Guidance for Industry

- **Submission of Clinical Trial Application for Evaluating Safety and Efficacy**
- **Requirements for permission of New Drugs Approval**
- **Post approval changes in biological products: Quality safety and Efficacy Documents**
- **Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products**

CENTRAL DRUGS STANDARD CONTROL ORGANISATION
CDSCO CDSCO
सत्यमेव जयते
MINISTRY OF HEALTH, GOVERNMENT OF INDIA

Guidance for Industry on Submission of Clinical Trial Application for Evaluating Safety and Efficacy

(General considerations for conducting Clinical Trial as per Drugs and Cosmetics Act 1940 and Rules 1945)

Document No. - CT/71108

Version – 1.1

OBJECTIVE

This Guidance has been developed in conformity with Drugs and Cosmetics and Rules there under and GCP Guidelines of India for the purpose of submission of Clinical Trial application. The clinical trial sponsor is required to submit application (Form 44) for the purpose of conducting clinical trial in India and submit documents as per Schedule Y of the Drugs and Cosmetics Act 1940 and Rules there in. The sponsor is also responsible for implementing and maintaining Quality Assurance system to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice Guidelines issued by CDSCO, Directorate General of Health Services, Govt. of India as well as all applicable statutory provisions of Drugs and Cosmetics and Rules there under. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations.

Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity. In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions, if any, and the reason for discontinuation of the study or non-pursuit of the new drug application. Any expected serious adverse event (SAE) occurring during a clinical trial should be communicated promptly (with in 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study.

The manufacturer / sponsor have to submit application on Form 44 for permission of Clinical Trial under the provisions of Drugs and Cosmetic Act

1940 and Rules 1945. As the Form 44 is an application for grant of permission to import or manufacture a new drug or to undertake Clinical Trial, the Central Drugs Standard Control Organization prescribes information to be submitted for Biologicals for Clinical Trial to simplify the submission requirements. The requirements in respect of Chemistry and Pharmaceutical information has been elaborated for Biological in this document while requirement for conduction of Clinical trial and other requirements remains the same as per Schedule Y of Drugs and Cosmetic Rules 1945.

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

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

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BIOLOGICAL PRODUCTS:

PHASE-I & PHASE- II CLINICAL TRIAL

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SECTION A	**GENERAL INFORMATION**
SECTION B	**CHEMISTRY MANUFACTURING CONTROL**
SECTION C	**NONCLINICAL DATA**
SECTION D	**PROPOSED PHASE-I / II STUDIES**

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SECTION A:
GENERAL INFORMATION

1. **Introduction about Company**

   Brief description about company

2. **Administrative Headquarters**

   Provide address of company Headquarters

3. **Manufacturing Facilities**

   Provide address of company Headquarters

4. **Regulatory permissions/approvals**

   a. No objection certificate for Form-29 as issued by Central License Approving Authority.

   b. Form 29 as issued by State Licensing Authority.

   c. Permission – to conduct toxicology permission (For r-DNA products)

5. **Regulatory and intellectual property status in other countries.**

   a. Countries where the drug is

      a. Marketed

      b. Approved

      c. Approved as IND

      d. Withdrawn, if any, with reasons

   b. Patent information status in India & other countries

SECTION B:

CHEMISTRY MANUFACTURING CONTROL

1. Product Description

A brief description of the drug and the therapeutic class to which it belongs.

1.1 Name of the product

1.2 Generic name / INN name

1.3 Route of administration

1.4 Dosage of strength

1.5 Qualitative and Quantitative Composition

2. Product Development

2.1 Strain details

Name and source (if any)

Incase of products derived form r-DNA technology, the following details shall also be furnished

2.1.1. Clone development (for recombinant products)

- **Details on source Nucleic acid**

Nucleic acid sequence

- **Vector(s)**

Details about vector, please enclose the map of the vector gene

- **Host(s) that carrying the vector(s)/ target gene(s) :**

2.2 Substrate details (For cell culture based products)

Details of name and source of substrate

2.3 Master seed and Working seed details

3. Information on Drug Substance

3.1 Production of Drug substance

3.1.1 Raw materials

- List of raw materials
- Specification & test methods of raw materials
- Human or animal origin (If any) and its TSE / BSE compliance

3.1.2 Description of Manufacturing Process and Process Control

3.1.3 Process flow chart

Operations flow sheet

3.1.4 In process control steps & intermediates

Include process control step at each stage of Drug substance

3.2 Characterization of Drug substance

3.2.1 Physicochemical Characterization

3.2.2 Biological characterization

3.3 Control of Drug substance

3.3.1 Specification

3.3.2 Analytical procedures and validation / standardization studies

(Data expected to be submitted for recombinant products however not for biological like Vaccines etc.)

3.3.3 Certificate of analysis (Pilot scale batches)

3.4 Reference standard materials

3.5 Container closure system

3.5.1Packing materials: Specifications & test methods

3.5.2 Labelling information of Drug Substance

3.6 Stability data

3.6.1 Write-up for stability study Program

3.6.2 Specification and Test Methods: Stability study

3.6.3 Accelerated Stability Data (3 months) on pilot scale batches

3.6.4 Real time Stability Data (3 months) on pilot scale batches

4. Information on Drug Product

4.1 Description & composition

4.2 Components of Drug product

4.3 Manufacturing process

Description of facility where clinical trial material will be manufactured.

4.4 Manufacturing process flow chart

4.5 Control of critical steps & intermediates

4.6 Equipment and Premises: Details of equipments, instruments etc involved in manufacturing for testing of product)

4.7 Control of Excipients

4.7.1Specifications

4.7.2Analytical procedures

4.7.3 Excipients human or animal origin (If any) and its TSE / BSE compliance

4.8 Control of Drug Product

4.8.1Specifications

Final product specifications should be included in detail with reference to the pertaining compendia.

Non-pharmacopeial tests must also be included.

4.8.2Analytical procedures

Describe in detail test methods followed in the analysis of the final product. Include detailed pharmacopeial references when appropriate. Data expected to be submitted for recombinant products however not for biological like Vaccines etc.

4.8.3 Certificate of analysis (Pilot scale batches)

4.9. Reference standards

4.10. Container closure system

4.10.1 Packaging Materials: Specifications and Test methods

4.10.2 Art work – Packaging material (label, primary carton, secondary carton and Pack Insert.

4.10.3 Packaging Specifications

4.11 Stability data

4.11.1 Write-up for stability study Program

4.11.2 Specification and Test Methods: Stability study

4.11.3 Accelerated Stability Data (3 months) on pilot scale batches

4.11.4 Real time Stability Data (3 months) on pilot scale batches

SECTION C:

NONCLINICAL DATA (Compliance as per Schedule Y)

References:

1. Schedule – Y, Amendment version 2005, Drugs and Cosmetics Rules, 1945

SECTION D: PROPOSED PHASE-I/II STUDIES (Compliance as per Schedule Y)

1. Protocol for Phase-I / II studies

References:

1. Schedule – Y, Amendment version 2005, Drugs and Cosmetics Rules, 1945.
2. GCP guidelines published by CDSCO, DGHS, Govt. of India.
3. Ethical Guidelines for Biomedical Research on Human Subjects published by Indian Council of Medical Research, New Delhi.

Biological products: Phase-III

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      a. Marketed

      b. Approved

      c. Approved as IND

      d. Withdrawn, if any, with reasons

   b. Patent information status in India & other countries

SECTION B:

CHEMISTRY MANUFACTURING CONTROL

Module 3	
Quality Information (Chemical, Pharmaceutical and Biological)	
3.1	**Table of contents for Module 3**
3.2	**Quality contents/Body of data**
3.2.S	**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 the drug substance
3.2.S.1.2	Structural formula, molecular formula and relative molecular weight (if applicable)
3.2.S.1.3	Description and characterization of drug substance
3.2.S.1.4	General Description And History of starting material
3.2.S.1.4.1	Strain
3.2.S.1.4.2	System of seed/master/working banks
3.2.S.1.4.3	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 and intermediate steps
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 drug substance
3.2.S.2.11	Reprocessing
3.2.S.2.12	Filling procedure for the drug substance, 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 drug substance**
3.2.S.3.1	Physicochemical Characterization
3.2.S.3.2	Biological Characterization

3.2.S.3.3	Impurities
3.2.S.4	**Quality control of 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 drug substance**
3.2.S.7.1	Protocol of stability study, results and conclusions
3.2.S.7.2	Post-approval stability program
3.2.S.7.3	Storage and shipping conditions of drug substance
3.2.P	**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 manufacturer and 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	Determination and characterization of impurities
3.2.P.5.7	Justification of specifications
3.2.P.6	**Reference standards of materials**
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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, of drug product, results and conclusions
3.2.P.8.2	Stability testing of diluents and reconstituted product in case of freeze dried products
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**
3.2.A.2	**Safety evaluation of adventitious agents**
3.3	**Literature/ Bibliographic Reference**

SECTION C:

NONCLINICAL DATA (Compliance as per Schedule Y)

References:

1. Schedule – Y, Amendment version 2005, Drugs and Cosmetics Rules, 1945

SECTION D: PROPOSED PHASE-III STUDIES (Compliance as per Schedule Y)

1. Protocol for Phase-III studies

References:

1. Schedule – Y, Amendment version 2005, Drugs and Cosmetics Rules, 1945.
2. GCP guidelines published by CDSCO, DGHS, Govt. of India.
3. Ethical Guidelines for Biomedical Research on Human Subjects published by Indian Council of Medical Research, New Delhi.

