), other modes of administration or new combined vaccines - the appropriate toxicological studies must be provided
4.3	**Bibliographic references**

Module - 5

5.1	**Table of contents of the Module**
5.2	**Reports on Field trial**
5.2.1	Efficacy Study
5.2.2	Safety Study
5.3	**Animal Ethics Committee Approval of the Centre**
5.4	**CPCSEA Approval of the Centre undertaking Study.**
5.5	**Synopsis of the Field Trial Study duly signed by the Principal Investigator.**
5.6	**Special Consideration**
5.7	**Bibliographic references**

Annexure A to Module I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE BIOLOGICALPRODUCT
{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
<Excipient(s):>
Give full list of excipients.

3. DOSAGE FORM

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.2 Method of administration

4.3 Contraindications
<Hypersensitivity to the active substance(s) or to any of the excipients <or {name of the residue(s)}>

4.4 Special warnings and precautions for use

4.5 Interaction with other medicinal products and other forms of interaction
<No interaction studies have been performed>
<Interaction studies have only been performed in adults>

4.6 Pregnancy and lactation

4.7 Effects on ability to drive and use machines
<{Invented name} has <no <or negligible> influence><minor or moderate influence><major influence> on the ability to drive and use machines>
<No studies on the effects on the ability to drive and use machines have been performed>
<Not relevant>

4.8 Undesirable effects
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

4.9 Overdose
<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: {group}, ATC code: {code}
<This biological product has been authorised under a so-called “conditional approval” scheme.
This means that further evidence on this medicinal product is awaited.
<This biological product has been authorised under “Exceptional Circumstances”.
This means that <due to the rarity of the disease><for scientific reasons>
<for ethical reasons> it has not been possible to obtain complete information on this biological product.

5.2 Pharmacokinetic properties

5.3 Preclinical safety data
<Non-clinical data reveal no special hazard for animals based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.>in target species
<Adverse reactions not observed in Field studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to Field trial should be reported

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities
<Not applicable.>
<In the absence of compatibility studies, this medicinal product must not be mixed with other biological products.>
<This biological product must not be mixed with other medicinal products.

6.3 Shelf life
<...><6 months><...><1 year><18 months><2 years><30 months><3years><...>

6.4 Special precautions for storage
<For storage conditions of the <reconstituted><diluted> medicinal product.
6.5 Nature and contents of container
<Not all pack sizes may be marketed.>

6.6 Special precautions for disposal
<No special requirements.>
<Any unused product or waste material should be disposed off in accordance with Environment and Protection Acts.>

7. <MARKETING AUTHORISATION>
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. <MARKETING> AUTHORISATION NUMBER(S)

9. DATE OF FIRST < AUTHORISATION> / RENEWAL OF THE <AUTHORISATION>
<{DD/MM/YYYY}><{DD month YYYY}>
{MM/YYYY}

Post approval changes in Biological Products: Quality Safety and Efficacy Documents

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Objectives

a. To assist with the classification of changes made to veterinary biological products that have received a marketing authorization (MA).

b. To provide MA holders with recommendations on the data to support a change which would be considered sufficient to allow a determination of the impact of the change on the quality of the approved products as it relates to safety, efficacy and/or effective use of the products.

1.2 Scope and Application

This guidance document applies to MA holders intending to make changes to veterinary biological products that have received an approval to market the products.

1.3 Background

This would include an emphasis on applying a science-based and risk-based approach to the veterinary biological products quality assessment. As such, the guidance documents were needed to outline the information needed to support quality, safety and efficacy changes to new veterinary biological products which apply a modernized, science-based, and risk-based approach to this area.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Reporting Categories

The following criteria are meant to provide guidance with respect to the classification of a change. Specific change examples based on the application of these criteria are provided in this guidance. For assistance in classifying a change, MA holders are advised to contact Central Drugs Control Organisation.

2.1.1 Level I - Supplements (Major Quality Changes)

Level I - Supplements (Major Quality Changes) are changes that have a *substantial potential* to have an adverse effect on the identity, strength, quality, purity, or potency of a biological product as these factors may relate to the safety or effectiveness of the product.

In general, a change that is supported by extensive documentation and/or requiring extensive assessment of the supporting documentation would be considered a Level I - Supplement (Major Quality Change) (e.g., a change supported by *in vivo* studies). This is to allow DCG(I) the opportunity to apply the principles of risk management by having the necessary time for an appropriate assessment of the documentation. This assessment will take into consideration any potential impact upon market availability as well as the adverse effects on the identity, strength, quality, purity, or potency of the biological product.

The changes included in this reporting category shall be filed, along with the recommended supporting data, to DCG(I).

2.1.2 Level II - Notifiable Changes (Moderate Quality Changes)

Level II - Notifiable Changes (Moderate Quality Changes) are changes that have a *moderate potential* to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety or effectiveness of the product.
The changes included in this reporting category should be filed, along with the recommended supporting data, to DCG(I) as a Notifiable Change (NC).

2.1.3 Level III - Annual Notification (Minor Quality Changes)

Level III - Annual Notification (Minor Quality Changes) are changes that have *minimal potential* to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety or effectiveness of the product.

3. DOCUMENTATION

3.1 General Information

The examples presented in Quality post approval changes (Biologics)are intended to assist with the classification of changes made to the quality information. The information summarized in the tables provides recommendations for:

a. The **conditions to be fulfilled** for a given change to be classified as a Level I, II, or III change. If the conditions outlined for a given change are not fulfilled, the particular change will be assessed by the DCG(I) in the lights of scientific justification provided by the MA holders and accordingly the level shall be decided;

b. The supporting data for a given change, either to be submitted to DCG(I)and/or maintained by the MA holders. Where applicable, the corresponding sections of the application for the supporting data have been identified.

c. The reporting category (e.g., Supplement, Notifiable Change or Annual Notification).
For convenience, the change examples are organized according to the format defined by the DCG(I).

3.2 Supporting Data - Level I and Level II Changes

All data recommended to support the change should be provided with the submission. Where applicable, these data should be provided in the format defined by the Common Technical Documents (CTD).

Supporting Data Common to Level I and Level II Changes
The following should be included, where applicable, in the submission package for Level I and Level II Quality changes:

a) a covering letter (including a list of changes describing each insufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);

b) where relevant, a side-by-side comparison of the previously approved and the changed information;

c) An electronic or hard copy of the Quality Overall Summary or the applicable DCG(I) Quality Overall Summary template (only those sections affected by the proposed change(s) should be included, sections not affected by the change(s) should be deleted from the QOS).

In addition to the above *common information*, recommendations are included in Appendices 1 outlining the *specific* information to support the various quality changes. It should be noted that the common information is not repeated for the various changes outlined in the appendices.

When cross-references are made to previously submitted information, details on the cross-referenced information should be indicated in the covering letter (e.g., brand name of the drug product, MA holder’s name, submission type, file number, date approved).

3.3 Supporting Data - Level III Changes

Any data that may have been generated by the MA holder in support of a Level III change should be submitted annually but should be available to DCG(I)within fifteen (15) calendar days, if requested.

3.4 Stability Testing

If stability studies are recommended to support a change, these studies should be conducted in accordance with Guidelines for Stability Testing of Veterinary Drug Substances and Drug Products in this guidance document.

4. Quality Post-Approval Changes (Veterinary Biologics)

The change examples presented below are intended to assist with the classification of changes made to the Quality information of Veterinary biologic products.

4.1 VETERINARY BIOLOGICAL DRUG SUBSTANCE

4.1.1 General Information

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the name of the drug substance	1	1	Annual Notification

Conditions

1. Confirmation that information on the drug substance has not changed as a result of the submission (e.g., cross reference(s) should be provided to the previously approved drug submission, quoting the date approved and Approval Number(s)).

Supporting Data

1. Product Monograph (e.g., Title Page, Storage and Stability, Composition and Packaging (Part I), and Pharmaceutical Information and Inner and Outer Labels.

4.1.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change to a Veterinary Biological drug substance manufacturing facility, involving:			
a. replacement or addition of a manufacturing facility and/or manufacturer of the bulk drug substance, the starting material or any intermediate of the drug substance	1-2	1-6,8-11	Supplement
b. conversion of a drug substance manufacturing facility from single-product to multi-product	3-4	11-12	Notifiable Change
c. introduction of prokaryotes including yeast into a multi- product eukaryotic fermentation suite	3-4	12-13	Notifiable Change
d. introduction of a different host/media-type into an approved multi-product facility for which a master cleaning protocol for the introduction of new host/media-type has not been approved	None	7,14	Notifiable Change
e. addition of product(s) to an approved multi-product manufacturing area	3-4	11-13	Annual Notification
f. deletion of a manufacturing facility or manufacturer for a starting material, bulk intermediate, or drug substance	None	None	Annual Notification

Conditions

1. No changes have been made to the starting material and the expression system.
2. The production process and controls are the same as those used by the original manufacturer.
3. The addition of product does not involve changes to the validated cleaning and change-over procedures.
4. The addition of product does not involve additional containment requirements.

Supporting Data

1. Updated or new DMF (with a Letter of Access) or relevant drug substance information
2. Name, address, and responsibility of the changed production facility or facility involved in manufacturing and testing.
3. For drug substances or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance).
4. Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the changed drug substance.
5. Process validation and/or evaluation studies (e.g., for aseptic processing and sterilization).
6. Comparability of the approved and changed product with respect to physico-chemical characterization & biological activity.
7. Information on the in-process control testing.
8. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug substance.
9. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available, as well as commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.
10. Updated post-approval stability protocol and stability commitment to place the first production scale batch of the drug product manufactured using the changed drug substance into the stability programme, as applicable.
11. Information on the changed production facility involved in manufacturing and testing, including cleaning and shipping validation, as appropriate.
12. Information describing the change-over procedures for shared product-contact equipments and the segregation procedures, as applicable.
13. Results of the environmental monitoring studies in critical classified areas.
14. Information on the cleaning procedures (including validation and the master cleaning protocol) demonstrating lack of carry-over or cross-contamination.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the Veterinary Biological drug substance manufacturing process, involving:			
a. a critical change	None	1-3,5-12	Supplement

	1-2	1-3,5-11	Notifiable Change
b. a non-critical change	1-4	2,3,5- 7,9,10	Annual Notification
Scale-up of the manufacturing process:			
a. at the fermentation stage	5-9	4,8-11	Notifiable Change
b. at the purification stage	1,6-7,10	8-11	Notifiable Change
Change in source/supplier of auxiliary materials/reagents of biological origin (e.g., fetal calf serum, insulin)	None	9,12,13	Notifiable Change
Introduction of reprocessing steps	None	7,9-11	Notifiable Change

Conditions

1. The change does not concern the sterilization procedures of a sterile drug substance.
2. The change does not impact the viral clearance data or the source of a chemical nature of an inactivating agent for a vaccine.
3. No change in the drug substance specifications.
4. No change in the impurity profile of the drug substance.
5. No change in the proportionality of the raw materials.
6. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
7. The change does not result in a change to the drug substance specification.
8. The scale-up consists in the addition of identical fermentors.
9. The change does not affect the purification process.
10. The scale-up is linear.

Supporting Data

1. Updated or new DMF (with a Letter of Access) or relevant drug substance information.
2. Flow diagram of the changed manufacturing process (es) and a brief narrative description of the changed manufacturing process (es).
3. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the changed drug substance.
4. Information on the characterization and testing of the post-production cell bank for recombinant product, or of the drug substance for non-recombinant product.
5. For drug substances or drug substances manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance).
6. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed drug substance.
7. Process validation and/or evaluation studies (e.g., for aseptic processing and sterilization).
8. Comparability of the approved and changed product with respect to physico-chemical characterization &biological activity.

9. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug substance.
10. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.
11. Updated post-approval stability protocol and stability commitment to place the first production scale batch of the drug product manufactured using the changed drug substance into the stability programme, as applicable.
12. Information assessing the risk with respect to potential contamination with adventitious agents.
13. Information demonstrating comparability of the auxiliary materials/reagents of both sources.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Changes to the cell bank:			
a. generation of new Master Cell Bank (MCB) from the same expression construct with same or closely related cell line; or	1	1,5-8	Notifiable Change
generation of a new MCB from expression construct with the same coding sequence and the same cell line; or	None	1-8	Supplement
adaptation of a MCB into a new fermentation medium	None	3	Notifiable Change
b. generation of a new MCB for a recombinant product or a viral vaccine	1	1-3,5-7	Notifiable Change
c. generation of a new Working Cell Bank (WCB)	2,3,4	1-2	Annual Notification
Changes to the seed bank:			
a. new Master Seed Bank (MSB)	None	3-9	Supplement
Working Seed Bank (WSB) extended beyond an approved passage level	4		Notifiable Change
b. generation of a new MSB or WSB	2,3,4	3,4	Annual Notification

Conditions

1. The new MCB is generated from a pre-approved Master or Working Cell Bank.
2. The new cell/seed bank is generated from a pre-approved MCB/MSB.

3. The new cell/seed bank is at the pre-approved passage level.
4. The new cell/seed bank is released according to a pre-approved protocol.

Supporting Data

1. Qualification of the cell bank.
2. Information on the characterization and testing of the post-production cell bank for recombinant product, or of the product for non-recombinant product.
3. Comparability of the approved and changed product with respect to physico-chemical characterization, biological activity, and impurity profile.
4. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for the new seed lot.
5. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the drug substance derived from the new cell/seed bank.
6. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.
7. Updated post-approval stability protocol and stability commitment to place the first production scale batch of the drug product using the changed drug substance into the real time/real temperature stability programme.
8. Supporting non-clinical data or a request for a waiver of *invivo* studies.
9. Supporting Field Trial data.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in a facility involved in the manufacture of a drug substance, such as:			
a. for an active ingredient manufactured in an *open* system, any changes which affect the trends or action limits of the environmental monitoring program	None	1-2	Notifiable Change
b. relocation of equipment to another room in the same facility	1-3	3,4	Annual Notification
c. modification to a non-critical manufacturing area (e.g., construction of a new warehouse in the facility)	2,3	3,6	Annual Notification
d. change in the location of steps in the production process	1	1,4,5	Annual Notification

Conditions

1. The change in the location of steps has no impact on the risk of contamination or cross-contamination.
2. The modification has no direct product impact.
3. Re-qualification of the equipment follows the original qualification protocol, if applicable.

