FOREWORD

The Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India had published Guidance for Industry (Doc. No. CT/71108 Version – 1.1) for Biologicals in the year 2008. It was prepared in line with the international guidelines and in accordance with Drugs and Cosmetics Rules, 1945 and Drugs Cosmetics Act, 1940. Now, the Guidance for Industry (Biologicals) (Docs. No. CT/032024 Version – 1.2; MA/032024 Version – 1.2 and QI/032024 Version – 1.2) is updated to align with New Drugs and Clinical Trials Rules, 2019 and SUGAM application process after consultation with the stakeholders and it is published after considering the public suggestions / comments / objections.

Dr. Rajeev Singh Raghuvanshi
Drugs Controller General (I)

Guidance For Industry (Biologicals)

- **Submission of Clinical Trial Application for Evaluating Safety and Efficacy (Doc. No. CT/032024 Version – 1.2)**
- **Requirements for Permission of New Drugs Approval (Doc. No. MA/032024 Version – 1.2)**
- **Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products (Doc. No. QI/032024 Version – 1.2)**

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 (Biologicals)

(General considerations for conducting Clinical Trial as per New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940)

Document No. - CT/032024

Version –1.2

OBJECTIVE

This Guidance has been developed in conformity with New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act 1940 and GCP Guidelines of India for the purpose of submission of Clinical Trial application. The clinical trial sponsor is required to submit application (Form CT-04) for the purpose of conducting clinical trial in India and submit documents as per New Drugs and Clinical Trials Rules, 2019 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 New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act,1940. 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 (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study.

The manufacturer / sponsor has to submit application in Form CT-04 for permission of Clinical Trial under the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetic Act, 1940.

The requirements in respect of Chemistry and Pharmaceutical information has been elaborated for Biologicals in this document while requirement for conduction of Clinical trial and other requirements remains the same as per New Drugs and Clinical Trials Rules, 2019.

Though the nomenclature of the sections mentioned in this guidance is specific to India, the content is aligned with ICH requirements.

NOTES:

- The manufacturer / sponsor shall submit the application in Form CT-04 (online) through SUGAM / NSWS portal.
- Whenever new rules are published, the new Rules will prevail over this guidance.

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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**

NOTE: The manufacturer / sponsor shall submit the application in Form CT-04 (online) through SUGAM / NSWS portal.

1. SECTION A: GENERAL INFORMATION

1.1 Enclosure Sheet

1.2 Covering letter

1.3 Name of Applicant

1.4 Name of Drug

1.5 Dosage forms, Composition and packing details

1.6 Form CT-10/CT-16 & Challan Details (for linked applications) (Redundant)

1.9 Introduction about Company

1.10 Administrative Headquarters

1.11 Manufacturing Facilities

1.12 Information about Test license

1.12.1 Form CT-11 or Form CT-17 (For imported products) issued by Central Licensing Authority for Clinical Trial, Bioavailability or Bioequivalence study or for Examination, Test and Analysis.