OTHER REQUIREMENTS (SCHEDULE Y):

Part 1: Contents of the proposed protocol for conducting Clinical Trials

1. Title Page:
   a. Full title of the clinical study.
   b. Protocol/Study number and protocol version number with date.
   c. The IND name/number of the investigational drug.
   d. Complete name and address of the sponsor and contract research organization, if any.
   e. List of the Investigators who are conducting the study, their respective institutional affiliations and site locations.
   f. Name(s) of clinical laboratories and other departments and/or facilities participating in the study.
2. Table of contents:

A complete Table of Contents including a list of all Appendices

1. Background and Introduction

   a. Pre-clinical experience

   b. Clinical experience previous clinical work with the new drug should be reviewed here and a description of how the current protocol extends existing data should be provided. If this is an entirely new indication, how this drug was considered for this should be discussed. Relevant information regarding pharmacological, toxicological and other biological properties of the drug/biological/medical device and previous efficacy and safety experience should be described.

2. Study Rationale

This section should describe a brief summary of the background information relevant to the study design and protocol methodology. The reasons for performing this study in the particular population included by the protocol should be provided.

3. Study objective(s) (primary as well as secondary) and their logical relation to the study design.
4. Study Design:
    a. Overview of the Study Design: Including a description of the type of study (i.e. double-blind, multicentre, placebo controlled, etc.) a detail of the specific treatment groups and number of the 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 the study.
5. Study Population: The number of subjects required to be enrolled in the study at the investigative site and by all sites along with a brief description of the nature of the subject population required is also mentioned.
6. Subject Eligibility-
    a. Inclusion criteria
    b. Exclusion criteria
7. Study Assessments- Plan, procedure and methods to be described in detail.
8. Study Conduct stating the types of study activities that would be included in this section would be: medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom

measurement, dispensation and retrieval of medication, subject cohort assignment, adverse event review, etc.
Each visit should be described separately as Visit 1, Visit 2 etc.

Discontinued Subjects: Describes the circumstances for subject withdrawal, dropouts, or other reasons for discontinuation of subjects. State how drop-outs would be managed and if they would be replaced. Describe the method of handling of protocol waivers, if any. The person(s) who approves all such waivers should be identified and the criteria used for specific waivers should be provided.

Describes how protocol violations will be treated, including conditions where the study will be terminated for non-compliance with the protocol.

9. Study Treatment-
    a. Dosing schedule (dose, frequency and duration of the experimental treatment). Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency and duration of concomitant treatment should be stated.
    b. Study drug supplies and administration: A statement about who is going to provide the study medication and that the investigational drug formulation has been manufactured following all regulations. Details of the product stability, storage requirements and dispensing requirements should be provided.
    c. Dose modification for study drug toxicity: Rules for changing the dose or stopping the study drug should be provided.
    d. Possible drug interactions.
    e. Concomitant therapy: The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a subject is not allowed to use during parts of or the entire study. If any washout periods for

prohibited medications are needed prior to enrolment, these should be described here.

f. Blinding procedures: A detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the subject.

g. Un-blinding procedures: If the study is blinded, the circumstances in which un-blinding may be done and the mechanism to be used for un-blinding should be given.

10. Adverse Events (See Appendix XI): Description of expected adverse events should be given.

Procedures used to evaluate an adverse event should be described.

11. Ethical Considerations: Give the summary of:

a. Risk/benefit assessment.
b. Ethics Committee review and communications.
c. Informed consent process.
d. Statement of subject confidentiality including ownership of data and coding procedures.

12. Study Monitoring and Supervision: A description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected to perform monitoring.

Case Record Form(CRF) completion requirements, including who gets which copies of the forms and any specifics required in filling out the forms CRF correction requirements, including who is authorized to make corrections on the CRF and how queries about study data are handled and how errors, if any, are to be corrected should be stated.

Investigator study files, including what needs to be stored following study completion should be described.

13. Investigational Product Management-

a. Give Investigational product description and packaging (stating all ingredients and the formulation of the investigational drug and any placebos used in the study).
b. The precise dosing required during the study.
c. Method of packaging, labeling and blinding of study substances.
d. Method of assigning treatments to subjects and the subject identification code numbering system.
e. Storage conditions for study substances.
f. Investigational product accountability: Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed and returned/ destroyed.
g. Describe policy and procedure for handling unused investigational products.

14. Data Analysis-

Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.

Statistical Analysis: Give complete details of how the results will be analyzed and reported along with the description of statistical tests to be used to analyze the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data, method of evaluation of the data for treatment failures, non-compliance, and subject withdrawals; rationale and conditions for any interim analysis, if planned.

Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable.

15. Undertaking by the Investigator (as per the Appendix VII of Schedule Y)
16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

Part 2: Appendix XI to Schedule Y

Data elements for reporting Serious Adverse events occurring in Clinical Trial

1. Patients Details-

   Initials and other relevant identifier (hospital/OPD record number etc)

   Gender

   Age and/or date of birth

   Weight

   Height

2. Suspected Drug(s)-

   Generic name of the drug

   Indication(s) for which suspected drug was prescribed or tested

   Dosage form and strength

   Daily dose and regimen (specify units e.g.-mg, ml, mg/kg)

   Route of administration

   Starting date and time of day

   Stopping date and time or duration of treatment

3. Other Treatment(s)-

   Provide the same information for concomitant drugs (including non-prescription/OTC drugs) and non-drug therapies, as for the suspected drug (s).

4. Details of Suspected Adverse Drug Reaction(s)-

   Full description of reaction(s) including body site and severity as well as the criterion (or criteria) for regarding the report as

serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.

Start date (and time) of onset of reaction

Stop date (and time) or duration of reaction

Dechallenge and rechallenge information

Setting (e.g. hospital, out-patient clinic, home, nursing home)

5. Outcome-

Information on recovery and any squeal: results of specific tests and/or treatment that may have been conducted.

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction: any post-mortem findings.

Other information: Anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.

6. Details about the Investigator-

Name

Address

Telephone number

Profession (Specialty)

Date of reporting the event to Ethics Committee overseeing the site

Signature of the Investigator.

Part 3: Guidance Notes for Protocol Summary

Trial Title and Protocol Number/Code

Provide the title and protocol number/code of the trial. The version number of the protocol should also be provided.

Background and Rationale

A brief, concise introduction into the clinical problem and previous treatments and developments, i.e. pertinent data from previous preclinical/clinical pharmacology studies and therapeutic exploratory studies taking into account relevant scientific literature (citations by consecutive numbering, with list at end of this section: important or not readily available references may be included with the paper submission, if appropriate). This section should also contain information on the new drug.

Rationale: Reasoning and justification for the proposed new approach/therapy.

Trial Objectives

Statement of the precise goal(s) of the trial (may be subdivided into primary and secondary objectives) which may include testing of the null hypothesis i.e. testing a new drug population/indication etc., as applicable.

Study Design and Duration

1. The statement of study design should include the method of randomization, blinding and the comparative agent, if applicable.
2. A “Brief outline of the study be able to support any claims related to the proposed study.
3. The design of the study should be able to support any claims related to the proposed study.

4. Total study duration (anticipated starting/finishing dates).
5. Duration for each subject including post treatment period etc.

Total Number of Sites and Number of Indian Sites

Total number of trial sites with list of countries/geographical areas and number of sites in India.

List of Investigators

Qualified Investigators at each Indian site.

Sample Size

Rationale and calculation for sample size requirement, anticipated drop-out rate etc. The sample determination may include H_0 testing and desired power of the study.

Patient Population

Description of specific characteristics of the trial participants (e.g. disease/stage/indication/conditions/treatment etc.) as applicable and of diagnostic criteria and assessment.

Inclusion Criteria

Enumeration of conditions determining participation in the proposed clinical trial.

Exclusion Criteria

Enumeration of conditions determining participation in the proposed clinical trial.

Drug Formulation

Brief description of the study drug(s) and formulation to be used in the clinical trial. The relationship to the formulations used in the preclinical and/ or other

clinical trials should be delineated, as applicable. This may also include disclosures of the formulation intended to be marketed and/or any bridging studies which may be necessary, planned, initiated and/or already [performed if different formulations have been used during clinical development.

Dosage Regimen

Rationale for dose selection

Description of the schedule(s) for using the study drug(s) including escalations/maintenance/reductions/discontinuation, as applicable.

Description of other supportive measures and dose modifications for specific adverse events (anticipated toxicities), as applicable.

Washout Period

Description for pre-, during- and post-trial, as applicable.

Pre-study Screening and Baseline Evaluation

Description of the process of clinical validation for participation in the clinical study, including methodology/schedule of events.

Treatment/Assessment Visits

Schedule of all events/visits/procedures during the clinical study.

Concomitant Medication

Enumeration and description of all-/allowed drug/medications, in addition to the study drugs.