Supporting Data

1. Information on the in-process control testing.
2. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug substance, including technology transfer validation, equipment qualification, as appropriate.
3. Information demonstrating re-qualification of the equipment or re-qualification of the change.
4. Information illustrating the manufacturing flow, including the floor plans.
5. Results of the environmental monitoring studies in critical classified areas.
6. Information on the changed production facility involved in manufacturing and testing, including cleaning and shipping validation, as appropriate.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category

Change in equipment used in drug substance manufacturing process, such as:

a. equipment having different specifications from those originally approved	None	1-3	Notifiable Change
b. addition of new product-contact equipment used in a critical step (e.g., change in equipment model for a continuous centrifuge, water bath for inactivation)	None	1-3	Notifiable Change
c. equipment change for an identical/ equivalent equipment	1	3	Annual Notification

Conditions

1. Re-qualification of the equipment follows the original qualification protocol.

Supporting Data

1. Information on the in-process control testing.
2. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug substance, including technology transfer validation, equipment qualification, as appropriate.
3. Information demonstrating re-qualification of the equipment or re-qualification of the change.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the controls for the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts)	1-5	1-6	Notifiable Change
Change in the controls performed at critical steps used in the manufacture of the drug substance	1-5	1-6	Notifiable Change

Conditions:

1. No change in the drug substance specifications.
2. No adverse change in the impurity profile of the drug substance.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
4. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The change does not affect the sterilization procedures of a sterile drug substance.

Supporting Data

1. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the changed drug substance.
2. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed drug substance.
3. Updated, signed and dated specifications of the drug substance, if affected by the change.
4. Copies or summaries of analytical procedures, if new analytical procedures are used.
5. Copies or summaries of validation reports, if new analytical procedures are used.
6. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug substance.

4.1.3 Control of the Drug Substance

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the standard claimed for the drug substance (e.g., from a Professed to pharmacopoeial standard)	None	1-6	Notifiable Change
	1,2,3	1-6	Annual Notification
Change in the specifications for the drug substance to comply with an updated pharmacopoeial monograph	1,2	2-6	Annual Notification

Conditions

1. The change is made exclusively to comply with the (same) pharmacopoeia.
2. No change to the specifications for functional properties of the drug substance.
3. No deletion or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specifications.

Supporting Data

1. Product Monograph (e.g., Title Page, Composition and Packaging, and Pharmaceutical Information section) and Inner and Outer Labels.
2. Updated, signed and dated, changed drug substance specifications.2

3. Where a House analytical procedure is used and a standard is claimed, results of an equivalency study between the House and compendial methods.
4. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least three (3) batches of the changed drug substance.
5. Justification of the changed drug substance specifications (e.g., demonstration of the suitability of the monograph to control the drug substance, including impurities).
6. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category

Change in the specifications for the drug substance, involving:

a. deletion of a test	5	1,4,5-6	Notifiable Change
b. replacement or addition of a test	None	1-6	Notifiable Change
	1-4,6	1-6	Annual Notification
c. relaxation of an acceptance criterion	None	1,4,5-6	Notifiable Change
d. tightening of an acceptance criterion	1-4,6	1,4,5-6	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. Acceptance criterion for any Class 3 residual solvent is within the limits.
5. The deleted analytical procedure has been demonstrated to be redundant with respect to the remaining analytical procedures.
6. The change does not concern sterility testing.

Supporting Data

1. Updated, signed and dated, changed drug substance specifications.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used.
4. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the House and compendial methods.
5. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least three (3) batches of the changed drug substance.
6. Justification of the changed drug substance specifications (e.g., test parameters, acceptance criteria, or analytical procedures).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category

Change in the specifications for the drug substance, involving:

a. deletion of an analytical procedure	1	5	Notifiable Change
b. replacement or addition of an analytical procedure	1,3	1-5	Notifiable Change
c. minor changes to an approved analytical procedure	1-5	1-5	Annual Notification
d. a change from in house analytical procedure to a Pharmacopoeial analytical procedure	1-5	1-5	Annual Notification

Conditions

1. No change in the approved acceptance criteria.
2. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The change does not concern sterility testing.

Supporting Data

1. Updated, signed and dated, changed drug substance specifications.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used.
4. Comparative results demonstrating that the approved and changed analytical procedures are equivalent.
5. Justification of the changed drug substance specifications (e.g., test parameters, acceptance criteria, or analytical procedures).

4.1.4 Reference Standards or Materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Qualification of a reference standard	None	1	Notifiable Change
Subsequent qualification of a reference standard	2,3	1	Annual Notification
Update the reference standards from pharmacopoeial to In- House	1	1	Notifiable Change
Update the reference standards from In-House to pharmacopoeial	2,3	1	Annual Notification

Conditions

1. The In-House reference standard is validated against an official (e.g., pharmacopoeial) reference standard.
2. Qualification of the reference standard is performed according to the approved protocol (i.e. no deviation from the approved protocol)
3. The reference standard is not for a bacterial or a viral vaccine

Supporting Data

1. Information demonstrating qualification of the changed reference standards or materials (e.g., source, characterization, certificate of analysis).

4.1.5 Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the container closure system(s) for the storage and shipment of the drug substance	1	1,2,3	Notifiable Change
	1,2	1	Annual Notification

Conditions

1. Results demonstrate that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.
2. The change does not concern a sterile drug substance.

Supporting Data

1. Information on the changed container closure system (e.g., description, specifications).
2. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available, as well as commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.
3. Demonstration of compatibility if the drug substance is a liquid.

4.1.6 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the re-test period (or shelf life) for the drug substance, involving:			
a. Extension	1,4,5,6	1-4,6	Notifiable Change
	1,2,3,5,6	1,2,5	Annual Notification
b. Reduction	1,5	1-5	Notifiable Change
c. Addition of storage condition for the drug substance	1	1-5	Notifiable Change

Conditions

1. No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance.
2. The approved shelf life is at least 24 months.
3. Full long term stability data is available covering the changed shelf life and are based on stability data generated on at least three production scale batches.
4. Full long term stability data is not available covering the changed shelf life or are not based on stability data generated on at least three production scale batches. If the proposed shelf life is beyond the available long term data, the extrapolation is in accordance with VICH guideline.
5. Stability data was generated in accordance with the approved stability protocol.
6. Significant changes were not observed in the stability data.

Supporting Data

1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. Proposed storage conditions and re-test period (or shelf life, as appropriate).
3. Updated post-approval stability protocol and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (i.e. full real time/real temperature stability data covering the changed re-test period (or shelf life) generated on at least three (3) production scale batches).
6. Results of stability testing (i.e., less than full real time/real temperature stability data covering the changed re-test period (or shelf life) and/or not generated on at least three (3) production scale batches) and a commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the labelled storage conditions for the drug substance, involving:			
a. addition of a cautionary statement	None	1	Notifiable Change
b. deletion of a cautionary statement	1	1	Notifiable Change
c. relaxation of a temperature criterion	None	1	Notifiable Change
d. tightening of a temperature criterion	1	1	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Supporting Data

1. If applicable, stability testing results to support the change to the storage conditions.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change to the post-approval stability protocol or stability commitment	None	1-4	Notifiable Change

Conditions None

Supporting Data

1. Proposed storage conditions and re-test period (or shelf life, as appropriate).
2. Updated post-approval stability protocol and stability commitment.
3. Justification of the change to the post-approval stability protocol or stability commitment.
4. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment.

4.2 DRUG PRODUCT

4.2.1 Description and Composition of the Veterinary Biological Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Addition of a dosage form or strength	1	1-13	Supplement

Conditions:

1. None of the excipients are prohibited by the *DCG(I) regulation*.

Supporting Data

1. Supporting Field trial or comparative bioavailability data or a request for a waiver of *in vivo* studies, e.g.,
2. Letters of Access (e.g., Drug Master Files (DMFs)), if new excipients are included.
3. Product Monograph (e.g., Title Page, Storage and Stability, Dosage Forms, Composition and Packaging, and Pharmaceutical Information section) and Inner and Outer Labels.
4. Confirmation that the information on the drug substance has not changed (e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, MA holder's name, submission type, control number, date approved) or revised information on the drug substance, if any of the attributes have changed.
5. Description and composition of the dosage form.
6. Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative *in vitro* testing for the approved and changed products, discussion of any *in vitro* and/or *in vivo* studies.
7. Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation.

8. Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the *DCG(I) Regulations*).
9. Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used), Batch Analyses (certificate of analyses for one production scale batch).
10. Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
11. Stability Summary and Conclusions, e.g:
    - for a new dosage form and new strength: results of a minimum of six (6) months of accelerated or long term stability report of the changed drug product (including a minimum of three time points);
12. Updated post-approval stability protocol and stability commitment to place the first production scale batch of each strength of the changed product into the long term stability programme (bracketing and matrixing could be applied, if scientifically justified).
13. Executed Production Documents for one batch of each new dosage form or strength, Master Production Documents for the new dosage form or strength.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the description or composition of the drug product, involving:			
a. addition of a dosage form or change in the formulation (e.g., change in the amount of excipient, new diluent for lyophilized product)	1	1-12	Supplement
b. addition of a new strength (e.g., 50 mg dose vs 100 mg dose)	None	2-12	Supplement
c. change in the concentration of the active ingredient (e.g., 20 unit/mL *vs* 20 unit/2 mL)	None	2-12	Supplement
d. addition of a new presentation (e.g., addition of syringes to vials)	None	1-13	Notifiable Change
e. change in the volume of the dose (e.g., 4 mL *vs* 3 mL)	2-5	2-9,14	Notifiable Change

Conditions

1. None of the excipients are prohibited by the *Food and Drug Regulations*.
2. No change in the composition, manufacturing process or drug product specifications.
3. No change to the container closure system or to the recommended storage conditions of the drug product.
4. The change should not be a result of unexpected events arisen during manufacture or because of stability concerns.
5. No change in the route of administration and indication of the drug product.

Supporting Data

1. Letters of Access (e.g., Drug Master Files (DMFs)), if new excipients are included.
2. Product Monograph (e.g., Title Page, Storage and Stability, Dosage Forms, Composition and Packaging, and Pharmaceutical Information section) and Inner and Outer Labels.
3. Confirmation that information on the drug substance has not changed as a result of the submission (e.g., cross reference(s) should be provided to the previously approved drug submission, quoting the date approved and File Number(s)) or revised information on the drug substance, if any of the attributes have changed.
4. Description and composition of the dosage form.
5. Discussion of the components of the drug product, as appropriate (e.g., choice of excipients, compatibility of drug substance and excipients)
6. Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation.
7. Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).
8. Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used), Batch Analyses (certificate of analyses for three (3) batches).
9. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug product, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.
10. Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
11. Executed Production Documents for one batch of each new dosage form or strength, Master Production Documents for the new dosage form or strength.
12. Supporting field study data or a request for a waiver of *in vivo* studies.
13. For a new device (e.g., pre-filled syringes or pens), information to the Medical Device Bureau to qualify the proposed device.
14. Comparability study to justify that there is no change in potency of the product with proposed change.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the manufacturing process of the adjuvant	1	1-9	Notifiable Change

Conditions:

The change does not concern the source of the adjuvant.

Supporting Data

1. Product Monograph (title page, "Dosage Forms, Composition, and Packaging" section).
2. Inner and Outer Labels.

3. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the changed adjuvant.
4. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed adjuvant.
5. Process validation and/or evaluation studies (e.g., for manufacturing of the adjuvant).
6. Description of the general properties, characteristic features and characterization data of the product.
7. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the drug product with the approved and changed adjuvant, as applicable.
8. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed adjuvant, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.
9. Supporting non-clinical and clinical data.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in diluent, involving:			
a. replacement or addition of a source of a diluent	None	1-3	Notifiable Change
b. deletion of a diluent	None	None	Annual Notification

Conditions:

None

Supporting Data

1. Demonstration that the changed diluent results in the same properties of the product as with the approved diluent.
2. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed diluent.
3. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed diluent, or longer if less than three (3) time points are available, and updated stability of the product reconstituted with the new diluent.

4.2.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Changes involving a drug product manufacturer/manufacturing facility:			

a. replacement or addition of a drug product manufacturing facility	None	1-11	Supplement
b. replacement of a formulation/filling suite	1, 2, 3, 6,7	1-11	Notifiable Change
c. addition of an identical formulation/filling suite	1	1-11	Notifiable Change
d. replacement of a secondary packaging/ labelling/storage and distribution facility	2-3	1,2,4	Annual Notification
e. deletion of a drug product manufacturing facility	None	None	Annual Notification
f. Scale-up of the manufacturing process at the formulation/filling stage	4-7	5-8,12	Notifiable Change

Conditions:

1. The formulation/filling facility is a DCG(I) approved facility.
2. No change in the composition, manufacturing process or drug product specifications.
3. No change in the container/closure system.
4. The scale-up uses the same approved equipment.
5. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch-size (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized).
6. The change should not be a result of unexpected events arisen during manufacture or because of stability concerns.
7. The change does not affect the sterilization procedures of a sterile drug product.

Supporting Data

1. GMP and Establishment Licence information.
2. Updated or new DMF (with a Letter of Access) or relevant drug product information.
3. Confirmation that information on the drug product has not changed as a result of the submission (e.g., other than change in facility) or revised information on the drug product, if any of the attributes have changed.
4. Name, address, and responsibility of the changed production facility involved in manufacturing and testing.
5. Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the changed drug product.
6. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product, including technology transfer validation, equipment qualification, media fills, as appropriate.
7. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug product.

8. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug product, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCG(I) of any failures in the ongoing stability studies.
9. Information on the changed production facility involved in manufacturing and testing of the drug product, including cleaning and shipping validation, as appropriate.
10. Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as applicable.
11. Results of the environmental monitoring studies in classified areas.
12. Master Production Documents for each proposed strength, batch size, and manufacturing facility.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in a facility involved in the manufacture of a drug product, such as			
a. conversion of a drug product manufacturing facility from single-product to multi- product	1, 2, 3	1-3	Notifiable Change
b. conversion of production and related area(s) from campaign to concurrent for multiple product manufacturing areas	1	1-2	Notifiable Change
c. introduction of new product into an approved multi- product formulation/ filling suite	2,3	1-3	Annual Notification

Conditions

1. The manufacturing process is a closed process.
2. The newly introduced product has the same prophylactic, therapeutic or related classification.
3. The maximum allowable carry-over is not affected by the introduction of the new product.