1.12.2 Form 29 as issued by State Licensing Authority.

1.12.3 Permission to conduct toxicology permission (For r-DNA products)

1.13 Regulatory and intellectual property status in other countries.

1.13.1 Countries where the drug is

1.13.2 Marketed

1.13.3 Approved

1.13.4 Approved as IND

1.13.5 Withdrawn, if any, with reasons

1.14 Patent information status in India & other countries

1.15 Sponsor's name and Authorization letter

1.16 Study details

1.16.1 Protocol Title

1.16.2 Protocol Number

1.16.3 Phase of the study

1.16.4 Number of subjects to be enrolled

1.17 Executive Summary (as per the prescribed attached format)

1.18 Protocol Synopsis

1.19 Clinical development for proposed indication and any other Indication (including earlier study in humans)

2. SECTION B: CMC Data

2.1 Product Description

2.1.1 Name of the product

2.1.2 Generic name / INN name

2.1.3 Route of administration

2.1.4 Dosage of strength

2.1.5 Qualitative and Quantitative Composition

2.2 Product Development

2.2.1 Strain details: Name and source (if any)

2.2.1.1 Clone development (for recombinant products)

2.2.1.1.1 Details on source Nucleic acid: Nucleic acid sequence

2.2.1.1.2 Vector(s): Details about vector, please enclose the map of the vector gene

2.2.1.1.3 Host(s) that carrying the vector(s)/ target gene(s)

2.2.2 Substrate details (For cell culture based products): Details of name and source of substrate

2.2.3 Master seed and Working seed details

2.3 Information on Drug Substance

2.3.1 Production of Drug substance

2.3.1.1 List of raw materials and details

2.3.1.1.1 Specification & test methods of raw materials

2.3.1.1.2 Excipients Human or animal origin (If any) and its TSE / BSE compliance

2.3.1.1.3 Description of Manufacturing Process and Process Control

2.3.1.1.4 Process flow chart (with IPQC test parameters)

2.3.1.1.5 In process control steps & intermediates: Include process control step at each stage of Drug substance

2.3.1.2 Characterization of Drug substance

2.3.1.2.1 Physicochemical Characterization

2.3.1.2.2 Biological characterization

2.3.1.3 Control of Drug substance

2.3.1.3.1 Specification

2.3.1.3.2 Analytical procedures and validation / standardization studies

2.3.1.3.3 Certificate of analysis (Pilot scale batches)

2.3.1.4 Reference standard materials

2.3.1.5 Container closure system

2.3.1.5.1 Packing materials: Specifications & test methods

2.3.1.5.2 Labelling information of Drug Substance

2.3.1.6 Stability data

2.3.1.6.1 Write-up for stability study Program

2.3.1.6.2 Specification and Test Methods: Stability study

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

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

2.3.1.7 Manufacturing process for drug substance

2.3.1.7.1 Manufacturer(s)

2.3.1.7.2 Description of manufacturing process

2.3.1.7.3 Flow diagram of manufacturing process (with IPQC test parameters)

2.3.1.7.4 Control of critical and intermediate steps

2.3.1.7.5 Validation of manufacturing process (If done)

2.3.1.7.6 Manufacturing process development

2.3.1.7.7 Description of inactivation or detoxification process

2.3.1.7.8 Description of purification process

2.3.1.7.9 Description of conjugation process

2.3.1.7.10 Stabilization of drug substance

2.3.1.7.11 Reprocessing

2.3.1.7.12 Filling procedure for the drug substance, in-process controls

2.3.1.7.13 Selection and justification of critical steps

2.3.1.7.14 Description of batch identification system

2.4 Information on Drug Product

2.4.1 Description & composition

2.4.2 Components of Drug product

2.4.3 Manufacturing process

2.4.4 Manufacturing process flow chart with IPQC test parameters

2.4.5 Control of critical steps & intermediates

2.4.6 Equipment and Premises: Details of equipment, instruments etc. involved in manufacturing for testing of product)

2.4.7 Control of Excipients

2.4.7.1 Specifications

2.4.7.2 Analytical procedures

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

2.4.8 Control of Drug Product

2.4.8.1 Specifications

2.4.8.2 Analytical procedures

2.4.8.3 Certificate of analysis (Pilot scale batches)

2.4.8.3.1 Part 1

2.4.8.3.2 Part 2 (Optional)

2.4.8.3.3 Part 3 (Optional)

2.4.8.3.4 Part 4 (Optional)

2.4.9 Reference standards

2.4.10 Container closure system

2.4.10.1 Packaging Materials Specifications and Test methods

2.4.10.2 Art work Packaging material (label, primary carton, secondary carton and Pack Insert.)

2.4.10.3 Packaging Specifications

2.4.11 Stability data

2.4.11.1 Write-up for stability study Program

2.4.11.2 Specification and Test Methods: Stability study

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

2.4.11.3.1 Part 1

2.4.11.3.2 Part 2 (Optional)

2.4.11.3.3 Part 3 (Optional)

2.4.11.3.4 Part 4 (Optional)

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

2.4.11.4.1 Part 1

2.4.11.4.2 Part 2 (Optional)

2.4.11.4.3 Part 3 (Optional)

2.4.11.4.4 Part 4 (Optional)

3. SECTION C: NONCLINICAL DATA (Compliance as per New Drugs and Clinical Trials Rules, 2019)

3.1 Pre-Clinical Data

3.1.1 Animal Pharmacological data as per New Drugs and Clinical Trials Rules, 2019

3.1.2 Animal Toxicological data as per New Drugs and Clinical Trials Rules, 2019

3.1.2.1 Part 1 (Optional)

3.1.2.2 Part 2 (Optional)

3.1.2.3 Part 3 (Optional)

3.1.2.4 Part 4 (Optional)

3.1.2.5 Part 5 (Optional)

3.2 Name and address of the laboratory/ laboratories with accreditation certificate / Authorization for all animal toxicological reports

3.3 RCGM/GEAC clearance in case of r - DNA product

References:

1. New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940.

4. SECTION D: PROPOSED PHASE-I/II STUDIES

4.1 Human / Clinical pharmacology (Phase I) Data

4.1.1 Summary

4.1.2 Specific Pharmacological effects

4.1.3 General Pharmacological effects

4.1.4 Pharmacokinetics: - absorption, distribution, metabolism, excretion

4.1.5 Pharmacodynamics/early measurement of drug activity

4.1.6 Study Reports

4.2 Therapeutic exploratory trials (Phase II) Data

4.2.1 Summary

4.2.2 Study Reports

4.3 Therapeutic confirmatory trials (Phase III): -

4.3.1 Summary

4.3.2 Individual study reports with listing of sites and Investigators.

4.3.3 Study Reports

4.4 Special studies:

4.4.1 Summary

4.4.2 Bio-availability / Bio-equivalence

4.5 Other studies

4.5.1 Geriatrics

4.5.2 Pediatrics

4.5.3 Pregnant or Nursing women

5. TRIAL RELATED DOCUMENTS

5.1 Study Protocol (state the Version No. and Date)

5.1.1 Declaration that as per the protocol, whether the subjects will receive the Standard of Care

5.2 The study protocols, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per New Drugs and Clinical Trial Rules, 2019 & copy of approval of protocol from the IEC, if available.

5.3 Undertaking by the Sponsor/Sponsors representative/applicant to the licensing authority to provide medical management and compensation in case of clinical trial related injury or death for which subjects are entitled to compensation as required as per Chapter VI of NDCT Rules, 2019.

5.4 Declaration regarding financial status of the applicant vis-a-vis medical management and compensation to be paid to the trial participants (in case of injury or death in clinical trial).

5.5 Template of the CRF to be used

5.6 Investigator's Brochure

5.6.1 Affidavit declaring that the information about study drug as mentioned in Investigators Brochure is correct and based on available facts

5.7 List of Participating Sites, along with name and contact details of the Principal Investigators and EC Details

5.7.1 Details of the contract entered by the sponsor with the investigator / institutions with regard to financial support, amount of fees, honorarium, payments in kind etc. to be paid to the investigator. In case no contract has yet been entered with any Investigator / Institution, plan for financial support, fees, honorarium, and payments in kind etc. to be paid to the investigator

5.7.2 Undertaking by the Investigators as per as per Table 4 of Third Schedule including List of Investigators with qualification along with CV and MRC

5.7.3 Ethics committee approval if any

5.8 Proposed Draft of IMP Label

5.9 Copy of the Insurance Certificate (Certificate Only)

5.10 Assessment of risk versus benefit to the patient (for this proposal)

5.11 Innovations Vs existing therapeutic option (w.r.t. this proposal)

5.12 Unmet medical need in the country (of IMP/trial proposal)

5.13 Any published literature on the development of the IMP

5.14 In case of Phase II trial submit the report of Phase I trial

5.15 Post Marketing (Phase IV) Studies

5.15.1 Marketing Approval status of the drug under study

5.15.2 Product prescribing information

5.15.3 Summary of phase I, phase II & Phase III studies

5.16 Bioanalytical method and its development (as described in section 8 of further Guidance for information to be submitted with CT Applications in the guidance document).

5.17 Any other information (optional)

References:

1. New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act 1940.
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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1.3 Name of Applicant

1.4 Name of Drug

1.5 Dosage form, Composition and packing details

1.6 Form CT-10/CT-16 & Challan Details (for linked applications)

1.9 Introduction about Company

1.10 Administrative Headquarters

1.11 Manufacturing Facilities

1.12 Information about Test license

1.12.1 Form CT-11 or Form CT-17 (For imported products) issued by Central Licensing Authority for examination, test and Analysis purpose.