Rescue Medication and Risk Management

Description of available supportive measures/antidotes/ dosages/procedures (including follow-up) used to help reverse untoward effects or lack of efficacy resulting from any applications of drug(s)/procedures in connection with the clinical trial.

Premature Withdrawal/Discontinuation Criteria

Enumeration of all conditions/criteria and management for drug/patient's withdrawal or (premature) discontinuation, including voluntary withdrawal by subject without prejudice to future treatment by the physician.

Early stopping rules for the trial.

Efficacy Variables and Analysis

Description and validation of primary endpoint(s), i.e. responses/changes from baseline over time in relation to clinical trial events. Description and validation of related secondary changes (secondary endpoint) following from clinical trial events.

Safety Variables and Analysis

Monitoring/assessing adverse drug reactions/adverse events/toxicities/clinical laboratory parameters etc. in relation to clinical trial events.

Statistical Analysis

(The following points are presented for consideration while completing this section)

1. Analysis of trial parameters (primary/secondary endpoints), population, demographics, as applicable.
2. Efficacy analysis methods and results of efficacy end-point analysis.
3. Safety analysis methods and results of safety end-point analysis.
4. Exploratory end-point analysis: evaluation effect(s) (or lack of effects) of relevant biochemical/pharmacological etc parameters, as applicable.
5. Pharmacokinetic endpoint analysis, as applicable.
6. Interim analysis and role of Data Safety Monitoring Board, as applicable.

Further Guidance for information to be submitted with CT Applications:

1. **RCGM / GEAC approvals:** The environmental angle clearance from competent authority in accordance to the Environment Protection Act.
2. **Physicochemical characterization:** Tests for identity and purity like:

2 a. Recombinant products:

i. Comparative purity of proteins by SDS PAGE analysis with reference standard (if any)
ii. Peptide mapping of the protein.
iii. N-Terminal analysis of amino acids
iv. Preliminary analysis of product (protein) with respect to host cell protein and host cell DNA.
v. Neutralization assays if applicable.

2 b. Conventional products:

i. Comparative purity of proteins by SDS PAGE analysis with reference standard (if any)
ii. Peptide mapping of the protein.
iii. N-Terminal analysis of amino acids
iv. Preliminary analysis of product (protein) with respect to host cell protein and host cell DNA.
v. Neutralization assays if applicable.

3. **Biological Characterization:** Safety and potency tests (in vitro and in vivo) like:

3a. Recombinant products:

i. Characterization of master cell bank and working cell bank with respect to sterility, viability, purity, bacteriophages, plasmids etc.

ii. Purity (immunological) by Western blot method.

3 b. Conventional products:

i. Inactivation
ii. Detoxification
iii. Attenuation
iv. Stereotyping as applicable
v. Neutralization assays if applicable
vi. Neurovirulence testing, as applicable

For other Biologicals the following are applicable:

i. Characterization of MCB, WCB and cell substrate
ii. Purity of the product by a suitable method in case of whole cell vaccine.
iii. Purity of the product by SDS PAGE and Western Blot in case of toxins.
iv. Standardization of inactivation process.
v. Immunogenicity of the product.

4. **Validation studies (analytical methods):** For Phase I / II study the, the standardization studies (limited validation) like repeatability, precision and accuracy is expected to be documented. In case of Biotech products these data are required to be submitted at this stage also.
5. **Excipients (animal / human origin) – TSE / BSE compliance:** It is expected that the meat media used in the production of biological is certified by Department of Animal Husbandry of the concerned State in India. The firm must carry out its own risk assessment for selection of vendor and procurement of meat so as to exclude chances of TSE / BSE contamination. SOP for vendor selection and procurement of meat media and certificates issued by Animal Husbandry Department is to be submitted. For other excipients like FCS, gelatin, vitamins of animal, antibody origin should be procured from assured resources and

certificate of freedom from TSC/BSE should be submitted. In case of imported materials, for manufacturing certificate from organizations such as EDQM, EMEA etc is to be submitted.

6. **Clarification for submission of information for CT Phase III studies:**
   The information should be collated as per guidance for industry: preparation of Quality information for Drugs Submission for New Drug Approval (Module III): Biotechnological / Biological products.

7. **Samples of drug product:** Samples of drug substance and drug product (an equivalent of 50 clinical doses or double the quantity required (whichever is more) for complete testing of product with testing protocols, full impurity profile and release specifications should be forwarded to Central Drugs Laboratory, as and when required / instructed.

Guidance for Industry

Requirements for permission of New Drug Approval

The manufacturer / sponsor have to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945. As the Form 44 is an application for grant of permission to import or manufacture a new drug or to undertake Clinical Trial the Central Drugs Standard Control Organization prescribes information to be submitted for New Drugs Approval (Market Authorization) of Biological in the following format to simplify the submission requirements. 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 document design is as per the International submission requirements of Common Technical Document (CTD) and has five Modules.

Module I: Administrative/Legal Information

Module II: Summaries

Module III: Quality Information (Chemical, Pharmaceutical and Biological)

Module IV: Non-Clinical Information

Module V: Clinical Information

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

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

Soft Copies: They must be well labeled 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.

Document No. – MA/71108

Version - 1.1

Objective

The purpose of this document is to achieve greater harmonization in the information submitted in the application for Market Authorization for 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 use in humans, regardless of where they are manufactured , whether they are licensed in the country of origin or not, and considering the current requirements of Drugs and Cosmetic Act and Rules 1945.

MODULE - 1

1.1	**Comprehensive table of contents (Modules 1 to 5)**
1.2	**Administrative information**
1.2.1	**Application in Form 44 and Treasury Challan (fee)**
1.2.2	**Legal and statutory documents**
1.2.2.1	License and approvals: As applicable (a) Copy of Form 11 for imported drug product (b) Form-29 for indigenous drug (c) Clinical Trial no objection letters / approval (d) GEAC clearance
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 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 Pharmaceutical Product Certificate (PPC) as per WHO GMP certification scheme for imported drug products
	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 for imported products.
	g) Undertaking to declare (as per Annex. A)
1.2.2.3	A copy of Site Master File
1.2.2.4	Certificate of Analysis from Central Drug Laboratory (India) of three consecutive batches.
1.2.2.5	Product Permission Document (PPD) as per Annex B
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	Dispensing requirements
1.2.4.7	Route of administration
1.2.4.8	Commercial presentation
1.2.4.9	Conditions of storage or conservation
1.2.4.10	Summary of product characteristics As per Annex C
1.2.4.11	Product Labeling (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) Monograph for health professionals or information for prescription.
1.2.4.12	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 licensed 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	**Samples of drug product:** Samples of drug substance and drug product (an equivalent of 50 clinical doses or double the quantity required (whichever is more) for complete testing of product with testing protocols, full impurity profile and release specifications should be forwarded to Central Drugs Laboratory, as and when required / instructed.

MODULE - 2

2.1	**Table of contents of Module 2**
2.2	**Introduction**
2.3	**Quality overall summary**
2.3.S	Summary of drug substance
2.3.P	Summary of drug product
2.3.A	Appendices
2.4	**Overview of non-clinical studies**
2.4.1	Introduction and GLP statement
2.4.2	Overview of the non clinical testing strategy
2.4.3	Pharmacology
2.4.4	Pharmacokinetics
2.4.5	Toxicology
2.4.6	Integrated overview and conclusions
2.4.7	List of literature
2.5	**Non-clinical Summary**
2.5.1	Introduction
2.5.2	Written summary of pharmacology

2.5.3.	Tabular summary of pharmacology
2.5.4	Written summary of pharmacokinetics (if applicable)
2.5.5	Tabular summary of pharmacokinetics (if applicable)
2.5.6	Written summary of toxicology
2.5.7	Tabular summary of toxicology
2.6	**Overview of clinical 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	**Clinical summary**
2.7.1	Introduction
2.7.2	Table of contents
2.7.3	Summary of clinical studies of immunogenicity
2.7.4	Summary of clinical studies of efficacy
2.7.5	Summary of clinical 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	**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 the drug substance
3.2.S.1.2	Structural formula, molecular formula and relative molecular weight (if applicable)
3.2.S.1.3	Description and characterization of drug substance
3.2.S.1.4	General description and history of starting material
3.2.S.1.4.1	Strain
3.2.S.1.4.2	System of seed/master/working banks
3.2.S.1.4.3	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	Identification 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 drug substance**
3.2.S.3.1	Physicochemical Characterization
3.2.S.3.2	Biological Characterization
3.2.S.3.3	Impurities (name, manufacturer)
3.2.S.4	**Quality control of 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 primary and secondary packing
3.2.S.6.2	Tests and evaluation of packaging materials
3.2.S.7	**Stability of drug substance**
3.2.S.7.1	Protocol of stability study, results and conclusions
3.2.S.7.2	Post-approval stability program
3.2.S.7.3	Storage and shipping conditions of drug substance
3.2.P	**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 manufacturer and 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	Determination and characterization of impurities
3.2.P.5.7	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 primary and secondary packing
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, diluents and re-constituted products, thermo 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