Supporting Data

1. Information on the cleaning procedures (including validation) demonstrating lack of carry-over or cross-contamination.
2. Information describing the change-over procedures for shared product-contact equipments or the segregation procedures, as appropriate.
3. Information on the product(s) which share the same equipment (e.g., therapeutic classification).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in equipment used in drug product manufacturing process, such as:			

a. addition of new product- contact equipment used in a critical step (e.g., lyophilizer)	None	1-3	Notifiable Change
b. product-contact equipment change from dedicated to shared (e.g., formulation tank lyophilizer)	None	1,3,4	Notifiable Change

Conditions

None

Supporting Data

1. Information on the in-process control testing.
2. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product, including technology transfer validation, equipment qualification, media fills, as appropriate.
3. Information demonstrating qualification of the equipment or qualification of the change.
4. Information on the cleaning procedures (including validation) demonstrating lack of carry-over or cross-contamination.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates			
a. deletion of a test	None	1,4-5	Notifiable Change
	5	1,4-5	Annual Notification
b. replacement or addition of a test	None	1-5	Notifiable Change
	1-4	1-5	Annual Notification
c. relaxation of an acceptance criterion	None	1-5	Notifiable Change
	1-4	1-5	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change does not affect the sterilization procedures of a sterile drug product.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.

Supporting Data

1. Description of the changed process controls or acceptance criteria.
2. Description of the changed process controls or acceptance criteria of the critical steps and intermediates.

3. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product.
4. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least one production scale batch.
5. Master Production Documents.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the approved protocol for process validation and/or evaluation studies	1	1	Notifiable Change
	1,2	1	Annual Notification

Conditions

1. The change is to a protocol approved by DCG(I).
2. The change does not affect the sterilization procedures of a sterile drug product.

Supporting Data

1. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product.

4.2.3 Control of Excipients

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the standard claimed for the excipient (e.g., from In-House to pharmacopoeial standard)	None	1-4	Notifiable Change
	1,2,3	1-4	Annual Notification
Change in the specification for the excipient to comply with an updated pharmacopoeial monograph	1-2	1-4	Annual Notification

Conditions

1. The change is made exclusively to comply with the (same) pharmacopoeia.
2. No change to the specification for the functional properties of the excipient (e.g., particle size distribution) or that results in a potential impact on the performance of the drug product.
3. No deletion of or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specification.

Supporting Data

1. Updated excipient specifications.
2. Where an In-House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the House and compendial methods.
3. Justification of the changed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).

4. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in specification for the excipient, involving:			
a. deletion of a test	None	1-4	Notifiable Change
	5	1-4	Annual Notification
b. replacement or addition of an additional test	None	1-4	Notifiable Change
	1-4,6	1-4	Annual Notification
c. relaxation of an acceptance criterion	None	1-4	Notifiable Change
	1,3,4,6	1-4	Annual Notification
d. tightening of an acceptance criterion	1-4,6	1-4	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. Acceptance criterion for any Class 3 residual solvent is within the limits.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The change to the specifications does not affect the functional controls of the excipient (e.g., particle size distribution) nor result in a potential impact on the performance of the drug product.

Supporting Data

1. Updated excipient specifications.
2. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the House and compendial methods.
3. Justification of the changed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).
4. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Changes in the specifications for the excipient, involving the analytical procedure:			

a. deletion of an analytical procedure	None	1,3-4	Notifiable Change
b. replacement or addition of an analytical procedure	None	1-4	Notifiable Change
	3-5	1-4	Annual Notification
c. minor changes to an approved analytical procedure	1-5	1-4	Annual Notification
d. a change from a House analytical procedure to a Pharmacopoeial analytical procedure	1-5	1-4	Annual Notification

Conditions

1. No change in the approved acceptance criteria.
2. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The change does not concern sterility testing.

Supporting Data

1. Updated excipient specifications.
2. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the House and compendial methods.
3. Justification of the changed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).
4. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the source of an excipient from a vegetable or synthetic source to a TSE risk (e.g., animal) source	None	2,3	Supplement
Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	1,2	1,3,5,7	Notifiable Change
Change in manufacture of a biological excipient	1-3	4- 9	Notifiable Change
	2-3	2,3,5-7	Notifiable Change

Conditions

1. No change in the specifications of the excipient or drug product.

2. The change does not concern a human plasma-derived excipient.
3. Properties of the changed excipient are not different from those of the approved excipient.

Supporting Data

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Details of the source or the excipient (animal species, country of origin) and the steps undertaken in processing to minimize the risk of TSE exposure.
3. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the changed excipient with the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the changed excipient.
5. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) production scale batches of the changed excipient and of the drug product with the changed excipient.
6. Results from the stability testing of the changed excipient.
7. Results from the stability testing of the drug product with the changed excipient.
8. Information assessing the risk with respect to potential contamination with adventitious agents.
9. Supporting comparative Field study data.

4.2.4 Control of Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the standard claimed for the drug product (e.g., from a Professed to pharmacopoeial standard)	None	1-6	Notifiable Change
	1,2,3	1-6	Annual Notification
Change in the specification for the drug product to comply with an updated pharmacopoeial monograph	1,2	2 -6	Annual Notification

Conditions

1. The change is made exclusively to comply with the (same) pharmacopoeia.
2. No change to the specification that results in a potential impact on the performance of the drug product.
3. No deletion of or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specification.

Supporting Data

1. Product Monograph (e.g., Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section) and Inner and Outer Labels.
2. Updated, signed and dated, changed drug product specifications.

3. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the House and compendial methods.
4. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least two batches (minimum pilot scale) of the drug product tested according to the changed specification.
5. Justification of the changed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).
6. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for the drug product, involving:			
a. for sterile products, replacing the sterility test with process parametric release	None	1,2,5,8-10	Supplement
b. deletion of a test	None	2,7,9,10	Notifiable Change
c. replacement or addition of a test	None	2-5,7,9,10	Notifiable Change
	1-6	2-5,7,9,10	Annual Notification
d. change in animal species/strains for a test (e.g., new species/ strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)	None	6,7,11	Notifiable Change
e. relaxation of an acceptance criterion	None	2,5,7,9,10	Notifiable Change
	1,3-6	2,5,7,9,10	Annual Notification
f. tightening of an acceptance criterion	1-2	2,5,7,9,10	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. Acceptance criterion for any Class 3 residual solvent is within the limits.
5. The change to the specifications does not result in a potential impact on the performance of the drug product.
6. The change does not concern sterility or potency testing.

Supporting Data

1. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product.
2. Updated, signed and dated, changed drug product specifications.
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Copies or summaries of validation reports, if new analytical procedures are used.
5. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the House and compendial methods.
6. Information demonstrating qualification of the method and comparability with the approved method.
7. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least two batches (minimum pilot scale) of the drug product tested according to the changed specifications.
8. Description of the batches, certificates of analyses, and summary of results, of a sufficient number of batches to support the process parametric release.
9. Justification of the changed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).
10. Demonstration that consistency of quality and of the production process is maintained.
11. Copies of relevant certificate of fitness for use (e.g., veterinary certificate).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for the drug product, involving the analytical procedures:			
a. deletion of an analytical procedure	None	1,3-5	Supplement
b. replacement or addition of an analytical procedure	None	1-5	Notifiable Change
c. minor changes to an approved analytical procedure	1-4	1-5	Annual Notification
d. change from a House analytical procedure to a Pharmacopoeial analytical procedure	1-4	1-5	Annual Notification

Conditions

1. No change in the approved acceptance criteria.
2. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. The change does not concern sterility testing.

Supporting Data

1. Updated, signed and dated, changed drug product specifications.
2. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the In-House and compendial methods.
3. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least two batches (minimum pilot scale) of the drug product tested according to the changed specification.
4. Justification of the changed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).
5. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Changes affecting the quality control (QC) testing:			
a. transfer of the QC testing responsibilities for a non-pharmacopoeial assay (in- house) to a new company	None	1,2	Notifiable Change
b. transfer of the QC testing responsibilities for a pharmacopoeial assay (in- house) to a new company	None	1,2	Annual Notification
c. transfer of the QC testing responsibilities for a pharmacopoeial or a non- pharmacopoeial assay to a different facility (same company)	1	1,2	Annual Notification
d. introduction of additional laboratory facility in a facility to perform drug product testing	None	2	Annual Notification

Conditions:

1. The new QC testing site/facility is under the same QA/QC oversight

Supporting Data

1. Updated or new DMF or relevant drug product information.
2. Information demonstrating technology transfer validation and equipment qualification, as appropriate.

4.2.4Reference Standards or Materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Qualification of a reference standard	None	1	Notifiable Change

Subsequent qualification of a reference standard	2,3	1	Annual Notification
Update the reference standards from pharmacopoeial to House	1	1	Notifiable Change
Update the reference standards from In-House to pharmacopoeial	2,3	1	Annual Notification

Conditions

1. The House reference standard is validated against an official (e.g., pharmacopoeial) reference standard.
2. Qualification of the reference standard is performed according to the approved protocol (i.e. no deviation from the approved protocol)
3. The reference standard is not for a bacterial or a viral vaccine

Supporting Data

1. Information demonstrating qualification of the changed reference standards or materials (e.g., source, characterization, certificate of analysis).

4.2.6 Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Modification of a container closure system (e.g., new coating, adhesive, stopper)	None	1- 7	Notifiable Change
	1- 3	1-7	Annual Notification
Change from approved single dose container to multi-dose container	1	1-7	Notifiable Change
Deletion of a container closure system	None	1,3	Annual Notification

Conditions

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.
3. The change is made only to improve quality of the container (e.g., increase thickness of the glass vial).

Supporting Data

1. Product Monograph (e.g., Title Page, Storage and Stability, Dosage Forms, Composition and Packaging) and Inner and Outer Labels.

2. For sterile products, process validation and/or evaluation studies.
3. Information on the changed container closure system (e.g., description, materials of construction of primary packaging components, specifications).
4. Stability Summary and Conclusions, e.g.,
    - For a moderate change to the container closure system (e.g., change in fill weight / fill volume): 3 months long term/3 months accelerated data and, where applicable, results of photo stability studies.

- For a minor change to the container closure system: stability data at the time of filing would not be necessary (see below).

5. Updated post-approval stability protocol and stability commitment to place the first production scale batch of each strength of the changed product into the long term stability programme (bracketing and matrixing could be applied, if scientifically justified).
6. Information demonstrating suitability of the changed container/closure system (e.g., results from last media fills, preservation of protein integrity, and maintenance of the sterility in multi-dose container).
7. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity test.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the supplier for a container closure component, involving:			
a. replacement or addition of a supplier	None	1-3	Notifiable Change
	1,2	3	Annual Notification
b. deletion of a supplier	None	3	Annual Notification

Conditions

1. No change in the type of container closure, materials of construction, shape, dimensions or specifications.
2. The change does not concern a sterile container closure component.

Supporting Data

1. Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing)
2. For sterile products, process validation and/or evaluation studies.
3. Information on the changed container closure system (e.g., description, materials of construction of primary packaging components, specifications).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for a primary container closure component, involving:			
a. deletion of a test	None	1	Notifiable Change
b. replacement or addition of a test	None	1	Notifiable Change
	1-3	1	Annual Notification
c. relaxation of an acceptance criterion	None	1	Notifiable Change
d. tightening of an acceptance criterion	1,2	1	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of previously approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

Supporting Data

1. Updated changed specifications, including justification.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for a primary container closure component, involving analytical procedures:			
a. deletion, replacement or addition	3	1,2	Notifiable Change
b. minor changes	1-5	1,2	Annual Notification

Conditions

1. No change in the approved acceptance criteria.
2. The analytical procedure is of the same type.
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The change does not concern sterility testing.

Supporting Data

1. Updated changed specifications, including justification.
2. Description of the analytical procedure and, if applicable, validation data.

4.2.7 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the re-test period (or shelf life) for the drug product, involving:			
a. Extension	1,4,5,6	1-4,6-7	Notifiable Change
	1,2,3,5,6	1,2,5	Annual Notification
b. Reduction	1,5	1-5	Notifiable Change
c. Addition of storage condition for the drug product	1	1-5	Notifiable Change

Conditions:

1. No change to the container closure system in direct contact with the drug product or to the recommended storage conditions of the drug product.
2. The approved re-test period (or shelf life) is at least 24 months.
3. Full long term stability data *is* available covering the changed re-test period (or shelf life) and are based on stability data generated on at least three production scale batches.

4. Full long term stability data *is not* available covering the changed re-test period (or shelf life) or *is not* based on stability data generated on at least three production scale batches.
5. Stability data generated in accordance with the approved stability protocol.
6. Significant changes were not observed in the stability data.

Supporting Data

1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. Proposed storage conditions and re-test period (or shelf life, as appropriate).
3. Updated post-approval stability protocol and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (i.e., full real time/real temperature stability data covering the changed re-test period (or shelf life) generated on at least three (3) production scale batches).
6. Results of stability testing (i.e., less than full real time/real temperature stability data covering the changed re-test period (or shelf life) and/or generated on less than three (3) production scale batches), and a commitment to submit the stability report when completed and to notify DCG(I) of any failures in the on-going stability studies.
7. In case of imported product, copy of the approval from the country of origin or any other developed country.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the labelled storage conditions for the drug product or the diluted or reconstituted product, involving:			
a. addition of a cautionary statement	None	1	Notifiable Change
b. deletion of a cautionary statement	1	1	Notifiable Change
c. relaxation of a temperature criterion	None	1	Notifiable Change
d. tightening of a temperature criterion	1	1	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Supporting Data

1. If applicable, stability testing results to support the change to the storage conditions.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category

Change to the post-approval stability protocol or stability commitment	None	1-4	Notifiable Change

Conditions
None

Supporting Data

1. Proposed storage conditions and shelf life.
2. Updated post-approval stability protocol and stability commitment.
3. Justification of the change to the post-approval stability protocol or stability commitment.
4. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment.