1.12.2 Form 29 as issued by State Licensing Authority.

1.12.3 Permission to conduct toxicology permission (For r-DNA products)

1.13 Regulatory and intellectual property status in other countries.

1.13.1 Countries where the drug is

1.13.2 Marketed

1.13.3 Approved

1.13.4 Approved as IND

1.13.5 Withdrawn, if any, with reasons

1.14 Patent information status in India & other countries

1.15 Sponsor's name and Authorization letter

1.16 Study details

1.16.1 Protocol Title

1.16.2 Protocol Number

1.16.3 Phase of the study

1.16.4 Number of subjects to be enrolled

1.17 Executive Summary (as per the prescribed attached format)

1.18 Protocol Synopsis

1.19 Clinical development for proposed indication and any other Indication (including earlier study in humans)

2 SECTION B: CMC DATA

2.1	**Drug substance(s): Information must be submitted for each drug substance in the product.**
2.1.1	**General information, starting materials and raw materials**
2.1.1.1	Trade and/or non-proprietary name(s) of the drug substance
2.1.1.2	Structural formula, molecular formula and relative molecular weight (if applicable)
2.1.1.3	Description and characterization of drug substance
2.1.1.4	General Description and History of starting material
2.1.1.4.1	Strain
2.1.1.4.2	System of seed/master/working banks
2.1.1.4.3	Embryonated eggs and other cell substrates
2.1.1.5	General description of raw materials
2.1.1.6	Analytical certificates signed by the manufacturer and the applicant for registration
2.1.2	**Manufacturing process for drug substance**
2.1.2.1	Manufacturer(s)
2.1.2.2	Description of manufacturing process
2.1.2.3	Flow diagram of manufacturing process
2.1.2.4	Control of critical and intermediate steps
2.1.2.5	Validation of manufacturing process (in phase III or IV)
2.1.2.6	Manufacturing process development
2.1.2.7	Description of inactivation or detoxification process
2.1.2.8	Description of purification process
2.1.2.9	Description of conjugation process
2.1.2.10	Stabilization of drug substance

2.1.2.11	Reprocessing
2.1.2.12	Filling procedure for the drug substance, in-process controls
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2.1.4.1	Specifications
2.1.4.2	Analytical procedures
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2.1.4.4	Consistency and analysis of batches
2.1.4.5	Justification of specifications
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2.1.6	**Container closure system**
2.1.6.1	Specifications of packaging materials (primary and secondary packaging)
2.1.6.2	Tests and evaluation of packaging materials
2.1.7	**Stability of drug substance**
2.1.7.1	Protocol of stability study, results and conclusions
2.1.7.2	Post-approval stability program
2.1.7.3	Storage and shipping conditions of drug substance
2.2	**Drug product**
2.2.1	**Description and composition of drug product**

2.2.2	**Pharmaceutical development**
2.2.2.1	Drug substance (s)
2.2.2.2	Drug product
2.2.2.3	Justification of final qualitative/quantitative formula
2.2.2.4	Manufacturing process
2.2.2.5	Container closure system, compatibility
2.2.3	**Manufacture of drug product**
2.2.3.1	Manufacturer(s)
2.2.3.2	Batch formula
2.2.3.3	Description of manufacturing process
2.2.3.4	Control of critical and intermediate steps
2.2.3.5	Validation and/or evaluation of the process (in phase III or IV)
2.2.3.6	Description of batch identification system
2.2.4	**Control of excipients (adjuvant, preservative, stabilizers and others)**
2.2.4.1	Specifications
2.2.4.2	Analytical procedures
2.2.4.3	Validation of analytical procedures
2.2.4.4	Justification of specifications
2.2.4.5	Substances of human or animal origin
2.2.4.6	Use of new adjuvants, preservatives, stabilizers and excipients
2.2.5	**Control of drug product**
2.2.5.1	Specifications
2.2.5.2	Analytical procedures
2.2.5.3	Analytical certificates signed by manufacturer and applicant for registration

2.2.5.4	Validation of analytical procedures (in phase III or IV)
2.2.5.5	Consistency and analysis of batches (specifying no. of batches & release by CDL, if any)
2.2.5.6	Determination and characterization of impurities
2.2.5.7	Justification of specifications
2.2.6	**Reference standards of materials**
2.2.7	**Container closure system**
2.2.7.1	Specifications of packaging materials (primary and secondary packaging)
2.2.7.2	Tests and evaluation of packaging materials
2.2.8	**Stability of drug product**
2.2.8.1	Protocol of stability study, results and conclusions
2.2.8.2	Stability testing of diluents and reconstituted product in case of freeze-dried products
2.2.8.3	Post-approval stability program
2.2.8.4	Description of procedures to guarantee cold chain
2.3	**Appendix**
2.3.1	Details of equipment and facilities for production of drug product
2.3.2	Safety evaluation of adventitious agents
2.3.3	Literature/ Bibliographic Reference

3 SECTION C: NONCLINICAL DATA (Compliance as per New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act 1940)

3.1 Preclinical Data

3.1.1 Animal Pharmacological data as per New Drugs and Clinical Trials Rules, 2019

3.1.2 Animal Toxicological data as per New Drugs and Clinical Trials Rules, 2019

3.1.2.1 Part 1 (Optional)

3.1.2.2 Part 2 (Optional)

3.1.2.3 Part 3 (Optional)

3.1.2.4 Part 4 (Optional)

3.1.2.5 Part 5 (Optional)

3.2 Name and address of the laboratory/ laboratories with accreditation certificate/ Authorization for all animal toxicological reports.

References:

1. New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940.

4 SECTION D: PROPOSED PHASE-III STUDIES (Compliance as per New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940)

4.1 Human / Clinical Pharmacology (Phase I) Data

4.1.1 Summary

4.1.2 Specific Pharmacological effects

4.1.3 General Pharmacological effects

4.1.4 Pharmacokinetics: - absorption, distribution, metabolism, excretion

4.1.5 Pharmacodynamics/early measurement of drug activity

4.1.6 Study Reports

4.2 Therapeutic Exploratory trials (Phase II) Data

4.2.1 Summary

4.2.2 Study Reports

4.3 Therapeutic Confirmatory trials (Phase III) Data

4.3.1 Summary

4.3.2 Individual study reports with listing of sites and Investigators

4.3.3 Study Reports

4.4 Other studies

4.4.1 Geriatrics

4.4.2 Pediatrics

4.4.3 Pregnant or Nursing women

5 TRIAL RELATED DOCUMENTS

5.1 Study Protocol (state the Version No. and Date)

5.1.1 Declaration that as per the protocol, whether the subjects will receive the Standard of Care

5.2 The study protocols, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per New Drugs and Clinical Trial (NDCT) Rules, 2019 & copy of approval of protocol from the IEC, if available.

5.3 Undertaking by the Sponsor/Sponsors representative/applicant to the licensing authority to provide medical management and compensation in case of clinical trial related injury or death for which subjects are entitled to compensation as required as per Chapter VI of NDCT Rules, 2019.

5.4 Declaration regarding financial status of the applicant vis-a-vis medical management and compensation to be paid to the trial participants (in case of injury or death in clinical trial).