Non-Clinical Reports

4.1	**Table of contents of the Module**
4.2	**Reports on studies**
4.2.1	**Pharmacology**
4.2.1.1	**Pharmacodynamic studies (immunogenicity of product)**
4.2.1.2	**Pharmacodynamic 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 on:**
	Design of study and justification of animal model
	Animal species used, age and size of groups
	Dose, mode of administration and control groups
	Monitored parameters
	Local tolerance
4.2.3.2	**Special toxicology (for products to which it applies)**
	Special immunological investigations

	Toxicity studies on special populations
	Studies of genotoxicity and carcinogenicity
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

Reports of Clinical Studies

5.1	**Table of contents of the Module**
5.2	**Contents: Reports of clinical studies**
5.2.1	**Phase I studies**
5.2.2	**Phase II studies**
5.2.3	**Phase III studies**
5.2.3.1	**Bridging Studies**
5.2.4	**Special considerations**
5.2.5	**Adjuvant (s)**
5.2.6	**Phase IV studies and / or Pharmacovigilance Plan** (if applicable)
5.2.7	**Non-inferiority studies** (for combined vaccines, or approved vaccines prepared by new manufacturers)
5.2.8	**Co-administration studies with other vaccines**
5.2.9	**Case Report Forms and Individual Patient Listings**
5.3	**Bibliographic references**
	Abbreviations

Annexure A to Module I

Undertaking to declare that: -

1. We shall comply with all the conditions imposed on the (licensing and/or Market Authorisation) of the applied drugs as per the provisions of the Drugs and Cosmetics rules Act and Rule made there under.

2. We declare that we are carrying on the manufacture of the drugs at the premises specified in Module I of the submitted documents, 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. We shall comply with the provisions of Part IX of the Drugs and Cosmetics Rules, 1945.

4. Every drug manufactured by us for licensing and / market authorisation shall be as regard strength, quality and purity conforms with the provisions of Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules 1945, and their amendments from time to time.

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 product permission, licence and/or market authorisation to be granted to us. Where any change in respect of any of the drugs 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 applicable fee under Drugs and Cosmetics Rules 1945.

6. 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 licensing and/or Market Authorisation declared by any Regulatory Authority of any country where the drug is marketed/sold or distributed. The despatch and marketing of the drug in such cases shall be stopped immediately and the licensing authority shall be informed immediately. Further action in respect of stop marketing of drug shall be taken as per the directions of the licensing authority. In such cases, action equivalent to that taken with reference to the concerned drug(s) in the country of origin or 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.

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.

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.

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.

10. We hereby declare that the submitted information/documents are factual and relevant to the application for new drug approval.

Place:

Date:

Signature of the manufacturer

[*or his authorized agent*]

Seal / Stamp

Annexure B to Module I

Doc. No. PPD/71108 Ver.1.1

PRODUCT PERMISSION DOCUMENT (PPD-BIOLOGICAL)

FOREWORD

The *PPD-BIOLOGICAL* template should be completed to provide a condensed summary of the key Quality information for any biological product or any combination drug for use which has a biological component. For example PPD-BIOLOGICAL template should be used for Biotech product, a gene therapy, a plasma derived blood product, a natural therapeutic product, a conventional or combined vaccine. New Drug Submissions (NDSs) containing drug substances and their corresponding products that are filed with CDSCO pursuant to the various provisions of Drugs and Cosmetic Act 1940 and Rules made there under. The PPD-BIOLOGICAL constitutes part of the Product Permission package. The PPD-BIOLOGICAL provides an accurate record of technical data in the drug submission at the time the license / product is issued, and thereafter serves as an official reference document during the course of post-approval inspections and post-approval change evaluations as performed by CDSCO. The PPD-BIOLOGICAL is a condensed version of the Quality Overall Summary and represents the final, agreed upon key data from the drug submission review (e.g., identification of the manufacturer(s), drug substance / drug product specifications, stability conclusions). The PPD-BIOLOGICAL template is structured to permit the rapid assembly of the PPD-BIOLOGICAL by copying requisite information from the corresponding portions of the Quality Overall Summary filed with the

original drug submission. It is acknowledged that the numbering of the sections may not entirely be sequential.

For NDSs the PPD-BIOLOGICAL should be provided *upon request* (e.g., typically when the review of the drug submission is near completion). For SNDSs and Notifiable Changes (NCs), the PPD-BIOLOGICAL should be completed *in its entirety* (regardless of the proposed change), include information on *all dosage forms*, and be provided *at the time of filing*. It is acknowledged that when filing a Supplement or NC, the updated PPD-BIOLOGICAL could include changes that did not require prior approval by CDSCO

When completing the PPD-BIOLOGICAL template, this covering *Foreword* should be deleted.

- In case of Post licenser changes approval, information as per the relevant sections are to provided as Annexure to this PPD.

Annexure B to Module I

PRODUCT PERMISSION DOCUMENT

Guidance on the PPD-BIOLOGICAL

S.NO.	TIEMS	INFORMATION TO BE PROVIDED
1	**INTRODUCTION**	
1.1	Submission File#	
1.2	NDS Approval Date and Control#:	
1.3	PPD-BIOLOGICAL Revision Date and Control#:	
1.4	Proprietary Name:	
1.5	Non-proprietary name or common name of the drug substance:	
1.6	Company Name:	
1.7	Name of INDIAN Distributor / Agent:	
1.8	Therapeutic or Pharmacological Classification:	
1.9	Dosage form(s):	

1.10	Strength(s):	
1.11	Route(s) of Administration:	
1.12	Maximum Daily Dose:	
2.0	New Active Substance (NAS)?	
S	**DRUG SUBSTANCE (NAME, MANUFACTURER)**	
S.1	**Manufacture (name, manufacturer) and Address**	**Module 3.2.S.2**
S.1.1	*Manufacturer(s) (name, manufacturer)*	Information on the manufacturer(s): [Insert the completed Module 3.2.S.2]
S.1.2	*Description of Manufacturing Process and Process Controls (name, manufacturer)*	A flow diagram of the manufacturing process and process controls: [Insert the flow diagram(s), from the completed Module *3.2.S.2)*
S.1.3	*Control of Materials (name, manufacturer)*	A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance: [Insert the tabulated summary of the biological raw material(s) used, from the completed Module *3.2.S.2*] A summary of prepared reagents: [Insert the tabulated summary of prepared reagents from the completed

		Module *3.2.S.2*]
S.1.4	*Controls of Critical Steps and Intermediates (name, manufacturer)*	A summary of critical manufacturing steps, process controls performed, and acceptance criteria: [Insert a summary of critical manufacturing steps, process controls performed, and acceptance criteria from the completed Module *3.2.S.2*, under *Critical Steps*.] Highlight critical process intermediates, their quality and control: [Insert a summary of the quality, control and storage conditions of intermediates isolated during the process from the completed Module *3.2.S.2*, under *Intermediates*.]
S.2	**Characterization (name, manufacturer)**	
S.2.1	*Elucidation of Structure and other Characteristics (name, manufacturer)*	A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterization data (for example, primary and higher order structure and biological activity): [Insert a summarized description of this information from the completed Module *3.2.S.3*]
S.2.2	*Impurities (name, manufacturer)*	A tabulated summary of the impurities data: [Insert the tabulated summary on

		actual impurity levels detected from the completed Module *3.2.S.3.*]
S.3	**Control of Drug Substance (name, manufacturer)**	
S.3.1	*Specification (name, manufacturer)*	Specification for the drug substance: [Insert the specification for the drug substance from the completed Module *3.2.S.4]* The Drug Substance standard declared by the company responsible for routine testing: [Insert the declared drug substance standard from the completed Module *3.2.S.4*]
S.3.2	Stability (name, manufacturer) *Stability Summary and Conclusions (name, manufacturer)*	The proposed storage conditions retest date or shelf-life, where relevant: [Insert the proposed storage conditions, retest date or shelf-life, where relevant, from the completed Module *3.2.S.7*]
P	**DRUG PRODUCT (NAME, DOSAGE FORM)**	
P.1	**Manufacture (name, dosage form)**	**Module 3.2.P.3**
P.1.1	*Manufacturer(s) (name, dosage form)*	Information on the manufacturer(s): [Insert the completed Module *3.2.P.3.*]

P.1.2	*Batch Formula (name, dosage form)*	Information on the batch formula: [Insert the tabulated summary on the batch formula from the completed Module *3.2.P.3.*]
P.1.3	*Description of Manufacturing Process and Process Controls (name, dosage form)*	A flow diagram of the manufacturing process and process controls: [Insert the process flow diagram from the completed Module *3.2.P.3.*.]
P.1.4	*Controls of Critical Steps and Intermediates (name, dosage form)*	A summary of critical manufacturing steps, process controls performed, and acceptance criteria: [Insert a summary of critical manufacturing steps, process controls performed, and acceptance criteria from the completed Module *3.2.P.3*, under *Critical Steps*.] Highlight critical process intermediates, their quality and control: [Insert information on the quality and control of intermediates isolated during the process, from the completed Module *3.2.P.3.* under *Intermediates*.]
P.2	**Control of Excipients (name, dosage form)**	**Module 3.2.P.4**
P.2.1	*Excipients of Human or Animal Origin (name, dosage form)*	A summary of excipients of human or animal origin that are used: [Insert the tabulated summary of excipients of human or animal origin that are used from the completed Module *3.2P.4.]*