4.3 Efficacy

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the Efficacy parameter:			
a. New indication	1	1-4	Supplement

Conditions

1. No change in strength, dosage form and route of administration.

Supporting Data

1. Published data along with preclinical data.
2. Copy of EMEA approval with new indication or any other regulatory certificate issued by NRA or country of origin with new indication.
3. Copy of approved PI with new indication,
4. Published data or relevant literature on new indication.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the route of administration :			
a. New route of administration	1	1-4	Supplement

Conditions

1. No change in strength, dosage form and indication.

Supporting Data

1. Published data along with preclinical data.
2. Copy of EMEA approval with new indication or any other regulatory certificate issued by NRA or country of origin with new route of administration.
3. Copy of approved PI with new route of administration.
4. Published data or relevant literature on new route of administration.

5. APPENDICES

Appendix 1: Glossary

Container closure system:

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Critical manufacturing step:

A manufacturing process/step that may results in a potential change in the purity/impurity profile or due to the nature of the starting materials or resulting product/intermediate, requires containment within a specially designed manufacturing area or production facility, for example, the development and preparation of cell banks and seed lots, initial propagation, scale-up, blood and plasma pooling and fractionation, fermentation, harvesting, inactivation, purification, addition of adjuvants or preservatives, the conjugation and pooling of bulk concentrates and the final preparation of drug product including concentration/ diafiltration, formulation, sterile filtration, filling and lyophilization.

Dosage form:

A drug product that has been processed to the point where it is now in a form in which it may be administered in individual doses.

Drug product:

The dosage form in the final immediate packaging intended for marketing.

Drug substance:

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Equivalent equipment:

Equipment with the same technical parameters and fabricated with product-contact material of same or higher grade quality. Equivalent equipment should give a product of same quality as the one processed by the previous equipment.

Excipient:

Anything other than the drug substance in the dosage form.

Facility:

A building in which a specific manufacturing operation or multiple operations take place, and for the purposes of this guidance only, the product-contact equipment housed within the aforementioned building.

In-process control:

Check performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as part of in-process control.

Multi-product facility:

A facility where more than one product of the same type or products from different classes are fabricated (e.g., pharmaceutical and biological products).

Non-critical manufacturing step:

A manufacturing process/step that has no impact upon purity and impurity profile or requires no specific facility considerations, for example, buffer and media preparation, storage of intermediates, and packaging (note that some biological products may require critical temperature and/or light control during packaging).

Pilot scale:

A batch of a drug substance or medicinal product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale.

Presentation:

Container that contains the drug product. The container may be used directly or indirectly in the administration of the drug (e.g., vials, pre-filled syringes, pre-filled pens).

Reprocessing:

Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications.

Re-test period:

For biologics, also sometimes known as shelf life.

Shelf life (also referred to as expiration period):

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Strength:

Quantity of medicinal ingredient in a single dose.

Validation:

The documented act of demonstrating that any procedure, process, and activity will consistently lead to the expected results. Includes the qualification of systems and equipment.

GUIDELINES FOR STABILITY TESTING OF VETERINARY BIOLOGICAL DRUG SUBSTANCES AND DRUG PRODUCTS

1.1 Objective

These guidelines seek to exemplify the core stability data package required for registration of biological new drug substances and drug products, However, alternative approaches can be found in when they are scientifically justified.

It is recommended that these guidelines should also be applied to products that are already being marketed, with allowance for an appropriate transition period, e.g. upon re-registration or upon re-evaluation.

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.

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 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.

Stability testing of new Veterinary Biological drug substances and formulations:

1.) General case

Study conditions for Veterinary Biological drug substances and formulations intended to be stored under general conditions

Study	Storage condition	Minimum time period covered by data at submission
Long-term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months or 6 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.

2.) For storage in a refrigerator

Study conditions for Veterinary Biological drug substances and formulations intended to be stored in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated*	25°C ± 2°C/60% RH ± 5% RH	6 months

***For live vaccines, since accelerated temperature is not appropriate, stability studies to be carried out in real time temperature**

3). For storage in a freezer

Study conditions for Veterinary Biological drug substances and formulations intended to be stored in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	12 months

For drug substances intended for storage in a freezer, the retest period should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

4). For storage below -20°C

Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

2. General

The design of the formal stability studies for the drug product should be based on knowledge of the behaviour and properties of the drug substance (API), results from stability studies on the drug substance, and experience gained from pre-formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2.1. Selection of Batches

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. In the case of conventional dosage forms with APIs that are known to be stable, data from at least two primary batches should be provided.

Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container type and size of the drug product unless bracketing or matrixing is applied. Other supporting data can be provided.

2.2. Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.3. Specification

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Analytical procedures should be fully

validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage.

2.4.Analytical methods

A systematic approach should be adopted to the presentation and evaluation of stability information, which should include, as necessary, physical, chemical, biological and microbiological test characteristics.

Analytical methods should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. The assay methods chosen should be those indicative of stability. The test of related compounds or products of decompositions should be validated to demonstrate that they are specific to the products being examined and are of adequate sensitivity.

2.5.Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs (i.e., matrixing or bracketing), where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

2.6. Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical,

chemical, biological, and microbiological tests, including particular attributes of the dosage form.

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

2.7.In- use stability

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those which occur in practice appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The physical, chemical and microbial properties of the FPP susceptible to change during storage should be determined over the period of the proposed in-use shelf-life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf-life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semi-solids, preservations, per content and effectiveness, need to be studied.

A minimum of two batches, at least pilot-scale batches, should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf-life. If such results are not available, one batch should be tested at the final point of the submitted stability studied.

This testing should be performed on the reconstituted or diluted FPP throughout the proposed in-use period on primary batches as part of the stability studied at the initial and final time points and, if full shelf-life, long-term data are not available before submission, at 12 months or the last time point at which data will be available.

2.8. Stability Commitment

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.

- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

3.GLOSSARY / DEFINITIONS

The following definitions are provided to facilitate interpretation of the guidance.

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer term chemical effects at no accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Batch: The design quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Bracketing: The design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all-time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Commitment batches: Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Container closure system: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage form: A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient: Anything other than the drug substance in the dosage form.

Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Formal stability studies: Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Long-term testing: Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labelling.

Matrixing: The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Pilot scale batch: The production of the drug substance or drug product by a procedure fully representative of and simulating that to be applied at manufacturing scale. The methods of cell expansion, harvest and product purification should be identical except for the scale of production.

Primary batch: A batch of a drug substance or medicinal product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a medicinal product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch: A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Shelf-life (also referred to as expiration dating period): The time period during which a medicinal product is expected to remain within the approved shelf life

specification, provided that it is stored under the conditions defined on the container label.

Retest period: The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period.

Semi-permeable containers: Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Guidance Document
For Import and Registration of Biological bulk drugs and finished formulations in India

A. Preface

In India import, manufacturing, sale and distribution of drug is regulated under Drugs and Cosmetics Act 1940 and Drugs and Cosmetic Rules 1945 (hereinafter refer as Act) made there under. At present, bulk drug (Active Pharmaceutical Ingredients) and finished formulations are regulated under the said Act. Any substance falling within the definition of drug (Section 3b of the Act) required to be registered before import into the country. Not only drug but the manufacturing site needs to be registered for import. If the drugs, fall within the definition of New Drug (Rule 122 E of the Act), the new drug approval is the pre-requisite for submission of application for Registration and or import of drug. The application for Registration and import can be made to the Licensing Authority under the Act i.e. to the Drugs Controller General (I) at CDSCO, FDA Bhawan, Kotla Road, Near Bal Bhawan, New Delhi by the Local Authorized Agent of the foreign manufacturer having either manufacturing or sale Licence or by the foreign manufacturers' having a whole sale Licence in the country.

This guidance document is intended to provide non -binding guidance for use in the Import & Registration of bulk drug(s) and finished formulation(s) of Veterinary Biologicals in India.

I.PURPOSE:

To provide guidance for submission of application in Form 40 to CDSCO for Registration Certificate and issuing Licence for import of drugs into India with CDCSO authority India, for issuance of import registration certificate for import of drugs into India.

II.SCOPE:

This guidance is applicable to those drugs manufactured outside India, and the import registration to be issued (under Form 41) by the Central Drugs Standard Control Organization, (CDSCO) Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.

III.REFERENCE:

1. Drugs & Cosmetics Act, 1940 and Rules there under.
2. Schedule D(I) (for registration of the manufacturing Premises)
3. Schedule D(II) (for registration of the drugs).

IV.RESPONSIBILITY:

CDSCO: For implementing and to revise the same as notified, from time to time by the authority.

V.GUIDANCE:

1. An application shall be made to the Licensing Authority in Form 40, either by the manufacturer himself, having a valid wholesale Licence, for sale or distribution of drugs or by his authorized agent in India either having a valid Licence to manufacture for sale of a drug or having a valid wholesale Licence for sale or distribution of drugs.

1. **DETAILS TO BE CAPTURED IN FORM 40:**

The authorized signatory name, designation, department, along with the complete address of the Company.

i) Authorized Signatory:

The person authorized preferably Director approved by the Board of Directors in case of company or by the proprietor in case of proprietorship firm. The application to accompany affidavit in respect of authorized person or the Power of Attorney in the name of the authorized person.

The Form shall detail the Foreign Manufacturer's contact person in the manufacturing site complete address, (i.e. address of the manufacturing premises), with corporate office address, along with the Telephone number, Fax number and E-mail address.

ii) The address of manufacturing premises shall be captured as below:

Undertaking on the document contents by the responsible person at the manufacturing site (contact person in the manufacturing site)

- In respect of import of more than one drug or class of drugs manufactured by the same manufacturer, provided that drug or the classes of drugs, are manufactured at one factory or more than one factory functioning conjointly as a single manufacturing unit.
- In respect of the drugs manufactured in two or more factories situated in different places, for the manufacturing of the same or different drugs the name and address of both the manufacturing site should be included e.g. if the tablets are manufactured at one location and packed at another location, Name and Address of both the locations indicating the activity of each location.

The Form shall contain the complete and correct Name of the Drugs to be imported in India.

iii) The drug(s) name shall be captured as below:

- The brand name shall be captured.
- Different pack, pack size and/or different strengths of the same brand shall be captured.

Importer's undertaking letter declaring for the information specified in Schedule D (I) and Schedule D (II), provided by the original manufacturer.

iv) Fee structure for Import Registration under Form 40:

- Fees and Form(s) and the undertakings as per Schedule D(I) (for registration of the manufacturing premises) and Schedule D(II) (for registration of the drugs):
- Applicant shall make a payment of 10000 USD (or its equivalent to Indian Currency), as registration fee for the Manufacturing premises.
- Applicant shall make a payment of 5000 USD (or its equivalent to Indian Currency), as registration fee for a single drug and additional fee of 5000 USD for each additional drug in case the manufacturing site remains the same. Fees shall be paid through Bharatkosh payment mode or other modes as notified from time to time by the authority.

- Applicant is liable to pay 25000 USD (or its equivalent to Indian Currency) for Expenditure [Inspection fees + expenditure on inspection to be borned by company] as may be required for Inspection or Visit of manufacturing premises.
- 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 required for examination testing and analysis of drugs.
- Applicant has to pay a fee of one thousand eight hundred US Dollars (or its equivalent to Indian Currency) for making amendment in the registration certificate and for a duplicate copy of the registration certificate, if the original is defaced, damaged or lost.
- Registration time provided further that if the application is complete in all respects and information specified in D (I) & D (II) are in order, the licencing authority shall within 9 months from the date of receipt of application issue such Registration Certificate, and in exceptional circumstances and for the reasons to be recorded in writing, the Registration Certificate may be issued within such extended period not exceeding 3 months as the licencing authority may deemed fit.
- Undertaking for the compliance of the terms and conditions required, by the applicant to obtain the registration certificate and to keep the validity of the registration certificate
- The data specified in Schedule D (I) and Schedule D (II) shall be enclosed along with the covering letter and Table of content

v) Details to be captured in the Covering Letter:

- Information of the drugs to be imported
- Manufacturer information like address and contact details
- Brief information about the applicant and list of documents
- Document for the submission of the fees through Bharatkosh payment mode or other modes as notified from time to time by the authority
- Form 40
- Schedule D(I) documents as provided by the drug(s) manufacturer (Module 1 of CTD format)
- Schedule D(II) documents as provided by the drug(s) manufacturer (Module 2 to 5 of CTD format)
- Power of Attorney issued by the manufacturer
- Copy of Whole Sale Licence of Applicant
- Copy of Authorization letter of Applicant
- An Undertaking shall be submitted by the proprietor of the firm in case of proprietorship firm and in case of Private Limited Company, by the board of Directors.

B. Requirements for Common Submission Format for Registration of bulk drug(s) and finished formulation(s) in India

The following documents are required to be submitted in the following manner and order for the Import & Registration of the bulk drug(s) and finished product(s) in India:

Applicants are requested to submit application in 3 or more different files as follows:

1. **Covering Letter–** The covering letter is an important part of the application and should clearly specify the intent of the application (whether the application for the registration of the manufacturing site is being submitted for the first time, whether the application is for re-registration/renewal or is for the endorsement of additional products to an existing Registration Certificate) the list of documents that are being submitted (Index with page no's) as well as any other important and relevant information may be provided in the covering letter. The covering letter should be duly signed and stamped by the authorized signatory, indicating the name & designation of the authorized signatory along with the name and address of the firm. Any exemption to the submission requirement be clearly specified in the covering letter on the firm/company letter head and justified in the submissions.

2. **An Authorization letter** in original issued by the Director/Company Secretary/Partner of the Indian Agent firm revealing the name & designation of the person authorized to sign (along with the name and address of the firm) legal documents such as Form 40, Power of Attorney etc. on behalf of the firm should be submitted at the time of submission of the application for registration (Rule122A). It should have validity period as per company's policies. Duly self-attested photocopies of the Authorization letter may be submitted at the time of submission of subsequent applications.