5.5 Template of the CRF to be used

5.6 Investigator's Brochure

5.6.1 Affidavit declaring that the information about study drug as mentioned in Investigators Brochure is correct and based on available facts

5.7 List of Participating Sites, along with name and contact details of the Principal Investigators and EC Details

5.7.1 Details of the contract entered by the sponsor with the investigator/institutions with regard to financial support, amount of fees, honorarium, payments in kind etc. to be paid to the investigator. In case no contract has yet been entered with any Investigator / Institution, plan for financial support, fees, honorarium, and payments in kind etc. to be paid to the investigator

5.7.2 Undertaking by the Investigators as per as per Table 4 of Third Schedule of NDCT Rules, 2019 including List of Investigators with qualification along with CV and MRC

5.7.3 Ethics committee approval, if any

5.8 Proposed Draft of IMP Label

5.9 Copy of the Insurance Certificate (Certificate Only)

5.10 Assessment of risk versus benefit to the patient (for this proposal)

5.11 Innovations Vs existing therapeutic option (w.r.t. this proposal)

5.12 Unmet medical need in the country (of IMP/Trial proposal)

5.13 Any published literature on the development of the IMP

5.14 In case of Phase II trial submit the report of Phase I trial

5.15 Post Marketing (Phase IV) Studies

5.15.1 Marketing Approval status of the drug under study

5.15.2 Product prescribing information

5.15.3 Summary of phase I, phase II & Phase III studies

5.16 Bioanalytical method, its development and validation (as described in section 8 of further Guidance for information to be submitted with CT Applications in the guidance document.)

5.17 Any other information (optional)

References:

1. New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940.
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 (As per third schedule, Table 2 Contents of the Proposed Protocol for Conducting Clinical Trials, under New Drugs and Clinical Trials Rules, 2019):

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 Investigational New Drug (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:

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 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:

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 Case Record Form correction requirements, including who is authorized to make corrections on the Case Record Form 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 or 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 Table 4 of New Drugs and Clinical Trials and Rules, 2019.)

16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); Case Record Form (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: *Table 5 of New Drugs and Clinical Trials and Rules, 2019*

Data elements for reporting Serious Adverse Events occurring in Clinical Trial or Bioavailability or Bioequivalence Study

1. Patients Details:

   Initials and other relevant identifier (hospital or out-patient department (OPD) record number etc.)*

   Gender

   Age 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 Serious Adverse Event:

   Full description of event including body site and severity, as well as the criterion (or criteria) for considering the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the event*.

Start date (and time) of onset of event.

Stop date (and time) or duration of event.

De-challenge and re-challenge information.

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

5. Outcome

Information on recovery and any sequelae; results of specific tests or treatment that may have been conducted.

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected event; 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 and Address

Telephone number

Profession (Specialty)

Date of reporting the event to Central Licencing Authority:

Date of reporting the event to Ethics Committee overseeing the site

Signature of the Investigator or Sponsor.

Note: Information marked * must be provided

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 (DSMB), as applicable.

Executive Summary

Protocol Title and No.:
Section:

1	Investigational Product Name	
1.1	Therapeutic class/Indication	

2.	**Summary of Chemical and Pharmaceutical Information**	
2.1	Chemical Name	
2.2	Dosage Form/ composition	
2.2.1	Type of Product (eg: Recombinant, inactivated, live attenuated etc.) with platform	
2.2.2	Seed strain (as appropriate)	
2.2.3	Cell bank (as appropriate)	
2.2.4	If any recombinant inactive used during the process, kindly specify.	
2.3	Details of manufacturing site of IMP and its GMP status.	
2.4	Summary of stability data	Product / Primary Package / Storage Condition / Shelf-life

3	**Brief Summary of non-clinical studies**	
*	**Provide details of GLP facility, laboratory and its accreditation.**	
3.1	Animal Pharmacology	Summary: Specific pharmacological actions: General pharmacological actions: Follow-up and Supplemental Safety Pharmacology Studies: Pharmacokinetics: absorption, distribution, metabolism, excretion

Classifications	Study No.	Species	Dosing route	Duration	Test articles	Dose(mg/kg)	GLP Compliance	Result
Assay								
In Vitro Studies								
In Vivo Studies								

Mention “NA” if it is not applicable.

3.2	Animal Toxicology	a. Systemic toxicity studies, i. Single dose toxicity (should be carried out in 2 rodent species (mice and rats) using the same route as intended for humans) ii. Repeated dose toxicity (should be carried out in at least two

<table>
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mammalian species, of which one should be a non-rodent.)
b. -Developmental and Reproductive Toxicology (DART) Studies (For all drugs proposed to be studied or used in women of child bearing age)
Teratogenicity and Perinatal study
c. Local toxicity
i. Dermal toxicity (for products meant for topical/dermal application)
ii. Ocular toxicity (for products meant for ocular instillation)
iii. Inhalation toxicity (conducted with the formulation proposed to be used via inhalation route)
iv. Vaginal toxicity (for products meant for topical application to vaginal mucosa)
v. Photo allergy or dermal photo toxicity (required if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential)
vi. Rectal tolerance test (For all preparations meant for rectal administration)
d. Genotoxicity
e. Allergenicity/Hypersensitivity
f. Carcinogenicity
Mention “NA” if it is not applicable.
* The effect of the adjuvant should be demonstrated in preclinical immunogenicity studies. If no toxicological data exist for a new adjuvant, toxicity studies of the adjuvant alone should first be performed. In general, assessment of new or novel adjuvants should be undertaken as required for new chemical entity.
Summary Table
<table>
<tr><th>Study No & Title</th><th>Species</th><th>Dose and Dose Volume, ROA</th><th>Study Objective</th><th>Study Procedure</th><th>Study Results/Conclusions</th></tr>
<tr><td rowspan="2"></td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr>
<td>3.3</td>
<td>Whether toxicity study data submitted is as per requirement of New Drugs and Clinical Trial Rules, 2019. If not specify and same along with Justification.</td>
<td></td>
</tr>
</table>