P.3	**Control of Drug Product (name, dosage form)**	**Module 3.2.P.4**
P.3.1	*Specification(s) (name, dosage form)*	Specification(s) for the drug product: [Insert the specification(s) for the drug product from the completed Module *3.2.P.4.1*] The Drug Product standard declared by the company responsible for routine release testing and post-market stability testing: [Insert the declared drug product release standard from the completed Module *3.2.P.4.1*]
P.3.2	Container Closure System (name, dosage form)	A brief description of the container closure system for the drug product: [Insert a brief description of the container closure system for the drug product from the completed Module 3.2.P.7]
P.4	**Stability (name, dosage form)**	**Module 3.2.P.8**
P.4.1	*Stability Summary and Conclusion (name, dosage form)*	The proposed labeled storage conditions and retest date or shelf-life, including after reconstitution and in-use storage conditions (if applicable): [Insert the proposed labeled storage conditions and retest date or shelf-life, including after reconstitution and in-use storage conditions (if applicable) from the completed Module *3.2.P.8.1*]

P.4.2	*Post-approval Stability Protocol and Stability Commitment (name, dosage form)*	The post-approval stability protocol and stability commitment: [Insert the post-approval stability protocol and stability commitment from the completed Module *3.2.P.8.3*]
A	**APPENDICES**	**Module 3.2.A**
A.1	Facilities and Equipment (name, manufacturer)	Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product: [Insert information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product from the completed Module 3.2.A.1.]
A.2	Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)	A tabulated summary of the reduction factors for viral clearance: [Insert the tabulated summary of the reduction factors for viral clearance from the completed Module 3.2.A.2, under *Viral Clearance Studies*.] The calculation of estimated particles / dose, where relevant: [Insert the calculation of estimated particles/ dose, where relevant from the completed Module 3.2.A.2, under *Viral Clearance Studies*.]

Annexure C to Module I

SUMMARY OF PRODUCT CHARACTERISTICS

Doc. No. SPC/71108 Ver.1

Annexure C to Module I

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Excipient(s):>

Give full list of excipients.

3. PHARMACEUTICAL FORM

<The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.>

<The tablet can be divided into equal halves.>

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<This medicinal product is for diagnostic use only.>

4.2 Posology and method of administration

<{(Invented) name} is not recommended for use in children <above> <below> {age Y} due to <a lack of> <insufficient> data on <safety> <and> <or> <efficacy>

<The experience in children is limited.>

<There is no experience in children>

<There is no relevant indication for use of {(Invented) name} in children.>

<{(Invented) name} is contraindicated in children

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

Pharmacotherapeutic group: {group}, ATC code: {code}

<This medicinal product has been authorised under a so-called “conditional approval” scheme.

This means that further evidence on this medicinal product is awaited.

<This medicinal 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 medicinal product.

5.2 Pharmacokinetic properties

5.3 Preclinical safety data

<Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.>

<Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

<Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:>

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 medicinal products.>

<This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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

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 of in accordance with local requirements.>

7. <MARKETING AUTHORISATION> <PREQUALIFICATION> HOLDER

{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

Document No. - PAC/1108

Version – 1.1

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Appendix 1: Glossary

1. INTRODUCTION

1.1 Objectives

a. To assist with the classification of changes made to biological products that have received an approval.

b. To provide sponsors 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 sponsors intending to make changes to biologics 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 pharmaceutical and biological products quality assessment of these products. As such, the guidance documents were needed on the information to support quality changes to new 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, sponsors are advised to contact Drug Controller General of India (DCGI).

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 DCGI 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 DCGI. The appropriate fee must also be paid, in accordance with the prevailing rules at the time of submission of the notification. If, within 30 days of the date of the acknowledgement of receipt of

a valid notification, the DCGI has not sent the holder its opinion, the notified shall be deemed to have been accepted by DCGI.

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 DCGI as a Notifiable Change (NC).

If, within 15 days of the date of the acknowledgement of receipt of a valid notification, the DCGI has not sent the holder its opinion, the notified shall be deemed to have been accepted by DCGI.

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.

The changes included in this reporting category may be implemented by the sponsor without the prior review by DCGI of the data supporting such a change. Supporting data for the Level III changes recommended in this guidance documents should be submitted on annual basis; however, the data on such changes should be available to DCGI within fifteen (15) calendar days, if requested at any time.

3. DOCUMENTATION

3.1 General Information

The change 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 DCGI in the lights of scientific justification provided by the sponsor and accordingly the level shall be decided;

b. The *supporting data* for a given change, either to be submitted to DCGI and/or maintained by the sponsor. 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 DCGI.

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 *DCGI*, where applicable.

Supporting Data Common to Level I and Level II Changes

The following should be should also 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 in sufficient 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 DCGI 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, manufacturer's/sponsor's name, submission type, control number, date approved).

3.3 Supporting Data - Level III Changes

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

3.4 Comparative Studies

3.4.1 Comparative In vivo Studies

A number of changes outlined in Appendices 1 include recommendations for supporting comparative *in vivo* studies (e.g., bridging clinical studies for Biologics).

Sponsors should consult the applicable ICH and WHO guidance documents when conducting comparative *in vivo* studies.

3.5 Stability Testing

If stability studies are recommended to support a change, these studies should be conducted in accordance with applicable DCGI guidance on:

a. *Stability Testing of New Drug Substances and Products;*

b. *Stability Testing of Existing Drug Substances and Products;*

c. *Stability Testing of Biotechnological/Biological Products.*

4. Quality Post-Approval Changes (Biologics)

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

4.1 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	1-3	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.
2. Information on the changed nomenclature of the drug substance (e.g., Recommended INN, compendial name, chemical name(s)).
3. Evidence that the changed name for the drug substance is recognized (e.g., proof of acceptance by WHO, a copy of the INN list).

4.1.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change to a 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	3-4	11-13	Annual

manufacturing area			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, and impurity profile.
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 DCGI 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 drug substance manufacturing process, involving:			
a. a critical change	None	1-3,5-12	Supplement
b. a non-critical change	1-2	1-3,5-11	Notifiable 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 bioreactors.
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, and impurity profile.

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 DCGI 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 (e.g., impact on the viral clearance studies, BSE/TSE risk).
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 a different expression construct with the same coding sequence and the same cell line; or adaptation of a MCB into a new fermentation medium	None None	1-8 3	Supplement 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); Working Seed Bank (WSB) extended beyond an approved passage level	None 4	3-9	Supplement 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 DCGI 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 and clinical data or a request for a waiver of *in vivo* studies.
9. Supporting clinical 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 Characterization

There are not any quality change examples for this section at the present time that have not been addressed in other sections.

4.1.4 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 ICH 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 a 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).

4.1.5 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 House	1	1	Notifiable Change
Update the reference standards from 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).

4.1.6 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 DCGI of any failures in the ongoing stability studies.
3. Demonstration of compatibility if the drug substance is a liquid.

4.1.7 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the re-test period (or shelf life) for the drug 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
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 *are* 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 *are 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 ICH's Q1E guideline,
5. Stability data were generated in accordance with the approved stability

protocol.

6. Significant changes (as defined in ICH's Q1A guideline) 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 DCGI 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 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 *DCGI regulation*.

Supporting Data

1. Supporting clinical 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, manufacturer's/sponsor'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 *DCGI 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 and six (6) months of long term testing 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	2-11,13	Supplement
d. addition of a new presentation (e.g., addition of syringes to vials)	None	1-11,13,14	Notifiable Change

Conditions

1. None of the excipients are prohibited by the *Food and Drug Regulations*.

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 Control 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. Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.
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 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 DCGI of any failures in the ongoing stability studies.
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 clinical data or a request for a waiver of *in vivo* studies.
13. Supporting clinical data (usually PK/PD only) or a request for a waiver of *in vivo* studies.
14. For a new device (e.g., pre-filled syringes or pens), information to the Medical Device Bureau to qualify the proposed device.

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 DCGI 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
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 DCGI 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 equipments.
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 DCGI 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 equipments 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	None	1-5	Notifiable

test	None	1-5	Change
	1-4	1-5	Annual Notification
c. relaxation of an acceptance criterion	None	1-5	Notifiable Change
d. tightening of an acceptance criterion	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 DCGI. 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 a 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	1,2	1-4	Annual Notification

pharmacopoeial monograph			

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 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 specifications for the excipient, involving:			
a. deletion of a test	None	1-4	Notifiable Change

	5	1-4	Annual Notification
b. replacement or addition of a 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 ICH 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
Change in the specifications for the excipient, involving the analytical procedures:			
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	1,2	1,3,5,7	Notifiable Change

excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source			
Change in manufacture of a biological excipient	1-3	4-9	Notifiable Change
	2,3	2,3,5-7	Notifiable Change
	1-3	2,3,5-7	Annual Notification

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 (e.g., impact on the viral clearance studies, BSE/TSE risk).
9. Supporting comparative clinical data (usually PK/PD only).