3. A duly filled Form 40 as per the performa prescribed in the Drugs & Cosmetics Rules, signed & stamped by the (Local Authorized Agent/manufacturer) along with name & designation and date. Form -40 Should be signed by the (Local Authorized Agent or manufacturer and should have valid sale or manufacturing Licence in India.

4. Fees through Bharatkosh payment mode or other modes as notified from time to time by the authority.

5. **Power of Attorney -** The authorization by a manufacturer to his 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 along with the application for Registration Certificate. Apostille Power of Attorney from Hague convention member countries is also acceptable. Performa for Power of Attorney is enclosed at Annexure. The authorized agent will be responsible for manufacturer 's business activity, in India.

While submitting the Power of Attorney, the following points should be kept in mind: -

- It should be co-jointly signed and stamped by the manufacturer as well as the Indian Agent indicating the name & designation of the authorized signatories (along with the name and address of the firm).
- It should clearly list the names of all the proposed drugs if possible along with their specific Indication and/or intended use. Further, the names of the proposed drug should correlate with those mentioned in the Form 40, Free Sale Certificate or Certificate of pharmaceutical product (COPP) as per WHO-GMP certification scheme.
- The names & addresses of the manufacturer (Contract manufacturer name from different sources) as well as the Indian Agent stated in the Power of Attorney should correlate with the Form 40. Multiple sites are in tabular form.
- It should be valid for the period of said Registration Certificate. It implies that a fresh POA is to be submitted at the time of re-validation of RC.

6. A duly attested/notarized (in India) and valid copy of Wholesale Licence for sale or distribution of drugs under Drugs and Cosmetics

Rules in Form 20B & 21B or its renewal in Form 21C issued to the manufacturer (subsidiary office/representative of the parent company or its agent by the State Licensing Authority in India. If the agent is a manufacturer, a duly attested / notarized (in India) and valid copy of manufacturing Licence issued by the State Licensing Authority.

7. **Schedule D(I)** undertaking as per the performa prescribed in the Drugs & Cosmetics Act & Rules, signed & stamped by the manufacturer/Authorized agent indicating the name and designation of the authorized signatory is required to be submitted as per performa for Schedule D(I) is enclosed at Annexure IV along with CTD module 1 covering the Schedule D(I) requirement.

8. **Modules 2-5 covering the schedule D (II) requirements**

Standard of drug: Second Schedule of the Act prescribes standards to be complied with by imported drugs and by drugs manufactured for sale / sold stocked or exhibited for sale or distributed in the country. If the drug is in IP it must meet the standards of identity, purity and strength otherwise USP, BP or EP.

9. **Label submission**:

True copy of label as per Rule 96 of the Act. If the product is not mentioned in any of the pharmacopoeia, then internal standards should be specified along with supporting data like identity, purity, strength and in such a case the approval of the drug or biological from the country of origin or where registered should be detailed with necessary documentation.

Testing of drugs:

– In case of registration of product, if the product is certified by NRA in the country of origin then consecutive three batches can be certified by notified laboratory before marketing in India.

The applicant shall pay the fee to the notified laboratory as per the norms.

The applicant should enclose adequate samples for reanalysis purpose from each of the three consecutive batches along with specifications, Method of analyses, COA tested in their laboratory, impurity Standards, marker compounds, Reference Standard along with its COA where ever applicable

10. **Duly notarized/Apostilled/Attested (by Indian Embassy the country of origin**) and valid copy of **Free Sale Certificate/Certificate to Foreign Government/ Certificate of Marketability**/for each drug issued by the National Drug Regulatory Authority of the country of origin. Free Sale Certificate should state that the proposed drug is freely sold in Country of Origin and can be legally exported.
In case the drug is manufactured in one country but not sold in that country and hence the Free Sale Certificate is not issued by the Country of Origin, then the Free Sale Certificate can be obtained from any developed country where the drug is registered and freely marketed.

11. **Duly notarized/Apostilled/Attested (by Indian Embassy the country of origin)** and valid copy of **GMP Certificate of WHO guideline** or **Certificate of Pharmaceutical Product (COPP)** as per WHO GMP Certification Scheme/ **Product Registration Certificate issued by NRA** and or proof of **DMF approval by NRA** and / or **CEP (EDQM certificate**) for each drug issued by the National Drug Regulatory Authority of the country of origin. Format for COPP is enclosed at Annexure.

12. **Duly notarized/Apostilled/Attested** (by Indian Embassy the country of origin) and valid copy of the **Manufacturing Licence and or Market Authorization Certificate** in respect of applied drugs issued by the National Drug Regulatory Authority of the country of origin). Free sale certificate of other countries if available is also be submitted.

13. **Duly notarized/Apostilled/Attested** (by Indian Embassy in the country of origin) and valid copy of **Product Registration Certificate** wherever applicable in respect of the foreign manufacturing sites)

Note:

a. Soft copy of the **Plant Master File** and **Drugs Master File** may also be submitted along with the application.
b. All certificates submitted should be within the valid period.
c. All the regulatory and legal documents may be provided as a separate file and Plant Master File and Drug Master File may be provided as separate files.
d. In case, the item considered as drug as per the definition of section 3 (b) of the Act in India but not registered as drug in the country of origin a legal undertaking from the manufacturer and approval of the item from the competent authority of the country of origin duly notarized and apostilled should be submitted.

e. The application of r-DNA products should be made separately as per the guidance document for submissions for biological.
f. In case of bulk drug, if the same is approved in EU/USA etc. DMF approval number may mention on the covering letter itself.
g. In case of toll manufacturer to be registered for a drug, the POA should be signed by the Market Authorization holder (legal manufacturer) in the country of origin. Agreement should be submitted as a proof that the legal manufacturer has agreement with the toll manufacturer to manufacture the products.
h. POA should be supplemented with declarations in respect of sites involved in the manufacturing and testing of the applied drugs as per the format given hereunder:

a. **For Biological Bulk Drugs (API)**

Name of site Intermediates are manufactured	Name Where API is manufactured Name	Name of site where API tested	Name where packed	Name Dispatch site of API

b. **For Finished Formulations (FF)**

Name of API source	Name of site Where formulation is made	Name of site Of Packing Name of site	Name of site of Secondary packing	Name of site of testing and Release	Name of Dispatch site of FF

14. **Renewal of registration or re-registration:**

At the time of application for renewal of registration or re-registration, the application is to be made 9 months before the expiry of the Registration Certificate. In addition, regulatory documentary compliance like Form 40, POA, GMP / COPP, Registration certificate, DMF (soft copy if no change), Licence (sale or manufacturing Licence of drugs of the agent) etc., the following undertaking / information is to be submitted:

i. Undertakings by the manufacturer or his authorized agent in India in respect of any administrative action taken due to adverse reaction, viz. market withdrawal, regulatory restrictions, or cancellation of authorization, 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.

ii. Undertaking by the manufacturer or his authorized agent in India in respect 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.
iii. Undertaking by the manufacturer or his authorized agent in India in respect of any change in the constitution of the firm including name and /or address of the registered office/ factory premises operating under this Registration Certificate.
iv. Details of drugs imported in India during last three years.
v. Submission of original RC issued.

C. **Requirements for Common Submission Format for Import Licence in Form 10 of Bulk Drug (s) and Finished Formulation (s) in India.**

The following documents are required to be submitted in the following manner and order for issue of the Import Licence in Form 10 of the drugs for import into India: -

1. **Covering Letter**– The covering letter is an important part of the application and should clearly specify the intent of the application (whether the application for the Import Licence in Form 10 of the proposed drug is being submitted for the first time or the application is for renewal). The list of documents that are being submitted (Index with page no's) as well as any other important and relevant information may be provided in the covering letter. The covering letter should be duly signed and stamped by the authorized signatory, indicating the name & designation of the authorized signatory along with the name and address of the firm.
2. **An Authorization letter**- in original issued by the Director/Company Secretary/Partner of the Indian Agent firm revealing the name & designation of the person authorized to sign (along with the name and address of the firm) legal documents such as Form 8 and Form 9 etc. on behalf of the firm should be submitted at the time of submission of the application for Import Licence. It should have validity period as per company's policies.

Duly attested photocopies of the Authorization letter may be submitted at the time of submission of subsequent applications.

3. **Form 8 -** A duly filled (Application for Licence to import drugs (excluding those specified in Schedule X) to the Drugs and Cosmetic Rules, 1945) as per the Performa prescribed in the Drugs & Cosmetics Rules, duly signed & stamped by the Indian Agent along with name & designation of the authorized signatory. Form 8 Performa is enclosed at Annexure.
4. **Form 9**- A duly filled and Notarized (Form of undertaking to accompany an application for an Import Licence) as per the Performa prescribed in the Drugs &Cosmetics Rules, signed & stamped by the Authorized Agent or manufacturer with name & designation of the authorized signatory. If the Form -9 is issued by the manufacturer, it should be duly notarized and authenticated from Indian Embassy of the country of origin. Form 9 Performa is enclosed at Annexure.

b) I legally undertake to state that the Form-9 undertaking with respect to the manufacturing site M/s…….. and the product submitted along with the Form-8 has been issued by the competent person of the firm M/s……..

Deponent

VERIFICATION

Verified on this day of (Month), (Year) that the contents of my above Legal Undertaking are true and correct and that no part of it is false and nothing material concealed in form.

Deponent

5. **Requisite Fee**- As prescribed in the Drugs & Cosmetics Act &Rules viz. Rs.10000 for 1 proposed Drug and Rs.1000 for each additional Drug to be imported may be submitted through Bharatkosh payment mode or other modes as notified from time to time by the authority. The Receipt is required to be submitted along with the application for Import Licence.
6. **A duly attested** (by gazetted officer)/notarized (in India) and valid copy of **wholesale Licence for sale or distribution** of drugs or manufacturing Licence (should be enclosed with the product permission list), under Drugs and Cosmetics Rules issued by the State Licensing Authority.
7. A Valid copy of Registration **Certificate in Form 41** issued by CDSCO with respect to proposed Drug, duly authenticated by Indian Agent.
8. The required documents as per Registration Certificate in Form 41 issued by the CDSCO. (If Applicable)

NOTES:

- Name and address of the manufacturer, manufacturing premises, Indian Agent and drug(s) proposed to be imported should correlate with the name mentioned in the Registration Certificate in Form 41.
- If an endorsement to an existing Licence is required, copy/details like Licence no., date of issue & validity) of the
- Form 10 Licence along with its endorsements should be furnished along with the application.
- All Form-9 issued by foreign manufacturer will be sent for verification to Indian Agent being responsible for business activities of the foreign manufacturer in the country in all respects.
- At the time of application for renewal of registration or re-registration, the application is to be made 3 months before the expiry of the Import Licence. In addition, regulatory documentary compliance like Form 8, Form 9, Copy of Registration certificate, Licence

copy (sale or manufacturing Licence of drugs of the agent) etc., is to be submitted. In addition, following information is required to be submitted.

- Details of drugs imported in India during last three years. Details of sampling of drugs in India and results thereof. Submission of original Import Licence issued.

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 his authorised agent in India shall comply with the conditions of the import Licence issued under the Drugs and Cosmetics 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 24-A.
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.

D. Rules Related to Import and Registration of bulk drug(s) and finished formulation(s) in India.

Rule 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 8-A 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, and shall be accompanied by a Licence fee of ten thousand rupees for a single drug and an additional fee at the rate of 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 one hundred rupees for each drug:
2. Any application for import Licence in Form 8 or Form 8-A, as the case may be, shall be accompanied by a copy of Registration Certificate issued in Form 41 under Rule 27-A.
   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 10-A, as the case may be, without the issuance of Registration Certificate under Rule 27-A, for reasons to be recorded in writing.

   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 fifteen hundred rupees shall be paid for a duplicate copy of the Licence issued under this Rule, if the original is defaced, damaged or lost.]

Rule 24: 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 wholesale 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 ale Licence for sale or distribution of drugs under

these rules, and shall be companied by the fee specified in sub-rule (3) and the information‘s 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 his 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 along with the application for Registration Certificate.

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

   (ii) A fee of five thousand US dollars [or its equivalent in Indian rupees] shall be paid along with the application in Form 40 for the registration of a single drug meant for import into and use in India and an addition fee at the rate of 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 company shall be one thousand US dollars [or its equivalent in Indian rupees] for each drug.

4. The fees shall be paid through a through Bharatkosh payment mode or other modes as notified from time to time by the authority.

5. The applicant shall be liable for the payment of a fee of twenty-five thousand US dollars [or its equivalent in Indian rupees] for expenditure as may be required for inspection or visit of the manufacturing premises or 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 India or abroad, as may be required for examination, tests and analysis of drug.

7. A fee of one thousand eight hundred US dollars [or its equivalent in Indian rupees] shall be paid for amendment in the registration certificate and 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 pharmacopoeial conformity.

Rule 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 sing 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.

Rule 27A: Grant of Registration Certificate-

1. On receipt of an application for Registration Certificate in the Form and manner specified in Rule 24-A, the licensing authority shall, on being satisfied, that, if granted, the conditions of the Registration Certificate will be observed, issue a Registration Certificate in Form 41:
   Provided further that if the application is complete in all respects and information specified in Schedules D-I and D-II 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.

   If the applicant does not receive the Registration Certificate within the period as specified in the 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.]

Rule 28A: Duration of Registration Certificate-

A Registration Certificate, unless, it is sooner suspended or cancelled, shall be 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.

Rule 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 an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, 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 ay, after such enquiry into the matter as it considers necessary and after give the appellant an opportunity for representing his views in the matter, pass such orders in relation thereto as it thinks fit.

Guidance for Test Licence (Form 11)

(A.) INTRODUCTION TO FORM 11 LICENCE

IMPORT OF DRUGS FOR EXAMINATION, TEST OR ANALYSIS—

Test licence or form 11 licence is given for the Small quantities of Veterinary Biological product, the import of which is otherwise prohibited under section 10 of the Drugs and Cosmetics Act and Rules, 1945, may be imported for the purpose of examination, test or analysis subject to the following conditions: —

(*a*) No Veterinary Biological product shall be imported for such purpose except under a licence in Form 11;

(*b*) The licencee 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 licencee 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 licencee 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 licencee 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 of the Act and of which the licensing authority has given to him not less than one month's notice.