<table>
<tr><td>4.</td><td colspan="2">Summary of clinical studies</td></tr>
<tr><td>4.1</td><td>Phase I</td><td>Human / Clinical pharmacology (Phase I)
• Summary
• Specific Pharmacological effects:
• General Pharmacological effects:
• Pharmacokinetics, absorption, distribution, metabolism, excretion
• Pharmacodynamics
(Note: mention details of mfg./imported batches used)</td></tr>
<tr><td>4.2</td><td>Phase II</td><td>Therapeutic exploratory trials (Phase II)
• Summary
• Study reports as given in Table 6 of New Drugs and Clinical Trial Rules, 2019
(Note: mention details of batches used)</td></tr>
<tr><td>4.3</td><td>Phase III</td><td>Therapeutic confirmatory trials (Phase III)
• Summary
• Individual study reports with listing of sites and Investigators.
• (Note: mention details of batches used)</td></tr>
<tr><td>4.4</td><td>Special studies</td><td>• Summary
• Bio-availability / Bio-equivalence.</td></tr>
<tr><td>4.5</td><td>Other studies e.g. geriatrics, paediatrics, pregnant or nursing women</td><td></td></tr>
<tr><td>4.6</td><td>Summary of Phase I/II/III</td><td><table><tr><td>Phases</td><td>Description</td><td>Subject Disposition</td><td>Primary Endpoint Conclusion/Results</td><td>Secondary Endpoint Conclusion/Results</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr></table>(Note: mention details of batches used) either in 4.1-4.3 or here</td></tr>
<tr><td>4.7</td><td>Proof of concept studies, if any</td><td></td></tr>
<tr><td>5.</td><td colspan="2">Justifications for the proposed studies:</td></tr>
<tr><td>5.1</td><td>Scientific rationale for the study and justification of dose level and treatment duration (Provide reference to specific studies which have been used to arrive at dose/ treatment duration, if available)</td><td></td></tr>
<tr><td>5.2</td><td>Justification for inclusion of special populations e.g. pediatrics, geriatrics, pregnant women etc., if any.</td><td></td></tr>
<tr><td>5.3</td><td>Comparator (if placebo is used as a comparator, provide justification in light of requirement</td><td></td></tr>
</table>

	of therapy for trial subjects	
5.4	Assessment of risk versus benefit to the Patients / participants	
5.5	Innovation vis-à-vis existing therapeutic Option	
5.6	Unmet medical need in the country	
5.7	Justification for clinical trial waiver, if appropriate	

Section II: Summary of protocol:

Sr. No.	Item	Details
1.	Protocol Title along with version no and date	
1.1	Study Treatment • Investigational Product Name • Comparator • Dosage Form, • Dosing Schedule • Route of Administration	
2.	Study Population (Total no of Subjects, Age –groups etc.)	
3.	Study design including flow chart of the study, if available along with randomization and dose escalation, blood sampling if applicable.	
3.1	Study Procedure and Study Visits	
4.	Subject eligibility criteria Inclusion and Exclusion criteria	
5.	Primary outcome / endpoint	
6.	Secondary outcome(s) / endpoint	
7.	Laboratories participating in the study along with their GLP/ accreditation status.	
8.	Assessment and Statistical analysis plan	
9.	If multi-country study, Names of the participating countries in the proposed study	
10.	Regulatory status of the protocol under consideration. If approved whether copy of approval/copy of notification have been submitted. (and if clinical trial with same proposed protocol is completed (provide detailed summary).	

11.	Names of EC who have already approved or rejected the study proposal.	
12.	Whether undertaking of all the investigators mentioning approved protocol details and signed and stamped by P.I as per New Drugs and Clinical Trial Rules, 2019 has been submitted.	
13.	Total number of subjects proposed to be enrolled globally, if applicable (GCT)	
14.	Total number of subjects proposed to be enrolled in India	
15.	Whether patient information sheet and informed consent form, as per New Drugs and Clinical Trial Rules, 2019 submitted. Please annex copy.	

Section III: Regulatory Status of Drug

Sr. No.	Subject	
1.	Regulatory status of Investigational Product (IP) including comparator, if any, globally, if approved and marketed, copy of package insert and SmPC circulated in those countries.	
2.	Regulatory status of IP including comparator, if any, in India.	
2.1	RCGM/GEAC (if applicable) approval for recombinant products.	
3.	Any safety or regulatory concerns	
4.	Details of CDL certified batches used for clinical trials.	

Section IV: Description of PI & Sites

(ensure MRC is renewed, with evidence of GCP training and experience in clinical trial)

Sr. No.	Name of PI along with educational qualification and designation	Site Name & Address	Nature of Site Govt/Pvt /Trust etc.	Institutional Ethics Committees Name & Address	Private Clinic/ Private Hospital / Nursing Home/ Govt. Hospital	Super specialty/ Multispeci alty Facilities	ECR No (To assure that P.I /Co-PI is not a part of committee, if he/she is conflict of interest is notified.

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, 1986.

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 & 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 TSE/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 3): Biotechnological / Biological products.

7 **Samples of drug product:** Samples of 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.

8 **Bioanalytical Method, Development and its Validation:**

The sponsor should provide the development and its validation as applicable, of the bioanalytical procedures, for testing biomarkers (immunogenicity) in biological matrices such as blood, serum, plasma, urine, and tissue such as skin.

The bioanalytical method development shall cover the design, operating conditions, limitations, and suitability of the method for its intended purpose and to ensure that the method is optimized for validation. The below key points should be considered by the sponsor (MA holder);

- Immunogenicity testing should be done using validated methods
- The testing wherever applicable should report sera units in international units
- Total antibody (e.g. IgG) and wherever applicable functional antibodies (e.g. IgG) should be determined using validated methods
- In case the sponsor (MA holder) uses commercial diagnostic kits, then such kits should be validated to prove its performance for immunogenicity assay.
- Suitable reference standard (antigen/antibody) should be used in and method should be validated. The source of the standard should be documented.

Bioanalytical method validation shall prove that the optimized method is suited for the analysis of the study samples. For Phase 3 study sample testing, the sponsor (MA holder) should conduct a full validation of any new bioanalytical method for the analysis of biomarkers, and should conduct a full validation for any major revisions to an existing validated method.

Guidance for Industry Requirements for Permission of New Drug Approval (Biologicals)

Document No. – MA/032024

Version -1.2

The manufacturer / sponsor has to submit application in Form CT-18 / Form CT-21 for permission to import or manufacture of New Drugs Approval under the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetic Act 1940. 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 New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetic Act 1940 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 1: Administrative/Legal Information
Module 2: Summaries
Module 3: Quality Information (Chemical, Pharmaceutical and Biological)
Module 4: Non-Clinical Information
Module 5: Clinical Information

Objective: The purpose of this document is to achieve greater harmonization in the information submitted in the application for grant of permission to import / manufacture for Biologicals. Since the same information will be requested and submitted in various countries, the licensing process and ultimately the availability of New Biological Drugs 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 New Drugs and Clinical Trials Rules, , 2019 under Drugs and Cosmetic Act 1940.

Notes:

- The manufacturer / sponsor shall submit the application in Form CT-21 (online) through SUGAM / NSWS portal. For imported products, the manufacturer / authorized agent in India shall submit the application in Form CT-18 (online) through SUGAM / NSWS portal
- Whenever new Rules are published, the new rules will prevail over this guidance.