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	None	6,7,11	Notifiable Change

species/strains for a test (e.g., new species/ strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)			
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 ICH 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	Notifiable Change
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 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 (with a Letter of Access provided in Module 1) or relevant drug product information.
2. Information demonstrating technology transfer validation and equipment qualification, as appropriate.

3.2.P.5 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 House	1	1	Notifiable Change
Update the reference standards from 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	None	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	1,2,3	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	Notifiable Change
	1,2,3,5,6	1,2,5	Annual Notification
b. Reduction	1,5	1-5	Notifiable Change
Addition of storage condition for	1	1-5	Notifiable

the drug product			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 *are* 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 *are not* available covering the changed re-test period (or shelf life) or *are not* based on stability data generated on at least three production scale batches. If the proposed re-test period (or shelf life) is beyond the available long term data, the extrapolation is in accordance with ICH's Q1E guideline.
5. Stability data were generated in accordance with the approved stability protocol.
6. Significant changes (as defined in ICH's Q1A guideline) 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 DCGI 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 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 Phase-I, Phase-II and Phase-III 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 Phase-I, Phase-II and Phase-III 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 drug 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 or 100,000 tablets or capsules, whichever is the larger.

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 equipments.

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3.2.S.2 DRUG SUBSTANCE (NAME, MANUFACTURER)

Manufacture (name, manufacture)

Information on the manufacturer(s): [Insert the completed Module 3.2.S.2]

Description of Manufacturing Process and Process Controls (name, manufacturer)

A flow diagram of the manufacturing process and process controls: [Insert the flow diagram(s), from the completed Module 3.2.S.2]

Control of Materials (name, manufacturer)

A description of the Source and Starting material and Raw materials of biological origin used in the manufacture of the drug substance: [Insert the tabulated summary of the biological raw material(s) used, from the completed Module 3.2.S.2]

Control of critical steps and Intermediates (name, manufacturer)

A summary of critical manufacturing steps, process controls performed, and acceptance criteria: [Insert a summary of critical manufacturing steps, process controls performed, and acceptance criteria from the completed Module 3.2.S.2 under Critical Steps]

Highlight critical process intermediates, their quality and control: [Insert a summary of the quality control and storage conditions of intermediates isolated during the process]

3.2.S.3 Characterization (name, manufacturer)

- Physicochemical Characterization
- Biological Characterization

Impurities (name, manufacturer)

A tabulated summary of the impurities data: [Insert the tabulated summary on actual impurity levels detected from the completed Module 3.2.S.3]

Control of Drug Substance (name, manufacturer)

Specification (name, manufacturer)

Specification for the drug substance: [Insert the specification for the drug substance from the completed Module 3.2.S.4]

The drug substance standard declared by the company responsible for routine testing: [Insert the declared drug substance standard from the completed Module 3.2.S.4.1]

Stability (name, manufacturer)

Stability Summary and Conclusions (name, manufacturer)

The proposed storage conditions retest data or shelf-life, where relevant: [Insert the proposed storage conditions, retest data or shelf-life, where relevant, from the completed Module 3.2.S.7]

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

Manufacture (name, dosage form)

Manufacturer(s) (name, dosage form)

Information on the manufacturer(s): [Insert the completed Module 3.2.P.3]

Batch Formula (name, dosage form)

Information on the batch formula: [Insert the tabulated summary on the batch formula from the completed Module 3.2.P.3]

Description of Manufacturing Process and Process Controls (name, dosage form)

A flow diagram of the manufacturing process and process controls: [Insert the process flow diagram from the completed Module 3.2.P.3.]

Controls of Critical Steps and Intermediates (name, dosage form)

A summary of critical manufacturing steps, process controls performed, and acceptance criteria: [Insert a summary of critical manufacturing steps, process controls performed, and acceptance criteria from the completed Module 3.2.P.3.4, under Critical steps]

Highlight critical process intermediates, their quality and control: [Insert information on the quality and control of intermediates isolated during the process, from the completed Module 3.2.P.3.4]

Control of Excipients (name, dosage form)

A summary of excipients of human or animal origin that are used: [Insert the tabulated summary of excipients of human or animal origin that are used from the completed Module 3.2.P.4]

3.2.P.5 Control of Drug Product (name, dosage form)

Specification(s) (name, dosage form)

Specification(s) for the drug product: [Insert the specification(s) for the drug product from the completed Module 3.2.P.5.1]

The drug product standard declared by the company responsible for routine release testing and post-market stability testing: [Insert the declared drug product release standard from the completed Module 3.2.P.5.1]

Container Closure System (name, dosage form)

A brief description of the container closure for the drug product: '[Insert a brief description of the container closure system for the drug product from the completed Module 3.2.P.7]

Stability (name, dosage form)

Stability Summary and Conclusion (name, dosage form)

Stability Summary and conclusion (name, dosage form)

The proposed labelled storage conditions and retest date or shelf life, including after reconstitution and in-use storage conditions (if applicable): [Insert the proposed labelled storage conditions and retest date or shelf-life, including after reconstitution and in-use storage conditions (if applicable) from the completed Module 3.2.P.8]

Post-approval Stability Protocol and Stability Commitment (name, dosage form)

The post-approval stability protocol and stability commitment: [Insert the post-approval stability protocol and stability commitment from the completed Module 3.2.P.8.3]

A APPENDICES

Facilities and Equipment (name, manufacturer)

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product: [Insert information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product from the completed Module 3.2.A.1.]

Safety Evaluation Adventitious Agents (name, dosage form, manufacturer)

A tabulated summary of the reduction factors for viral clearance: [Insert the tabulated summary of the reduction factors for viral clearance from the completed Module 3.2.A.2, under *Viral Clearance Studies*.]

MODULE 3:
QUALITY INFORMATION (CHEMICAL, PHARMACEUTICAL & BIOLOGICAL)

3.1 TABLE OF CONTENTS OF MODULE 3

A Table of Contents for the filed application should be provided.

3.2 QUALITY CONTENTS

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

Information must be provided for each Drug Substance

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the drug substance should be provided. For example:

• Recommended International Non-proprietary Name (INN);
• Compendial name if relevant;
• Chemical name(s);
• Company or laboratory code;
• Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and
• Chemical Abstracts Service (CAS) registry number.

3.2.S.1.2 Structure (name, manufacturer)

The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate. A brief description of the structural formula(e) of other drug(s) of similar structure, should be provided where useful.

3.2.S.1.3 **Description and Characterization of drug substance**

3.2.S.1.4 **General description and history of starting material**

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity. The following information should also be provided: strain/cell substrate, system of seed/master/working banks, and embryonated eggs.
Analytical certificates signed by the Manufacturer and the Applicant for Registration should be submitted.

3.2.S.1.4.1 **Strain/cell substrate**

3.2.S.1.4.2 **System of seed, Master, Working bank**

3.2.S.1.4.3 **Embryonated egg and other cell substrate**

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

Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

Description of Manufacturing Process and Process Controls (name, manufacturer)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls.

For example: Information should be provided on the manufacturing process, which typically starts with avial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.

Rather then providing separate flow diagrams for the fermentation and purification processes, the applicant may consider providing an overall process flow diagram, including the relevant information described under each step below. e.g. in-process control testing, size and scale of equipment, batch size, pooling, hold times, and method of transfer. An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided. Since pooling may occur at more than one step, it may be more appropriate to describe the batch size and scale under the respective step(s), both within the flow diagram(s) and in the detailed description.

A brief description of batch identification system should be provided.

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives, major equipment and process controls, including in process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria. Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided.

Purification and modification reactions

A **flow diagram** should be provided that illustrates the purification steps (i.e. unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates.

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided.

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided.

The container closure system(s) used for storage of the drug substance and storage and shipping conditions for the drug substance should be described.

Quality control of Drug substance

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation.

For non-biological-sourced raw materials (e.g. nonmedicinal ingredients, prepared reagents) information should also be provided on the manufacturer, pharmacopoeial grade or standard, and storage (if the material is kept at non-ambient conditions). If the material is not of a pharmacopoeial grade, the specification, should be included.

Detailed information on Prepared Reagents, including their composition, specifications of the raw materials used in their preparation, a description of their preparation and sterilization, storage conditions, and shelf-life, should also be provided. In addition, a tabulated summary should be provided.

Name of Prepared Reagent	Specifications of Raw Materials	Storage conditions	Shelf-life

Control of Source and Starting Materials of Biological Origin

Summaries of viral safety information for biologically-sourced materials should be provided.

Detailed information on the suitability for use of the biological raw materials that are utilized as processing aids (e.g. auxiliary material), should be provided, including their source, country of origin, manufacturer, method of manufacture, microbiological controls performed, and specifications.

In addition, a summary of the biological raw material(s) that are utilized as processing aids, including the source, country of origin, manufacturer, manufacturing step where used, and a brief description on the suitability for use based upon the controls evaluated (e.g. history, testing, screening), should be provided.

Biological raw material	Biological source	Country of origin	Manufacturer	Step	Suitability for use

Source, history, and generation of the cell substrate

Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described. This information could also include a flow diagram on the derivation of the cell substrate.

Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug and supporting literature references should be provided.