Purpose: To harmonize the submission documents for applications seeking for licence to import "Drugs" for test and analytical purposes. This will also facilitate the examiners/ reviewers to take uniform decisions and thereby shorten the application processing time.

Scope: The focus of this guide line is only on drugs for veterinary use which undergo systemic circulation.

Documents to be furnished to the O/o DCG (I) to obtain a Form-11 Licence, are listed below: -

Application in form-12 shall be made or countersigned by: -

i) The Head of the Institution in which the test and analytical works would be carried out, OR
Proprietor or Director of the company or firm by which the tests are to be carried out or any company authorized signatory with copy of authority letter issued by above mentioned designatory should be enclosed with application.

ii) Bharatkosh receipt for the payment of requisite fees.

iii) Justification and utilization break-up, detailing the test parameters vis-a-vis quantities of the drugs, batch manufacturing plan. However, recently this has been observed that in many cases the manufacturers, CROs and other importers are submitting applications for the Import of reasonably large quantities of API and /or drug formulations which do not comply with the provisions of Rule-33. There is no provision as such to define the term "Small Quantity" under this Rule.
However, to facilitate the research and development activities on pharmaceutical products and contract research facilities to boost up the scientific and technological activities in this knowledge based industry, it is decided that import of apparently large quantities of drugs should be justified with test parameters, batch sizes, no. of batches, categories of batches etc. vis-à-vis official monographs, official guidelines only.

DOCUMENTS NEEDED FOR SUBMISSION OF APPLICATIONS FOR GRANT OF FORM 11 LICENCES: -

B.1 **COVERING LETTER**: -

A covering letter is a very important part of the application; it is a letter of introduction attached alongwith application which clearly specifies the purpose for submission of application. A cover letter must contain the following points: -

(i) Name and Address of the firm.
(ii) Purpose of submission.
(iii) List of documents attached with the application.
(iv) Duly signed and stamped by authorized signatory.
(v) Application Reference number.

(B.2) **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 analysiswill be conducted.

(B.3) **Requisite Fee**:-Requisite amount should be paid through Bharatkosh payment mode. A fee of Rs 5000/-for first product and Rs 2000/- for of each additional product (irrespective of strength dosage form and pack size) must be submitted along with the application.

(B.4) **FORM 29** -

Form 29 is a licence to manufacture drugs for the purpose of Examination Testing and Analysis. An application for a licence in Form 29 shall be made to the Licensing Authority appointed by the State Government for the purpose 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. Every application in Form 29 shall be accompanied by a fee of [rupees two hundred fifty].
A licence in Form 29 shall, unless sooner cancelled, be in force for a period of one year from the date of issue, and may thereafter be renewed for periods of one year at a time.

Conditions of licence:
A licence in Form 29 shall be subject to the following conditions-

- The licencee 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;

- The licencee shall allow any [4]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;

- The licencee 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.

Note: -when a firm applying for import of bulk drugs under form 11 licence for the purpose of testing and analysis then they have to submit a copy of valid form 29 in case of New Drug however form 25 with manufacturing permission of same drug going to be imported is needed in case of old drug bulk API. Testing location address mentioned in form 29 must be same as mentioned in form12.

(B.5) **UTILIZATION/JUSTIFICATION**

Quantities of drugs imported under form11 licence should be justified with test parameters, batch sizes; no. of batches, categories of batches etc. utilization/justification submitted by the firm should include the following points:

- Utilization/justification should be duly signed by the Authorized Signatory.
- Details of each testing parameters mentioning the quantity required for each tests.
- If the firm wants to conduct BE studies, then detail utilization Break up for BE studies must be submitted.

Licence to Manufacture Vaccine under Form 28 D (CLAA)

PROCEDURE FOR CLAA APPROVAL OF VETERINARY VACCINES UNDER FORM-28D:

The applicant shall submit the application on Form 27D in triplicate accompanied by a plan of the premises list of equipment's and machinery to be employed for manufacture and testing; Memorandum of Association/Constitution of the firm; copies of qualifications and experience of competent technical staff and documents relating to ownership or tenancy of the premises.

A copy of the application together with the relevant enclosures shall have to be submitted separately to the following authorities:

(i) State Licensing Authority (SLA)
(ii) Concerned Zonal/Sub-Zonal Officers of CDSCO

The list of items indicating names of the drugs should clearly specify the composition, Pharmacopoeial specification as well as pack sizes under which each item is intended to be manufactured.

For new applicants it is necessary that the exact date on which the Unit shall be ready for inspection would be indicated.

The above procedure has been devised for submitting application in triplicate to the different Authorities involved with a view to cut down the gestation period for quick disposal by any one of them the grant or renewal of licences.

STATE LICENSING AUTHORITY (SLA):

On the basis of statement contained in the application form and its verification/scruitinization thereof, SLA shall cause the manufacturing and testing establishment to be inspected in accordance with provisions of rule 79, independently or jointly with CDSCO with or without an expert in the field, as deemed necessary, and on being satisfied that the applicant is in a position to fulfil the requirements as laid down in the said rules, he shall prepare a report to the effect and forward, along with his recommendation, the documents before issuing the licences to the applicant firm, for further approval of by CLAA.

a) 3 copies of the licences in Form 28D in case of a fresh/new licence or 3 copies of the certificate of renewal on Form 26H, as the case may be, accompanied by 3 copies of the list of items proposed to be manufactured (each leaf to be signed and stamped) as well as copies of Report of inspection and verification of the compliance of the improvements made. It would be much desirable if SLA forwards separate sets of licences etc. in cases where the applicant firm is undertaking manufacture of both LVPs and Sera & Vaccines.
(ii) If the SLA is not satisfied, he may, by order, for reasons to be recorded in writing, refuse to grant or renew the licence as the case may be.

(iii) SLA may also keep the Zonal Officer of CDSCO informed on the final action taken on the application received by them and its disposal thereof.

ZONAL/SUB-ZONAL OFFICER OF CDSCO:

i) As the concerned Zonal/Sub-Zonal officers are the pivotal coordination wings of CLAA, he may, on receipt of application and its scrutiny thereof, contact SLA in assisting for quick disposal of the case by proposing further action (like joint inspection etc.)

ii) To take up the matter with the applicant firm in case the application is considered deficient in terms of plant, equipment's etc.

iii) To keep the CLAA informed on the proposed action/inspection carried out etc. by forwarding recommendations on the observations made of the inspection carried out of the applicant firm.

After scrutinizing the documents by the Zonal Office of CDSCO, it may, if so required, carry out further joint inspection along with the SLA and a veterinary expert for GMP inspection of the facility in which the vaccine is being manufactured.

After satisfactory compliance of GMP facility as well as the product the joint inspection team may submit its recommendations in the form of a joint inspection report for granting licensing with class of the vaccine.

The joint inspection report shall be forwarded to the SLA by the concern Zonal office for granting licence in Form 28D,

There after SLA will prepare the FORM 28D licence and same shall be forwarded to the CDSCO for CLAA approval.

Based on the recommendations of joint inspection team observations and further to the satisfaction of the SLA CDSCO may convey CLAA approval in form 28D.

Note: While granting the approval of CLAA on form 28D by CDSCO the manufacture is required to obtained prior Form 46 approval.

FORM 27-D

[See Rule 75]

Application for grant or renewal of a licence to manufacture for sale or for distribution of Large Volume Parenterals / Sera and Vaccines excluding those specified in Schedule X.

1. I/We……...…….of…….…. hereby apply for the grant/renewal of a licence to manufacture for sale or distribution on the premises situated at …… the undermentioned Large Volume Parenterals/Sera and Vaccines, specified in Schedules C and C(1) to the Drugs and Cosmetics 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 and testing of the above mentioned drugs:

(a) Responsible for manufacturing	(b) Responsible for testing
1.	1.
2.	2.
3.	3.

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……....(Applicant)

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.

2. A copy of the application together with relevant enclosures shall be sent to Central Licence Approving Authority and concerned Zonal/Sub-Zonal officers of Central Drugs Standard Control Organisation.

FORM 28-D
[See Rule 76]

Licence to manufacture for sale or for distribution of Large Volume Parenterals/Sera and Vaccines specified in Schedules C and C(1) excluding those specified in Schedule X

Number of licence…… and Date of issue……

1. …… is hereby licenced to manufacture at the premises situated at…….. the following Large Volume Parenterals/Sera and Vaccines specified in Schedules C and C (1) 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.
3.	3.

4. The licence authorise & the sale by way of wholesale dealing and storage for sale by the licencee 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 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.

Dated……

Signature……
Designation
……
Licensing Authority

_____
Central Licence Approving Authority

Conditions of Licence

1. The licence and any certificate of renewal in force 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 licencee wishes to undertake during the currency of the licence to manufacture any drug specified in Schedules C and/or C(I) 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 Licencee 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 along with 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.

FORM 26-H

[See Rules 68-A, 76, 77, 78]

Certificate of renewal of licence to manufacture for sale of Large Volume Parenterals/Sera and Vaccines specified in Schedules C and C(1) excluding those specified in Schdule X.

1. Certified that licence No…….. granted on the…… to …… for the manufacture of following Large Volume Parenterals/Sera and Vaccines at the premises situated at……. has been renewed from……. to…….

2. Name(s) of drug(s)……
…
(each item to be separately specified).

3. Names(s) of competent technical staff:

(a) Responsible for manufacturing	(b) Responsible for testing
1.	1.
2.	2.
3.	3.

Dated……

Signature……
……
Designation
……
Licensing Authority

_____

Central Licence Approving Authority

FIELD TRIALS

INTRODUCTION:

Field trial: A scientific investigation of a veterinary vaccine under field conditions and in target animals (in terms of animal species and categories), using the product as recommended.

The efficacy and safety of veterinary vaccines shall in the first instance normally be demonstrated by experiments under laboratory conditions. It is also stated that, when efficacy cannot be demonstrated by laboratory trials, field efficacy trials alone may be acceptable.
Deviations from these guidelines may be acceptable provided they are scientifically justified.
The guidance should be followed for products intended for use in food-producing and companion animals.

SCOPE:

The scope of this guidance is to advise on how to perform field trials with veterinary vaccines, what criteria shall be taken into account, what data are expected and how the data shall be analysed. This document covers in particular field efficacy trials and, where relevant, safety trials.

APPLICATION FOR A FIELD TRIAL:

The application for field trial along with covering letter and trial protocol with all the supporting documents shall be submitted to CDSCO in hard copy as well as in soft copy.
The CDSCO is obliged to consult with the Department of Animal Husbandry, Dairying & Fisheries (DADF), Ministry of Agriculture and Farmers Welfare (MOA) prior to reaching a decision on an application for a trial.

Note:
The application should be completed by the person responsible to conduct or supervise the trial.

Hard copies: It must be well labelled with document number, name of the firm, date of submission etc. Number of volumes to be labelled as Volume No./ Total number of volumes e.g. if there are five volumes, volume three will be labelled as Volume: 3/5.

Soft Copies: It must be well labelled with document number, name of the firm, date of submission etc. Scanned copies of only signed document like test reports will be acceptable as soft copies. The table of content under each head should be linked to the files (s) or relevant document for easy tracking in CD's.

Firm should preserve/maintain one hard copy and soft copy of submitted documents in his safe custody for any future reference, if required.

Animal Ethics committee approval: Institutional Animal Ethics Committee and CPCSEA Approval of the Centre need to be submitted before initiation of the trial.

IVRI certification of batches to be used in trial: Only IVRI certified batches of the drug product shall be used in the field trial study.

SECTION A – INFORMATION ABOUT THE APPLICANT, TRIAL PERSONNEL AND LOCATION OF TRIAL

Information about the Applicant and Trial Personnel:

Provide details of the proposed licence holder (i.e. the name, address and contact details of the applicant with whom the CDSCO can correspond). In a commercial setting, the applicant may be the company with overall responsibility for the conduct of the trial. In an academic or practice setting, the applicant will usually be the principal investigator or veterinarian responsible for the conduct of the trial.

If the trial is being undertaken by an investigator at the request of a sponsor, the name, address of the sponsor should be provided, together with the name, address and contact details of the trial director with overall responsibility for the conduct of the trial in India.

A brief *curriculum vitae* of the trial director responsible for the conduct of the trial should be provided. The purpose of this information is to ensure that the person concerned has the appropriate qualifications, knowledge and expertise to oversee the conduct of the trial and ensure compliance with any conditions attaching to the CDSCO licence. The information is expected to assist the CDSCO in judging the feasibility of the proposed trial.

If veterinarians, other than those already listed as the trial director, are to be engaged to perform follow up actions in relation to any adverse reactions that might occur as a result of treatment with the test product or in relation to the supervision of animal welfare during the conduct of a trial, their names, addresses and contact details should be provided.

Location details:

Provide the information on the location(s) where the trial is to be conducted. Where various qualifying practices or individual farms are to be used and their location is unknown at the time of application, the expected number of practices and farms and their geographical location should be stated (e.g. 10 companion animal veterinary practices in Leinster, or 50 dairy farms with > 200 cows in county).

SECTION B – INFORMATION ABOUT THE FIELD TRIAL

Trial title:

The title of the field trial should be summarised, where the trial is being conducted to satisfy regulatory requirements.

Trial information:

Parameters:

The parameters to be measured shall be clearly defined in the study protocol and justified in relation to the indications and specific claims for the vaccine.

Conversely, justification shall be given for not measuring parameters that are usually related to the disease concerned.

Two types of parameters exist: the main parameters (e.g. mortality, morbidity, lesions, weight gain, epizootiological impact) and the indicators (e.g. serological response).

For an indicator to be acceptable as a correlate of vaccine efficacy, it shall be shown that a sufficient qualitative and quantitative correlation exists between the indicator measured and the claimed protection in the target species.

If relevant and available, test methods shall be employed that can differentiate naturally infected from vaccinated animals.

Trial protocol:

Contents of The Proposed Protocol for Conducting Field Trial-

1) **Title Page:**
   - Full title of the Field study.
   - Protocol, Study number, and protocol version number with date.
   - The Investigational New Drug (IND) name/number of the investigational drug.
   - Complete name and address of the responsible persons and contract research organization if any.
   - Name and address of the farm(s) and/or facilities participating in the study.