Check List for Form CT-18 / Form CT-21 Application – Drug Substance

Sections	Contents
MODULE 1: Administrative/Legal Information	
1.1	**Comprehensive table of contents (Modules 1 and 3)**
1.1.0.0.0	Covering letter
1.2	**Administrative information**
1.2.3	**Legal and statutory documents**
1.2.3.1	License and approvals: As applicable
1.2.3.1.1	Copy of Form CT-17 for imported drug Substance
1.2.3.1.2	Form CT-11 and Form-29 for indigenous drug substance
1.2.3.1.3	RCGM / GEAC clearance
1.2.3.2	Legal documents pertaining to application (to be notarized)
1.2.3.2.1	A copy of plant registration / approval certificate issued by the Ministry of Health / National Regulatory Authority of the country of origin.
1.2.3.2.2	A copy of approval, if any, showing the drug is permitted for manufacturing and/or marketing in the country of origin.
1.2.3.2.3	A copy of Pharmaceutical Product Certificate (PPC) as per WHO GMP certification scheme for imported drug products.
1.2.3.2.4	A copy of Free Sale Certificate (FSC) from the country of origin for imported drug products.
1.2.3.2.5	Certificate of Good Manufacturing Practices of other manufacturers involved in the vaccine production process.
1.2.3.2.6	Batch release certificate issued by NRA for imported products.
1.2.3.3	A copy of Site Master File
1.2.3.4	Certificate of Analysis from Central Drug Laboratory (India) of three consecutive batches.
1.2.3.5	Summary of Drugs Substance as per Annexure – D
1.2.4	**Coordinates related to the application**
1.2.4.1	Name, address, telephone, fax, e-mail of manufacturer of drug product

Sections	Contents
1.2.4.2	Name, address, telephone, fax, e-mail of the responsible official
1.2.4.3	Name, address, telephone, fax, e-mail of the authorized agent in India (for imported drug products)
1.2.4.4	Name, designation, address, telephone, fax, e-mail of the official responsible for releasing batches of drug product
1.2.4.5	Name, address, telephone, fax, e-mail of the manufacturing premises holding Market Authorization of the drug product (for imported drug products)
1.2.4.6	Name, address, telephone, fax, e-mail of manufacturer of drug substance
1.2.4.7	Name, address, telephone, fax, e-mail of other manufacturer(s) involved in the production process
1.2.5	**General information on drug substance**
1.2.5.1	Non-proprietary name or common name of drug substance
1.2.5.2	Composition (as per label claim)
1.2.5.3	Strength per dosage unit
1.2.5.4	Product Labeling (should conform to the specification under the Drug and Cosmetic Rules 1940 and Rules there under)
1.2.5.4.1	Primary package label
1.2.5.4.2	Secondary package label
1.2.5.5	Summary of the Packaging procedures for Indian Shipments (including box sizes, packing volume)
1.2.6	**Summary protocol of batch production and control.**
1.2.7	**List of countries where MA or import permission for the said drug substance is pending and the date of pendency.**
1.2.8	**List of countries where the drug substance has been licensed and summary of approval conditions.**
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**

Sections	Contents
Module 3 - Quality information (Chemistry, Pharmaceutical and Biological)	
3.1	**Table of contents of Module 3**
3.2	**Quality contents**
3.2.1	**Drug substance(s): Information must be submitted for each drug substance in the product.**
3.2.1.1	**General Information, starting materials and raw materials**
3.2.1.1.2	Structural formula, molecular formula and relative molecular weight (if applicable)
3.2.1.1.3	Description and Characterization of drug substance
3.2.1.1.4	General description and history of starting material (Strain, Gene Construct System of seed/Cell Line/master/working banks, Embryonated eggs and other cell substrates).
3.2.1.1.5	General description of raw materials
3.2.1.1.6	Analytical certificates signed by the manufacturer and the applicant for registration
3.2.1.2	**Manufacturing process for drug substance**
3.2.1.2.1	Manufacturer(s)
3.2.1.2.2	Description of manufacturing process
3.2.1.2.3	Flow diagram of manufacturing process along with IPQC test parameters
3.2.1.2.4	Identification of critical steps in-process and control
3.2.1.2.5	Validation of manufacturing process
3.2.1.2.6	Manufacturing Process Development
3.2.1.2.7	Description of inactivation or detoxification process
3.2.1.2.8	Description of purification process
3.2.1.2.9	Description of conjugation process
3.2.1.2.10	Stabilization of active ingredient
3.2.1.2.11	Reprocessing
3.2.1.2.12	Filling procedure for the active ingredient, in-process controls

Sections	Contents
3.2.1.2.13	Selection and justification of critical steps
3.2.1.2.14	Description of batch identification system
3.2.1.3	**Characterization of drug substance**
3.2.1.3.1	Physicochemical Characterization
3.2.1.3.2	Biological Characterization
3.2.1.3.3	Impurities (name, manufacturer)
3.2.1.4	**Quality control of drug substance**
3.2.1.4.1	Specifications
3.2.1.4.2	Analytical Procedures
3.2.1.4.3	Validation of Analytical Procedures
3.2.1.4.4	Consistency and analysis of batches
3.2.1.4.5	Justification of Specification
3.2.1.5	**Reference Standards**
3.2.1.6	**Container closure system**
3.2.1.6.1	Specifications of primary and secondary packaging
3.2.1.6.2	Tests and evaluation of packaging materials
3.2.1.7	**Stability of drug substance**
3.2.1.7.1	Protocol of stability study Results and conclusions
3.2.1.7.2	Post approval Stability Program
3.2.1.7.3	Storage and shipping conditions of drug substance
3.2.3	**Appendix**
3.2.3.1	Details of equipment and facilities for production of drug product: Master Formula, Batch Record and Set Release Documentation in Respect of Consistency Batches
3.2.3.2	Safety evaluation of adventitious agents
3.3	**Bibliographic References**

Check list for Form CT-18 / Form CT-21 Application – Drug Product

MODULE - 1

Administrative/Legal Information

1.1	**Covering letter**
1.1.0.0.0	**Comprehensive table of contents (Modules 1 to 5)**
1.2	**Administrative information**
1.2.3	**Legal and statutory documents**
1.2.3.1	License and approvals: As applicable
1.2.3.1.1	Copy of Form CT-17 for imported drug product
1.2.3.1.2	Form CT-11 and Form-29 for indigenous drug
1.2.3.1.3	Clinical Trial no objection letters / approval
1.2.3.1.4	RCGM/GEAC clearance
1.2.3.2	Legal documents pertaining to application (to be notarized):
1.2.3.2.1	A copy of plant registration / approval certificate issued by the Ministry of Health / National Regulatory Authority of the country of origin.
1.2.3.2.2	A copy of approval, if any, showing the drug is permitted for manufacturing and/or marketing in the country of origin.
1.2.3.2.3	A copy of Pharmaceutical Product Certificate (PPC) as per WHO GMP certification scheme for imported drug products
1.2.3.2.4	A copy of Free Sale Certificate (FSC) from the country of origin for imported drug products
1.2.3.2.5	Certificate of Good Manufacturing Practices of other manufacturers involved in the vaccine/biologicals production process
1.2.3.2.6	Batch release certificate issued by NRA for imported products.
1.2.3.2.7	Undertaking to declare (as per Annex. A)
1.2.3.3	A copy of Site Master File
1.2.3.4	Certificate of Analysis from Central Drug Laboratory (India) of three consecutive batches.