Cell banking system, characterisation, and testing

Information on the cell banking system, quality control activities, and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided. This information could also include, for example: details of testing performed on all cell banks, and a flow diagram on the derivation of the cell banks with details on cell concentration, volume, and the number of aliquots prepared. In addition, a tabulated summary of the specifications, and results of characterisation and testing performed on the cell banks could be provided.

Controls of critical Steps and Intermediates (name, manufacturer)

Critical Steps

Tests and acceptance criteria (with justification including experimental data) performed at critical steps of the manufacturing process to ensure that the process is controlled should be provided. This information should be provided in detail.

A summary of critical manufacturing steps, process controls performed, and acceptance criteria should also be provided. A discussion of the process control(s) selected for each critical manufacturing step and justification of the proposed acceptance criteria should also be provided.

Process Validation and/or Evaluation (name, manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included. Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification). The information provided in the study report should support the current manufacturing process proposed for commercial use, including data to demonstrate consistency in yield and production, and degree of purity. The validation study report for the extent of

reuse and regeneration of columns and membranes should be provided, including in-process test results and data from relevant manufacturing batches, to demonstrate consistency in the quality and safety of the drug substance during production. The suitability of any proposed reprocessing procedures should be described and the criteria for reprocessing of any intermediate or the drug substance should be discussed. If adjuvants are added to the drug substance, information and data from the adsorption and desorption study should be submitted.

Manufacturing Process Development (name, manufacturer)

The developmental history of the manufacturing process, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number (and subsequential drug product batch numbers), manufacturing date, scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided. The significance of the change should be assessed by evaluating its potential to impact the quality (e.g. biological activity, impurity profile) of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. A cross-reference to the location of these studies in other sections of Module 3 (e.g. Stability, Control of Drug Substance or Drug Product) and/or in other modules of the submission should be included.

A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency should also be provided.

3.2.S.3 Characterization of Drug substance (name, manufacturer)

This section should contain a description of all analytical testing performed to characterize the drug substance with respect to identify, purity, potency and stability. Test results should include actual data such as tabular data, legible copies of chromatograms or spectra, photographs of gels or immunoblots, actual histograms of cytometric analysis, or other appropriate formats. Data should be well organized and fully indexed to enable easy access. Results for quantitative assays should be presented as actual data, not generally as "Pass" or "Fail".

3.2.S.3.1 Physicochemical Characterization

In general, characterization may include, but is not limited to the following:

- UV/visible or mass spectrometry
- Amino acid analysis
- Carbohydrate analysis and, if appropriate, sequencing
- Peptide mapping
- Determination of disulfide linkage
- Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE), Native PAGE
- Isoelectric focusing (1D or 2D)
- Various chromatographic methods such as HPLC, GC, LC, or thin layer chromatography
- Nuclear Magnetic Resonance spectroscopy; and/or
- Assays to detect related proteins including delaminated, oxidized, processed, and aggregated forms including dimers, trimers etc and other variants, such as amino acid substitutes and adducts/derivatives, and other process contaminants such as sulfhydral reagents, urea, residual host proteins, residual DNA, and endotoxin.

Additional physicochemical characterization may be required for modified drug substances such as conjugates, multiple antigen peptides (MAP), or those undergoing further chemical or enzymatic modifications. The information provided should include the degree of derivatization or conjugation, the amount of unmodified substance, removal of free materials (e.g. toxins, linkers, etc), and the stability of the modified substance.

3.2.S.3.2 Biological Characterization

Further characterization of vaccines may include, but is not limited to the following:

- Specific identify testing such as Western blot analysis or ELISA
- Cytometric analysis
- Neurovirulence testing, if appropriate
- Serotyping
- Electrophoretic typing
- Inactivation studies
- Neutralization assays; and
- Titrations

A description and results of all relevant *in vitro* and *in vivo* biological testing (bioassays) performed on the manufacturer's reference standard lot or other relevant lots to demonstrate the potency and activity (ies) of the drug substance should be provided. This section should include a complete description of the protocol used for each bioassay, the control standards used, the validation of the inherent variability of the test, and the established acceptance limits for each assay. The characteristic of specific antibodies used in the immunochemical or serological assays should also be included.

3.2.S.3.3 *Impurities (name, manufacturer)*

Information on impurities should be provided. All potential impurities, including degradation products arising from manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches. The actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability, and proposed commercial batches) should be reported, for example, using a summary table.

Impurity	Proposed limit	Use of Batches and Lot Number							
		Batches used in toxicological studies				Batches used in clinical studies			
Product Related Impurities									
Total									
Process Related Impurities									
Residual Solvents									

3.2.S.4 Quality control of Drug substance (name, manufacturer)

3.2.S.4.1 *Specification (name, manufacturer)*

The specification for the drug substance should be provided. For example, the specification could be presented using a table with the specification reference number, specification approval date, test parameter(s), method type, method code, source, and acceptance limit(s) at release, shelf-life or for both.

3.2.S.4.2 *Analytical Procedures (name, manufacturer)*

The analytical procedures used for testing the drug substance should be provided.
A summary of the analytical procedures should also be provided. (This may be combined with the summary of the validation of analytical procedures.

3.2.S.4.3 *Validation of Analytical Procedures (name, manufacturer)*

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.
A summary of the validation of analytical procedures should also be provided. (This may be combined with the summary of the analytical procedures and a summary of the justification of the specification).

3.2.S.4.4 *Batch Analyses (name, manufacturer)*

Description of batches and results of batch analyses should be provided. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use. Confirmation should be provided that the batch analysis data results reported in the submission were generated by the company responsible for routine testing of the drug substance. Results which are close to or outside of current limits should be discussed. Any changes in specifications, test methods, limits and validation, and a rationale for those changes over the production history should also be described. A description of the lot numbering system should be provided.

A tabulated summary (or graphical representation where appropriate) of results (other than impurities) from in vivo (bioequivalence, pivotal clinical) study batches and recent production batches should also be provided.

Test Parameter	Range of Results for *in vivo* study batches (Total number of batches)	Range of results for recent production batches (Total number of batches)

3.2.S.4.5 *Justification of Specification (name, manufacturer)*

Justification for the drug substance specification should be provided.
A summary of the justification of the drug substance specification should also be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

3.2.S.6 Container Closure System (name, manufacturer)

A description of the container closure system(s) should be provided, including the supplier(s), identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). This description should include the information appearing on the label(s). Non-compendial methods (with validation) should be included, where appropriate.
For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For

functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 *Stability Summary and Conclusions (name, manufacturer)*

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate. As clarification, “results” refers to the conclusions from the various studies, addressing storage conditions tested, container closure system, batch number, completed and proposed test stations, study test parameters and frequency of testing, recommended shipping and monitoring conditions, and the proposed storage conditions, retest date or shelf-life, where relevant.

3.2.S.7.2 *Post-approval Stability Protocol and Stability Commitment (name, manufacturer)*

The post-approval stability protocol and stability commitment should be provided.

3.2.S.7.3 *Stability Data (name, manufacturer)*

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to

generate the data and validation of these procedures should be cross-referenced to other sections of Module 3 that contain this information. A tabulated summary (with graphical representation, where appropriate) of the results from the stability studies, should also be provided.

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

A description of the drug product and its composition should be provided. The information provided should include, for example

• Description of the dosage form;

• Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)

• Description of accompanying reconstitution diluent(s); and

• Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

3.2.P.2 Pharmaceutical Development (name, dosage form)

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and

drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

3.2.P.2.1 Drug Substance (name, dosage form)

The compatibility of the drug substance with excipients should be discussed.
Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.
For combination products, the compatibility of drug substances with each other should be discussed.

Excipients (name, dosage form)

The choice of excipients (including adjuvants), their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.
A confirmation that none of the non-medicinal ingredients (excipients) which appear in the final product are prohibited for use in drugs by the *Drugs & Cosmetics Act 1940*, should be provided.

3.2.P.2.2 Drug Product (name, dosage form)

Formulation Development (name, dosage form)
A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should

be discussed when appropriate. A tabulated summary of the composition of the formulations used in clinical trials and the batches affected, should also be provided

Composition of Formulation or Code#	**Batch#(s)**	**Strength**	**Type of Study Used In**

***3.2.P.2.3* Justification of final qualitative/quantitative formula should be provided.**

3.2.P.2.4 Manufacturing Process Development (name, dosage form)

The selection and optimisation of the manufacturing process in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified. Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process that can influence the performance of the product should be discussed. A cross-reference should be made to other sections and/or Modules where related study data may be found, such as to the drug product batch analysis data provided ,to the in-process control tests batch analysis, and to the batch analysis data on impurities provided

3.2.P.2.5 .Packaging/ Container Closure System (name, dosage form)

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the

dosage form (including sorption to container and leaching, and moisture or vapour transmission) safety of materials of construction (e.g. corking studies for multi-dose vials), and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product). In discussing the choice of materials and compatibility of the materials of construction, a summary of the Pharmacopeial tests for elastomeric components and plastics, and maintenance of pH, should be included. The results from the suitability and compatibility studies should be provided.