2) **Table of contents:**
   - Background and introduction.
   - Study rationale
   - Study objective (primary as well as secondary) and their logical relation to the study design.
   - Study design–
     a) Overview of the study design: Including a description of the type of study (i.e., multi centre, 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.
   - Study population: the number of subjects required in the study along with a brief description of the nature of the subject population required is also mentioned.
   - Subject eligibility
     a) Flow Inclusion criteria
     b) Exclusion criteria
   - Study assessments – plan, procedures and methods to be described in detail.
   - Adverse Events reporting
   - Study monitoring and supervision

- 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 and labelling 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 or destroyed.
  g) Describe policy and procedure for handling unused investigational products.

- Data Analysis: Provide details of the statistical approach to be followed to achieve efficacy endpoints (primary as well as secondary) and safety endpoints.

Controls and trial design:

The trial shall, unless justified, compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo controls.

Where vaccination of whole herds is proposed the need for this shall be justified. In such cases, comparison with animals vaccinated with a comparator product may be used when available. For modified live vaccines, whose vaccine agent(s) spread, it is necessary to separate vaccinates from controls. In such cases separate housing of these both groups is justified.

The choice of the controls shall be justified. It is necessary to define in the study protocol what purpose the control group serves. This shall include:

- Evidence that exposure to infection took place.
- A group of animals against which the vaccinated animals can be compared in a valid manner.

For such a comparison to be valid:

- The controls and vaccinated animals shall be as contemporaneous as possible, preferably investigated at the same time;
- The animals of both groups have to be randomised according to the experimental unit;"
- The environment in which the two groups of animals are housed shall be as equivalent as possible (i.e. same farm! barn/batch) or at least as similar as possible (e.g. same farm! different barn/same batch)
- The challenge infection shall be as similar as possible in the two groups of animals. This will not be the case if cohorts consist of exclusively vaccinated animals or controls. In this case, repetition of the trials under the same conditions is necessary, using truly randornised groups. The rearing of both groups together may affect the infection rate.

The use of historical data for control purposes is rarely acceptable but where they are used they shall have been shown to be consistent over a representative length of time and well

documented.
When investigating a combined vaccine, the control group may comprise animals vaccinated with a product formulated to contain all the components of the vaccine except the component under study.
Ideally, the trials shall be double blind, placebo controlled, but this is often difficult to realize in practice. The need for placebo controls depends on the study plan. If the parameter to be measured is a subjective one (e.g. coughing), then the trial must be done in a blind manner and either placebo controls shall be included or the person who measures this parameter shall have no information on the details of the vaccination.
It is recognized that in some circumstances (e.g. enzootic diseases) inclusion of controls may be difficult. However, even when this is not possible, sufficient evidence shall be presented that the vaccine is having a demonstrable beneficial effect.

SECTION C – PURPOSE OF THE FIELD TRIAL

Trial Purpose: The purpose of the trial, including the expected benefits, should be summarised.

Trial Details:
Details of the test product(s):

- Details of the product composition (e.g. certificate of product specification), and name of manufacturer.
- Where relevant (i.e. in the case the product is to be administered to a food-producing animal species), a statement as to whether the active substances in the test product(s) have an established maximum residue limit (MRL), and the proposed withdrawal period(s).
- Statement as to whether the product(s) contains a genetically modified organism (GMO).
- Statement as to whether the product(s) is compliant with the EU guidance on transmissible spongiform encephalopathies (TSE).
- Statement as to whether the product(s) is free from extraneous agents.

Proposed dosage and route of administration to be used: Information on the dose and dose regimen (including duration of therapy) as well as the route of administration of the test products (including placebo if relevant) should be given

The GLP/GCP status of the proposed trial:
As per national legislation relating to the conduct of field trials, the application procedure must also encompass safety tests on veterinary medicinal products in addition to efficacy tests. In the case of safety or bioequivalence trials, in accordance with the regulatory norms pharmacological, toxicological, residue and safety tests must be carried out in conformity with the provisions relating to Good Laboratory Practice (GLP) in an establishment that has a facility licence for GLP. Trials relating to the demonstration of efficacy must be carried out in conformity with the provisions relating to Good Practices as per CPCSEA

and must be in accordance with the international ethical and scientific quality standard for the designing, conducting, monitoring, recording, auditing, analysing and reporting of field trials on veterinary medicines, which should be followed when developing field trial data that are intended to be submitted to regulatory authorities.

Animals to be used:
The species of animals to be used should be indicated. Where relevant, information to characterise specific sub-populations should also be given (e.g. puppies > 12 weeks of age; in-calf heifers, etc)

Consent of animal owners: In the case that the animals being used in the trial are not the property of the applicant or sponsor, confirmation that the informed consent of the owners of the animals used in the trial will be obtained and documented is required.

Information on categories of animals to be used: Justification for the use of animals taken from the wild, or for the use of stray or feral animals, or the use of animals of an endangered species is required.

The trial animals should be disposed as per the CPCSEA guidelines after completion of the study.

SECTION D – DECLARATION AND UNDERTAKING

The declaration and undertaking must be signed by the applicant (i.e. the investigator, or the trial director on behalf of an applicant company).
In the event of the trial licence being granted, by signing the declaration and undertaking the signee is assuming the responsibility for the overall implementation and compliance of the trial with the legislation and with respect to fulfilment of the conditions and obligations as set out in the declaration and undertaking.
They are also confirming that they will comply with any conditions which may be included in the licence itself, including ensuring the security of any test products (those that do not have a marketing authorization granted by the DCG(I) which must be used only for the purpose of the trial.

Post Marketing Surveillance

Post Marketing Surveillance

All Marketing Authorization holders after obtaining the manufacture or import permission in form 46 or 45 respectively under D&C Act are required to 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.

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.

No claims except those mentioned above shall be made for the drug without the prior approval of the Licensing Authority

Periodic Safety Update Report:

PSUR are important pharmacovigilance documents. They provide an opportunity for MA holders to review the safety profile of their products and ensure that the SmPC and Package Leaflet within reasonable time frame.

As per the Drugs and Cosmetics Rules, 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 animal 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 product.

i) 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.

ii) All relevant filed 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 animal 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. New studies specifically planned or conducted to examine a safety issue should be described in the PSURs.

Annexures

ANNEXURE I:

‘**Form 44**
(See rules 122 A, 122 B, 122 D, 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 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:

Particularsof New Drug:

(1) Nameof the drug:
(2) DosageForm:
(3) Compositionof the formulation:
(4) Testspecification:
    (i) activeingredients:
    (ii) inactiveingredients:
(5) Pharmacologicalclassificationof the drug:
(6) Indicationsfor which proposed to be used:
(7) Manufacturerof the raw material (bulk drug substances):
(8) Patentstatus of the drug:

Datasubmitted along with the application (as per Schedule Y with indexing and page nos.)

A. Permission to market a new drug:-

(1) Chemicaland Pharmaceutical information
(2) AnimalPharmacology
(3) AnimalToxicology
(4) Details on Clinical trial
(5) Bio-availability,dissolution and stability study Data
(6) Regulatorystatus in other countries
(7) Marketinginformation:
    (a) Proposedproduct monograph
    (b) Draftsof labels and cartons
(10) Application for test licence

B. Subsequent approval / permission for manufacture of already approved new drug:

(a) Formulation:
    (1) Bio-availability/ bio-equivalence protocol
    (2) Nameof the investigator/centre
    (3) Sourceof raw material (bulk drug substances) and stability study data.

(b) Raw material (bulk drug substances)
    (1) Manufacturingmethod
    (2) Quality control parameters and/or analytical specification, stability report.
    (3) Animaltoxicity data

C. Approval / Permission for fixed dose combination:

(1) TherapeuticJustification
(authentic literature in pre-reviewed journals/text books)
(2) Dataon pharmacokinetics/pharmacodynamics combination
(3) Anyother 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) Numberand date of Approval/permission already granted.
(2) TherapeuticJustification for new claim / modified dosage form.
(3) Datagenerated 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).

Dated _____ Signature _____

Designation _____

Note- Delete, whichever is not applicable.

ANNEXURE-II

FORM 40

(See rule 24-A)

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 for 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. Names of drugs for registration.
   1 * * *
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 and Cosmetics Rules, 1945-Central*vide*ChallanNo._____ 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 and Cosmetics 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 No._____ Fax_____ _

E-mail_____

I/We* undertake to comply with all terms and conditions required to obtain Registration Certificate and to keep it valid during its validity period.

Place: _____

Date: _____

*Signature*_____

*Name*_____

*Designation*_____

Seal/Stamp of manufacturer or his authorised Agent in India.

(Note: In case the applicant is an authorized agent of the manufacturer in India, the Power of Attorney is to be enclosed).

**Delete whichever is not applicable.*

ANNEXURE -III

FORM 8

(SEE RULE 24)

APPLICATION FOR LICENCE TO IMPORT DRUGS (EXCLUDING THOSE SPECIFIED IN SCHEDULE X) TO THE DRUGS AND COSMETICS RULES, 1945.

1. 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. ……(name & 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 20th Nov., 2015 signed by the manufacturer as required by the Rule 24 of the Drugs and Cosmetics 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. …… issued in favour of M/s. ……(name & 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 there under. A copy of the said licence is enclosed.
6. A fee of .....…… has been credited to the Government under the Head of account "0210-Medical and Public Health, 104-Fees and Fines" under the Drugs and Cosmetics 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*.]

ss

ANNEXURE-IV

POWER OF ATTORNEY FOR ISSUE OF REGISTRATION CERTIFICATE AND/ORIMPORT LICENCE FOR IMPORT OF DRUGS IN INDIA

Whereas, M/s……., having Registered Office at …….. at……..,……

(Telephone ……, Fax ……, email:…….) hereinafter to be known as Authorised

Agent/Manufacturer of us intends to apply for a Registration Certificate and/or Import Licence under the Drugs and Cosmetics Rules, 1945, for the import, use and marketing into India, the .. (Product name), Manufactured by (Full address/ telephone no., /e-mail) here after to be known as the Manufacturer, having the factory premises at ……. (Full address/ telephone no., /e-mail), hereby delegate Power of Attorney that for the duration of the said Registration and /or Licence period:-

(1) The said applicant shall be our Authorized for the Registration Certificate and/or Import Licence of drugs imported into India, under rule 27-A and 24 of the Drugs and Cosmetics Rules; respectively for purposes of representations and /of signing of the Registration Applications in Form 40, Schedule D(I), Schedule D(II), Form 9 undertaking and /other allied documents.

(2) We shall comply with all the conditions imposed on the Registration Certificate and/or Import Licence, with relevant rules of the Drugs and Cosmetics rules, 1945.

(3) 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 in the distribution of functions between the factories:

(4) We shall comply with the provisions of Part IX of the Drugs and Cosmetics Rules, 1945:

(4) Every drug manufactured by us for import under the Registration Certificate and Import Licence 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.

(6) We shall from time to time report for any change of manufacturing process, or in packaging, or in labelling, or in testing, or in documentation of any 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 and Import Licence 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, along with the registration fee as specified in clause (ii) of sub rule (3) of rule 24-A.

(7) We shall from time to time report for any administrative action taken due to adverse reaction, viz. market withdrawal regulatory restriction, or cancellation of authorization and/or "not of standard quality report" of any drug pertaining to the Registration Certificate and/or Import Licence declared by any Regulatory Authority of any country where the drug is marketed/sold or distributed. The dispatch 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 in 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 within 48 hours time period.

(8) 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 there under.

(9) We shall allow the licensing authority and/or any person authorized 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 and/or Import Licence has been made.

(10) We shall allow the licensing authority or any person authorized by him in that behalf to take samples of the drugs concerned for test, analysis or examination, if considered necessary by the licensing authority.

(11) We shall comply with the any instructions or directions for the purpose of registration and Import of drugs in the country given by the Licensing authority.

PRODUCT (S) INFORMATION

NAME (S) OF THE PRODUCT:

Active Ingredients

Pharmacological Classification

Dosage Form

Signature on behalf of manufacturer, with name, designation, date and place.

Name: …

Place: ……..

Date:

Signature*:

(* Signatory Authority should be authorized by the Board of the Company/Directors)

Signature on behalf of Authorised Agent in India with name, designation, date and place.

Name: …….

Place: …….

Date:

Signature:

Delete whichever is not applicable.

ANNEXURE-V

SCHEDULE D (I)

(*See* rule 21 (d) and rule 24 A)

Information and undertaking required to be submitted by the manufacturer or his authorized 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 authorized 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 of 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 in the country of origin (duly notarized).

2.3 A copy of Good Manufacturing Practice (GMP) certificate, as per WHO-GMP guidelines, or Certificate of Pharmaceutical Products (CPP), issued by the National Regulatory Authority of the foreign country concerned, in relation to the bulk drugs or formulations or special products, 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 in 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 to 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 report for any change or manufacturing process, or in packaging, or in labelling, or in testing, or in documentation of any 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, along with the registration fee as specified in clause (ii) of sub rule (3) of rule 24-A.

3.6 We shall from time to time report for any administrative action taken due to adverse reaction, viz. market withdrawal regulatory restriction, orcancellation of authorization and/or ―not of standard quality report‖ of anydrug pertaining to the Registration Certificate declared by any Regulatory Authority of any country where the drug is marketed/sold or distributed. The dispatch 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 in 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 within 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 there under.

3.8 We shall allow the licensing authority and/or any person authorized 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 authorized 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

1 [*or his authorized agent*] *Seal*

/ Stamp

ANNEXURE-VI

1. **Plant Master File**.–The Licencee shall prepare a precise document in the form of Site Master File containing specific and factual Good

Manufacturing Practices about the production and/or control of pharmaceutical manufacturing preparations carried out at the licenced premises. It shall contain the following: -

1.1 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 on the premises; (d)Type of products Licenced 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) Short description of the Quality Management System of the firm; and

(h) Products details registered with foreign countries.

1.2 Personnel:

(a) Organizational chart showing the arrangement for quality assurance including production and quality control;

(b) Qualification, 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.