1.2.3.5	Product Permission Document (PPD) as per Annex B
1.2.4	**Coordinates related to the application**
1.2.4.1	Name, address, telephone, fax, e-mail of manufacturer of drug product
1.2.4.2	Name, address, telephone, fax, e-mail of the responsible official
1.2.4.3	Name, address, telephone, fax, e-mail of the authorized agent in India: (for imported drug products)
1.2.4.4	Name, designation, address, telephone, fax, e-mail of the official responsible for releasing batches of drug product
1.2.4.5	Name, address, telephone, fax, e-mail of the manufacturing premises holding Market Authorization of the drug product (for imported drug products)
1.2.4.6	Name, address, telephone, fax, e-mail of manufacturer of drug substance
1.2.4.7	Name, address, telephone, fax, e-mail of other manufacturer(s) involved in the production process
1.2.5	**General information on drug product**
1.2.5.1	Proprietary, commercial or trade name of drug product
1.2.5.2	Non-proprietary name or common name of drug product
1.2.5.3	Composition (as per label claim)
1.2.5.4	Dosage form
1.2.5.5	Strength per dosage unit
1.2.5.6	Dispensing requirements
1.2.5.7	Route of administration
1.2.5.8	Commercial presentation
1.2.5.9	Conditions of storage or conservation
1.2.5.10	Summary of product characteristics (As per Annex C)
1.2.5.11	Product Labeling (should conform to the specifications under the Drugs and Cosmetics Act 1940 and Rules thereunder)

1.2.5.11.1	Primary package label
1.2.5.11.2	Secondary package label
1.2.5.11.3	Package insert (in English) Monograph for health professionals or information for prescription.
1.2.5.12	Summary of the packaging procedures for Indian shipments (including box sizes, packing volumes).
1.2.6	**Summary protocol of batch production and control**
1.2.7	**List of countries where MA or import permission for the said drug product is pending and the date of pendency.**
1.2.8	**List of countries where the drug product has been licensed and summary of approval conditions.**
1.2.9	**List of countries where the drug product is patented.**
1.2.10	**Domestic price of the drug followed in the countries of origin in INR.**
1.2.11	**A brief profile of the manufacturer's research activity**
1.2.12	**A brief profile of the manufacturer's business activity in domestic as well as global market.**
1.2.13	**Information about the expert(s)/ Information regarding involvement of experts, if any**
1.2.14	**Environmental risk assessment**
1.2.15	**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

Summaries

2.1	**Table of contents of Module 2**
2.2	**Introduction**
2.3	**Quality overall summary**
2.3.1	Summary of drug substance
2.3.2	Summary of drug product
2.3.3	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**
3.2.1	**Drug substance(s): Information must be submitted for each drug substance in the product.**
3.2.1.1	**General information, starting materials and raw materials**
3.2.1.1.1	Trade and/or non-proprietary name(s) of the drug substance
3.2.1.1.2	Structural formula, molecular formula and relative molecular weight (if applicable)
3.2.1.1.3	Description and characterization of drug substance
3.2.1.1.4	General description and history of starting material (Strain, Gene Construct, System of seed/Cell Line/master/working banks, Embryonated eggs and other cell substrates).
3.2.1.1.5	General description of raw materials
3.2.1.1.6	Analytical certificates signed by the manufacturer and the applicant for registration
3.2.1.2	**Manufacturing process for drug substance**
3.2.1.2.1	Manufacturer(s)
3.2.1.2.2	Description of manufacturing process
3.2.1.2.3	Flow diagram of manufacturing process (along with IPQC test parameters)
3.2.1.2.4	Identification of critical steps in process and control
3.2.1.2.5	Validation of manufacturing process
3.2.1.2.6	Manufacturing process development
3.2.1.2.7	Description of inactivation or detoxification process
3.2.1.2.8	Description of purification process
3.2.1.2.9	Description of conjugation process
3.2.1.2.10	Stabilization of active ingredient

3.2.1.2.11	Reprocessing
3.2.1.2.12	Filling procedure for the active ingredient, in-process controls
3.2.1.2.13	Selection and justification of critical steps
3.2.1.2.14	Description of batch identification system
3.2.1.3	**Characterization of drug substance**
3.2.1.3.1	Physicochemical Characterization
3.2.1.3.2	Biological Characterization
3.2.1.3.3	Impurities (name, manufacturer)
3.2.1.4	**Quality control of drug substance**
3.2.1.4.1	Specifications
3.2.1.4.2	Analytical procedures
3.2.1.4.3	Validation of analytical procedures
3.2.1.4.4	Consistency and analysis of batches
3.2.1.4.5	Justification of specifications
3.2.1.5	**Reference standards**
3.2.1.6	**Container closure system**
3.2.1.6.1	Specifications of primary and secondary packing
3.2.1.6.2	Tests and evaluation of packaging materials
3.2.1.7	**Stability of drug substance**
3.2.1.7.1	Protocol of stability study, results and conclusions
3.2.1.7.2	Post-approval stability program
3.2.1.7.3	Storage and shipping conditions of drug substance
3.2.2	**Drug product**
3.2.2.1	**Description and composition of drug product**

3.2.2.2	**Pharmaceutical development**
3.2.2.2.1	Drug substance (s)
3.2.2.2.2	Drug product
3.2.2.2.3	Justification of final qualitative/quantitative formula
3.2.2.2.4	Manufacturing process
3.2.2.2.5	Container closure system, compatibility
3.2.2.3	**Manufacture of drug product**
3.2.2.3.1	Manufacturer(s)
3.2.2.3.2	Batch formula
3.2.2.3.3	Description of manufacturing process
3.2.2.3.4	Control of critical and intermediate steps
3.2.2.3.5	Validation and/or evaluation of the process
3.2.2.3.6	Description of batch identification system
3.2.2.4	**Control of excipients (adjuvant, preservative, stabilizers and others)**
3.2.2.4.1	Specifications
3.2.2.4.2	Analytical procedures
3.2.2.4.3	Validation of analytical procedures
3.2.2.4.4	Justification of specifications
3.2.2.4.5	Substances of human or animal origin
3.2.2.4.6	Use of new adjuvants, preservatives, stabilizers and excipients
3.2.2.5	**Control of drug product**
3.2.2.5.1	Specifications
3.2.2.5.2	Analytical procedures
3.2.2.5.3	Analytical certificates signed by manufacturer and applicant for registration