3.2.P.3 Manufacture of Drug Product (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

3.2.P.3.2 Batch Formula (name, dosage form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards. The anticipated range of commercial (production) batch sizes should be described in the batch formula(e). A tabulated summary of this information may be provided.

Master Formula# or Code		
Date Master Formula		

Approved		
Strength (Label Claim)		
Batch Size (# of dosage units)		
Ingredient, Test Standard		
Total (where applicable)		

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified. A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated. Proposals for the reprocessing of materials should be justified.

3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

Critical Steps:

Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps of the manufacturing process, to ensure that the process is controlled. This information should be provided in detail.

A summary of critical manufacturing steps, process controls performed, and acceptance criteria, should also be provided. A discussion of the process

control(s) selected for each critical manufacturing step and justification of the proposed acceptance criteria should also be provided.

Intermediates

Information on the quality and control of intermediates isolated during the process should be provided.

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided. The information provided in the study report should support the current manufacturing process proposed for commercial use, including in-process test results and data from relevant manufacturing batches to demonstrate consistency in yield and production, and degree of purity. The validation study report for the extent of reuse and integrity of membranes should be provided, including data to demonstrate consistency in the quality and safety of the drug product. If adjuvants are added to the drug product, information and data from the adsorption and desorption study should be submitted.
A summary of the process validation and evaluation studies should also be provided.

***3.2.P.3.6* A brief description of batch identification of system should be provided**.

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided for any (non-novel) non-compendial excipient (or adjuvant) for which detailed information is necessary to support its quality, safety, suitability for use, and 'approvability'. Applicants should consult the appropriate regional guidances and/or regulatory authorities for additional guidance.

3.2.P.4.2 Analytical Procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided, where appropriate. This includes analytical procedures used for testing excipients of human or animal origin and novel excipients.

3.2.P.4.3 Validation of Analytical Procedure

Description of validation of analytical procedure should be provided.

3.2.P.4.4 Justification of Specifications (name, dosage form)

Justification for the proposed excipient specifications should be provided, where appropriate.

***3.2.P.4.5* Substances of human or animal origin**

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). This information should also include the suitability for use, country of origin, manufacturer, and method of manufacture, and microbiological controls performed. A tabulated summary of excipients of human or animal origin that are used, including the source, country of origin, manufacturer, and a brief description on the suitability for use based upon the controls evaluated (e.g. history, testing, screening), should also be provided.

Excipient	Biological source	Country of Origin	Manufacturer	Suitability for Use

For any excipient of human or animal origin which is a drug product in its own right and which is currently approved for sale in India, a brief description on its quality, safety, and suitability for use, and confirmation that it is an approved excipient, should be provided. For any excipient of human or animal origin which is not currently approved for sale in India, the detailed quality information necessary to support its quality, safety, suitability for use, and 'approvability', should be submitted according to the drug substance and/or drug product CTD format.

3.2.P.4.6 Use of new adjuvants, preservatives, stabilizers and excipients

For excipient(s) (including adjuvants) used for the first time in a drug product or by a new route of administration, full details of manufacture (including manufacturer(s)), characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical details. For any excipient which is currently approved for sale in India and which is used for the first time in a drug product or by a new route of administration, a brief description on its quality, detailed information on its safety, and suitability for use, and confirmation that it is an approved excipient, should be provided under this section. For any novel excipient which is not currently approved for sale in India, the detailed information necessary to support its quality, safety, suitability for use, and 'approvability', should be submitted.

3.2.P.5 Control of Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

The specification(s) for the drug product should be provided. This would be the specification used by the company(ies) responsible for routine release testing and post-market stability testing. The specification could be presented using for example, a table with the specification reference number, specification approval date, test parameter(s), method type, method code, source, and acceptance limit(s) at release, shelf-life or for both. The drug product standard declared by the company responsible for routine release testing and post-market stability testing should be specified.

3.2.P.5.2 Analytical Procedures (name, dosage form)

The analytical procedures used for testing the drug product should be provided in detail. A summary of the analytical procedures should also be provided. (This may be combined with the summary of the validation of analytical procedures a summary of the characterisation of impurities and a summary of the justification of the drug product specification).

3.2.P.5.3 Analytical certificates signed by manufacturer and applicant for registration should be provided.

3.2.P.5.4 Validation of Analytical Procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.
A summary of the validation of analytical procedures should also be provided.
A summary of the characterisation of impurities and a summary of the justification of the drug product specification should be provided.

3.2.P.5.5 Batch Analyses (name, dosage form)

A description of batches and results of batch analyses should be provided. This information should include: a description of any deviations from the master formula or any abnormalities observed during production of any batches; a description of any incomplete analyses, if the tests described under *3.2.2.5.2* were not conducted (and if Certificates of Analysis have not been provided); a summary of any changes in specifications (analytical procedures and validation, where appropriate), and a rationale for those changes over the production history. All results, including those which are close to or outside of current limits, should be discussed. A description of the lot numbering system for the drug product, (if not fully described should be provided.

A tabulated summary (or graphical representation where appropriate) of results (other than impurities) from *in vivo* (bioequivalence, pivotal clinical) study batches and recent production batches should also be provided.

Test parameter	Range of Results for in vivo study batches (Total number of batches)	Range of results for recent production batches (Total number of batches)

3.2.P.5.6 Characterisation of Impurities (name, dosage form)

Information on the characterisation of impurities (including degradation products arising from manufacturing, storage, or detected in stability study batches) should be provided in detail, and the actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability, and proposed commercial batches) should be reported.

The information should also include a discussion of results which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification. A rationale for excluding any impurity test(s) from routine release testing due to trace levels, should also be provided, where applicable.
A summary of the characterisation of impurities should also be provided. Validation of analytical procedures and a summary of the justification of the drug product specification should be provided.

3.2.P.5.7 Justification of Specification(s) (name, dosage form)

Justification for the proposed drug product specification(s) should be provided.
A summary of the justification of the drug product specification should also be provided.

3.2.P.6 Reference Standards or Materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the drug product should be provided.

3.2.P.7 Container Closure System (name, dosage form)

A description of the container closure systems should be provided, including the supplier(s), identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate).
Non-compendial methods (with validation) should be included where appropriate.
For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided.

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life. For freeze-dried products, includes stability studies of freeze-dried material, diluents and reconstituted products thermo stability where applicable.

3.2.P.8.2 Freeze dried products: stability testing of freeze dried materials, diluents and re-constituted products, thermo stability, where applicable

3.2.P.8.3 Post-approval Stability Protocol and Stability Commitment (name,
dosage form)

The post-approval stability protocol and stability commitment should be provided.

***3.2.P.8.4* A description of procedures to guarantee cold chain shipment of materials should be provided.**

NOTE:

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included. Any incomplete analyses should be explained. A tabulated summary (with graphical representation, where appropriate) of the results from the stability studies, should also be provided.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product. (e.g. a dedicated or multi-use suite should be specified).

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multi-use, manufacturing step(s) where it is used) should be provided.

Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed. If the product is either fabricated in animals, sourced from animals, or animals are used in its testing and are housed in the facility, information on the animal housing quarantine procedures, the segregation of areas in which animal procedures are taking place, and confirmation of a sentinel program, should also be provided.

A summary of all facilities and equipment information in this section, should also be provided.

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For non-viral adventitious agents:

The detailed information regarding the routine manufacturing control of adventitious agents, such as bacteria, mycoplasma, and fungi, typically using well-established (e.g., pharmacopoeial) analytical procedures, should be provided.

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, and prions). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

A summary of the measures used to avoid and control non-viral adventitious agents during production, should also be provided.

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable.

A summary of the measures used to test, evaluate, and eliminate the potential risks viral adventitious agents during production, should also be provided.

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. A summary of the measures used to select, test, evaluate, and eliminate the potential risks of viral adventitious agents in any materials of animal or human origin that are used, should also be provided. This may also include a tabulated summary of the suitability for use of the biological raw materials described.

Biological material	Biological source	Country of origin	Manufacturer	Step	Suitability for Use

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination, should be provided.

A brief summary of the virological test(s) conducted during manufacturing (e.g., on cell substrate, unprocessed bulk or as post viral clearance testing), at which critical step(s) and intermediate(s), and the conclusion of the testing results, should also be provided.

A brief summary of the virological test(s) conducted on unprocessed bulk and the conclusion of the testing results, should also be provided.

Viral Testing of Unprocessed Bulk

Results for viral testing of unprocessed bulk should be included. The study report information should be provided in detail. A brief summary of the virological test(s) conducted on unprocessed bulk and the conclusion of the testing results, should also be provided.

Viral Clearance Studies

The rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing

steps that are capable of removing or inactivating viruses. The study report information should be provided in detail, including a description of the operational range of critical parameters used in the scale-down studies compared to those used in commercial-scale production. A tabulated summary of the reduction factors for viral clearance, should also be provided.

Excipients (name, dosage form)

Any extensive drug substance and/or drug product information which is necessary to support the quality, safety, suitability for use, and 'approvability' of any novel excipient, any (non-novel) noncompendial excipient, and/or any excipient of human or animal origin, should be provided. A summary of the excipients their suitability for use, and a discussion on their potential risk(s), should be provided.