1.3 Premises:

(a) Simple plan or description of manufacturing areas drawn to scale;

(b) Nature of construction and fixtures/fittings;

(c) Brief description of ventilation systems. More details should 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 should be mentioned;

(d) Special areas for the handling of the highly toxic, hazardous and sensitizing materials;

(e) Brief description of water system (schematic drawings of systems), including sanitation;

(f) Description of planned preventive maintenance programs for premises and of the recording system.

1.4 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 programs for equipment and of the recording system; and

(c) Qualification and calibration including the recording systems and arrangements for computerized systems validation.

1.5 Sanitation:

(a) Availability of written specifications and procedures for cleaning manufacturing areas and equipment.

1.6 Documentation. -

(a) Arrangements for the preparation, revision and distribution of;

(b) Necessary documentation for the manufacture;

(c) Any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls about air and water).

1.7 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;

(d) Brief description of general policy for process validation.

1.8 Quality Control:

(a) Description of the quality control system and of the activities of the Quality Control Department. Procedures for the release of the finished products.

1.9 Loan Licence manufacture (Toll manufacturing) and Licencee:

(a) Description of the way in which compliance of Good Manufacturing Practices by the loan Licencee shall be assessed.

1.10 Distribution, complaints and product recall:

(a) arrangements and recording system for distribution;

(b) Arrangements for the handling of complaints and product recalls.

1.11 Self inspection. -

(a) 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 Good manufacturing

Practices in all aspects of production.

1.12 Export of drugs. -

(a) Products exported to different countries;

(b) Complaints and product recall, if any

ANNEXURES:

1. Site plan. Layout (equipment layout, men & material flow lay out, pressure differential lay out)
2. HVAC schematics and details of areas (Where in clearly specify the filtration level & classification of core areas & rooms as required in section 3.3 of SMF)
3. Water system – Schematic diagrams along with the components
4. List of personnel (with designation, qualification & experience)
5. List of primary & secondary Impurity and Reference standards/cultures available with the firm (relevant to the applied products)
6. List of equipments used in production, testing and utilities with their make, model and capacity.

ANNEXURE-VII

SCHEDULE D (II)

[*See* rule 21 (d) and rule 24 A]

Information required to be submitted by the manufacturer or his authorized 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) as per WHO GMP certification Scheme issued by the National Regulatory Authority of the country of origin/ Product Registration Certificate issued by NRA and or proof of DMF approval by NRA and/ or CEP (EDQM certificate).

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).

1.4 GMP Certificate in WHO formats or Certificate of Pharmaceutical

Products (CPP) issued by

National Regulatory Authority of the country of origin (duly notarised) or Proof of DMF Approval by NRA and or CEP (EDQM certificate).

1.5 List of countries where marketing authorization 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 substances(s) and excipient(s)

List of active substance(s) separately from the constituent(s) of excipients.

2.3 Specifications of active and inactive ingredient (s) including pharmacopoeial references

2.4 Source of active ingredient(s), name and address.

2.5 Tests for identification of the active ingredient(s), Method of its assays and tests for impurity profile with reference standards for the impurities

(Protocol to be submitted along with 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 pharmacopoeial reference or in-house specification as approved by the registration authority, in the country of origin.

2.8 Stability data including accelerated stability and real time stability analysis.

2.9 Documentation on pack size.

2.10 Numerical expression on EAN bar code on the labels and cartons.

2.11 Safety documents on containers and closures.

2.12 Documentation on storage conditions.

2.13 Three samples of medicinal product/drug and outlet packing are to be submitted with batch certificates. Additional samples as well as reference substances with batch certificates including date of manufacture, shelf-life, and 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 labeling as per rule 96 of the Drugs and Cosmetics Rules

1945.

2.16 Package insert.

2.17 Details of safety handling procedure of the drug.

2.18 Details of PMS study report for marketing period not exceeding five years.

5. BIOLOGICAL AND BIOPHARMACEUTICAL INFORMATION OF DRUGS 3.1 Biological control tests applied on the starting material, if applicable.

3.2Biological 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.

3.7Acute 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.

15.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 are to be elaborated, as far as possible.

5. CLINICAL DOCUMENTATION

A new drug as defined under rule 122-E of the Drugs and Cosmetics Rules, 1945 is required to be permitted separately by the licensing authority under rule 122-A of the said rules prior to its registration. Such a new drug requires a brief summary and clinical documentation, along with permission under 122-A of the said rules for its Registration Certificate.

6. LABELLING AND PACKAGING INFORMATION OF DRUGS.

6.1 Labels 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 other forms of interaction.

Pregnancy and lactation, if contra-indicated

Effects on ability to drive and use machines, if contra-indicated. Undesirable effects/side effects.

6.3 Package insert should indicate the following pharmaceutical information: -

- 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

[or his authorized agent]

Seal/Stamp

NOTE:

14. 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.
15. 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 VIII

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…*

Checklists for submission of Applications

Central Drugs Standard Control Organization
Directorate General of Health Services
Offices of Drugs Controller General (India)
(Veterinary Division)

Checklist for Market Authorization/new drug approval

S. No	Content	Remarks
1.	Introduction about the company (Brief Description about the company)	☐ Yes ☐ No
2.	Administrative Headquarters (Provide address of company Headquarters)	☐ Yes ☐ No
3.	Manufacturing Facilities (Provide address of company (Headquarters)	☐ Yes ☐ No
4.	Whether the firm as submitted the 2 hard and 2 soft copies of the said product	☐ Yes ☐ No
5.	Module 1	☐ Yes ☐ No
6.	Module 2	☐ Yes ☐ No
7.	Module 3	☐ Yes ☐ No
8.	Module 4	☐ Yes ☐ No
9.	Module 5	☐ Yes ☐ No
10.	Manufacturing Facilities (Provide address of company Headquarters)	☐ Yes ☐ No
11.	Form 44 and TR Challan	☐ Yes ☐ No
12.	Regulatory permissions/approvals a) No objection certificate for Form 29 as issued by Central Licence b) Form 29 as issued by State Licensing Authority c) Permission to conduct toxicology permission (For r-DNA Products)	☐ Yes ☐ No
13.	List of countries where the drug product has been licenced and summary of approval countries	☐ Yes ☐ No
14.	Product Description (A brief Description class to which it belongs) a) Name of the product b) Generic name/INN name c) Route of administration d) Dosage of strength e) Qualitative and quantitative composition commercial presentation	☐ Yes ☐ No
	Module 2	
15.	Introduction	☐ Yes ☐ No
16.	Quality overall summary	☐ Yes ☐ No
17.	Overview of non-clinical studies	☐ Yes ☐ No
18.	Non-clinical summary	☐ Yes ☐ No
	Module 3	
19.	Table of contents for Module 3	☐ Yes ☐ No
20.	Quality contents	☐ Yes ☐ No
21.	Drug substance(s): Information must be submitted for each drug substance in the product	☐ Yes ☐ No
22.	General information starting materials and raw materials	☐ Yes ☐ No
23.	Manufacturing process for drug substance	☐ Yes ☐ No
24.	Characterization of drug substance	☐ Yes ☐ No

25.	Quality control of drug substance	☐ Yes	☐ No
26.	Reference standards	☐ Yes	☐ No
27.	Container closure system	☐ Yes	☐ No
28.	Stability of drug substance	☐ Yes	☐ No
29.	Drug product	☐ Yes	☐ No
30.	Description of composition of drug product	☐ Yes	☐ No
31.	Pharmaceuticals development	☐ Yes	☐ No
32.	Manufacturing of drug product	☐ Yes	☐ No
33.	Control of excipients (Adjuvant, preservative, stabilizers and others)	☐ Yes	☐ No
34.	Control of drug product	☐ Yes	☐ No
35.	Reference standards of materials	☐ Yes	☐ No
36.	Container closure system	☐ Yes	☐ No
37.	Stability of drug product	☐ Yes	☐ No
38.	Appendix	☐ Yes	☐ No
39.	Details of equipment and facilities for production of drug	☐ Yes	☐ No
40.	Product: master formula, batch record and set release	☐ Yes	☐ No
41.	Documentation in respect of consistency batches	☐ Yes	☐ No
42.	Safety evaluation of adventitious agents	☐ Yes	☐ No
43.	Bibliographic Reference	☐ Yes	☐ No
	Module 4		
44.	Reports on studies	☐ Yes	☐ No
45.	Pharmacology	☐ Yes	☐ No
46.	Pharmacodynamics studies(immunogenicity of product)	☐ Yes	☐ No
47.	Pharmacodynamics studies of adjuvant (if applicable)	☐ Yes	☐ No
48.	Pharmacokinetics	☐ Yes	☐ No
49.	Pharmacokinetics studies (in case of new adjuvant, new modes of administration)	☐ Yes	☐ No
50.	Toxicology	☐ Yes	☐ No
51.	General toxicology information on:	☐ Yes	☐ No
52.	Special toxicology (for products to which it applies)	☐ Yes	☐ No
53.	Toxicity of new substance used in formulation (new adjuvants, stabilizers, additives)	☐ Yes	☐ No
54.	Special considerations	☐ Yes	☐ No
55.	Bibliographic references	☐ Yes	☐ No
	Module 5	☐ Yes	☐ No
56.	Table of contents of the Module	☐ Yes	☐ No
57.	Reports on Field trial	☐ Yes	☐ No
58.	Efficacy Study	☐ Yes	☐ No
59.	Safety Study	☐ Yes	☐ No
60.	Copy of Animal Ethics Committee Approval of the Centre	☐ Yes	☐ No
61.	Copy of CPCSEA Approval of the Centre undertaking Study.	☐ Yes	☐ No
62.	Synopsis of the Field Trial Study duly signed by the Principal Investigator.	☐ Yes	☐ No
63.	Special Consideration	☐ Yes	☐ No
64.	Bibliographic references	☐ Yes	☐ No

Central Drug Standard Control Organization
Directorate General of Health Services
Office of Drugs Controller General (India)
(Biological Division)

Checklist for Registration Certificate (Form -41)

S.No	CONTENTS	YES	NO
1.	Covering Letter		
2.	TR-6 Challan of required amount; Bank's Stamp for Cheque reallization		
3.	Power of Attorney; sign/ stamp of both parties & Indian Embassy or Appostile		
4.	Application in Form-40, sign, date, stamp		
5.	Copy of the import Permission on Form-45 (Formulation) and / or Form-45A (Bulk).		
6.	Notarized copy of Whole sale/Manufacturing license.		
7.	Company's Authorization letter (in original) for the bearer to submit application and collect letter		
8.	SCHEDULE D (I) & SCHEDULE D (II) Sign, Date, Stamp by the overseas manufacturer.		
9.	Plant Master File (PMF), Notarised in foreign country		
10.	GMP certificate, Notarized in country of origin		
11.	Certificate of Pharmaceutical Products (COPP) Notarized in country of origin		
12.	Regulatory status of the drug in the country of origin. Table with registration, Launching, Withdrawal status.		
13.	Regulatory status of the drug worldwide. Table with registration, Launching, Withdrawal status.		
14.	Free Sale Certificate (FSC); Notarized in country of origin		
15.	Drugs Master File (DMF) Notarized in country of origin		
16.	Annexures -- A / C of Sch-D-II. Annx A: For Blood Products Annx C: For r-DNA product and Vaccines		

Central Drug Standard Control Organization
Directorate General of Health Services
Office of Drugs Controller General (India)
(Biological Division)

Checklist for Import License (Form -10)

S.No	CONTENTS	YES	NO
1.	Covering Letter		
2.	TR-6 Challan of required amount; Bank's Stamp for Cheque reallization		
3.	Application in Form-8, sign, date, stamp		
4.	Copy of the import Permission on Form-45 (Formulation) and / or Form-45A (Bulk).		
5.	Notarized copy of Whole sale/Manufacturing license.		
6.	Company's Authorization letter (in original) for the bearer to submit application and collect letter		
7.	Copy of Valid Registration Certificate		
8.	Undertaking in Form-9, attested by Indian Embassy / Appostiled (If Issued by the manufacturer).		
9.	Signed Stamped by the Indian Agent on Letter head.		

Central Drugs Standard Control Organization
Directorate General of Health Services
Office of Drugs Controller General (India)
(Biological Division)

Checklist for Test Licence to Import of Vaccine under Form-11

S.No	Check List for Form 12:	Closed Responses
1	Name of Applicant	☐ Yes ☐ No
2	Drug	☐ Yes ☐ No
3	Dosage Form and Composition	☐ Yes ☐ No
4	Application in Form 12	☐ Yes ☐ No
5	Fees	☐ Yes ☐ No
6	Justification and utilization breakup of the drug detailing the test parameters visà-vis quantities of the drugs, batch manufacturing plan	☐ Yes ☐ No

Annexure #1

Central Drug Standard Control Organization

Directorate General of Health Services

Office of Drugs Controller General (India)

(Biological Division)

Checklist for Pre Screening of Applications for variations under Post approval changes as per CDSCO Guidance for Industry.

Name of the firm: _____ **Date:** _____

TR-6 challan (if applicable) no:_____ **Date:**_____ **Ref.no:**_____

S.no.	Information and Documents	Status	
		Yes	No
1	Covering Letter-Purpose should be clearly mentioned with page number and Index.		
2	Whether change in Drug Substance or Drug Product along with **Description of change.**		
3	Change category: Supplement/Notifiable/Annual notification as per CDSCO Guidance for Industry.		
4	Copy of Market Authorization and other permissions/approvals for subject's product.		
5	Undertaking or satisfactory statement to fulfill conditions of proposed change as per CDSCO Guidance for industry.		
6	Side by side comparison of previously approved and changed information and declaration that other information is not changed or no change as a result of variation if applicable.		
7	Whether information as per CDSCO Guidance for industry for proposed variation is submitted.		
8	For imported products certified copy of approval from NRA of country of origin and from EMEA, USFDA etc. along with list of countries where proposed variation is approved.		
9	In case of annual notification declaration stating that supporting data for Level III change should be submitted on annual basis or within 15days whenever required by DCGI.		
10	Statements & evidences about effect of change on quality, stability, validation, animal toxicity & clinical (safety & efficacy) status of the product.		
11	For label change, Package insert change, extension in shelf life or change in specifications not mentioned in Indian pharmacopoeia one additional set of literature (hard & soft copy).		

Accepted/Returned due to incomplete application

Signature of the Reviewer

Signature of firm representative