3.2.2.5.4	Validation of analytical procedures
3.2.2.5.5	Consistency and analysis of batches
3.2.2.5.6	Determination and characterization of impurities
3.2.2.5.7	Justification of specifications
3.2.2.6	**Reference standards of materials**
3.2.2.7	**Container closure system**
3.2.2.7.1	Specifications of primary and secondary packing
3.2.2.7.2	Tests and evaluation of packaging materials
3.2.2.8	**Stability of drug product**
3.2.2.8.1	Protocol of stability study, results and conclusions
3.2.2.8.2	Freeze dried products: stability testing of freeze dried materials, diluents and re-constituted products, thermo stability, where applicable
3.2.2.8.3	Post-approval stability program
3.2.2.8.4	Description of procedures to guarantee cold chain
3.2.3	**Appendix**
3.2.3.1	Details of equipment and facilities for production of drug product: master formula, batch record and set release documentation in respect of consistency batches
3.2.3.2	Safety evaluation of adventitious agents
3.3	**Bibliographic Reference**

MODULE - 4

Non-Clinical Information

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
4.2.3.1.1	Design of study and justification of animal model
4.2.3.1.2	Animal species used, age and size of groups
4.2.3.1.3	Dose, mode of administration and control groups
4.2.3.1.4	Monitored parameters
4.2.3.1.5	Local tolerance
4.2.3.2	Special toxicology (for products to which it applies)
4.2.3.2.1	Special immunological investigations
4.2.3.2.2	Toxicity studies on special populations
4.2.3.2.3	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

Clinical Information

5.1	**Table of contents of the Module 5**
5.2	**Contents: Reports of clinical studies**
5.2.1	**Phase I studies**
5.2.1.1	Part 1
5.2.1.2	Part 2 (Optional)
5.2.1.3	Part 3 (Optional)
5.2.1.4	Part 4 (Optional)
5.2.1.5	Part 5 (Optional)
5.2.2	**Phase II studies**
5.2.2.1	Part 1
5.2.2.2	Part 2 (Optional)
5.2.2.3	Part 3 (Optional)
5.2.2.4	Part 4 (Optional)
5.2.2.5	Part 5 (Optional)
5.2.3	**Phase III studies**
5.2.3.1	Bridging Studies
5.2.3.1.1	Part 1
5.2.3.1.2	Part 2 (Optional)
5.2.3.1.3	Part 3 (Optional)
5.2.3.1.4	Part 4 (Optional)
5.2.3.1.5	Part 5 (Optional)
5.2.4	**Special considerations**

5.2.5	**Adjuvant (s)**
5.2.6	**Phase IV studies and / or Pharmacovigilance Plan** (if applicable)
5.2.6.1	Part 1
5.2.6.2	Part 2 (Optional)
5.2.6.3	Part 3 (Optional)
5.2.6.4	Part 4 (Optional)
5.2.6.5	Part 5 (Optional)
5.2.7	**Non-inferiority studies** (for combined vaccines, or approved vaccines prepared by new manufacturers)
5.2.7.1	Part 1
5.2.7.2	Part 2 (Optional)
5.2.7.3	Part 3 (Optional)
5.2.7.4	Part 4 (Optional)
5.2.7.5	Part 5 (Optional)
5.2.8	**Co-administration studies with other vaccines**
5.2.8.1	Part 1
5.2.8.2	Part 2 (Optional)
5.2.8.3	Part 3 (Optional)
5.2.8.4	Part 4 (Optional)
5.2.8.5	Part 5 (Optional)
5.2.9	**Case Report Forms and Individual Patient Listings**
5.2.10	**Bioanalytical method, its development and validation**
5.2.11	**Risk Management Plan**
5.3	**Bibliographic references**
5.4	**Abbreviations**

Annexure A to Module 1

Undertaking to declare that: -

1. We shall comply with all the conditions imposed on the (licensing and/or Market Authorization) of the applied drugs as per the provisions of the New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940.
2. We declare that we are carrying on the manufacture of the drugs at the premises specified in Module 1 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 authorization shall be as regard strength, quality and purity conforms with the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940 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 as per Guidance for Post Approval 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 by submitting a separate application, along with the applicable fee as per Guidance for Post Approval Changes.
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 Authorization declared by any Regulatory Authority of

any country where the drug is marketed/sold or distributed. The dispatch and marketing of the drug in such cases shall be stopped immediately and the licensing authority shall be informed immediately. Further action in respect of stop marketing of drug shall be taken as per the directions of the licensing authority. In such cases, action equivalent to that taken with reference to the concerned drug(s) in the country of origin or in the country of marketing will be followed in India also, in consultation with the licensing authority. The licensing authority may direct any further modification to this course of action, including the withdrawal of the drug from Indian market within 48 hours time period.

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 1

Doc. No. PPD/032024 **Ver.1.2**

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 licensure change approval, information as per the relevant sections are to be provided as Annexure to this PPD.

Annexure B to Module 1

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/ Brand 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	Proposed Indication	
1.13	Maximum Daily Dose:	
2.0	New Active Substance (NAS)?	

1	**DRUG SUBSTANCE (NAME, MANUFACTURER)**	
1.1	**Manufacture (name, manufacturer) and Address**	**Module 3.2.1.2**
1.1.1	Manufacturer(s) (name, manufacturer)	Information on the manufacturer(s): [Insert the completed Module 3.2.1.2.1]
1.1.2	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 3.2.1.2.2)
1.1.3	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 3.2.1.1] A summary of prepared reagents: [Insert the tabulated summary of prepared reagents from the completed Module 3.2.1.2]
1.1.4	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 3.2.1.2, 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 3.2.1.2, under Intermediates.]

1.2	**Characterization (name, manufacturer)**	
1.2.1	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 3.2.1.3]
1.2.2	Impurities (name, manufacturer)	A tabulated summary of the impurities data: [Insert the tabulated summary on actual impurity levels detected from the completed Module 3.2.1.3.]
1.3	**Control of Drug Substance (name, manufacturer)**	
1.3.1	*Specification (name, manufacturer)*	Specification for the drug substance: [Insert the specification for the drug substance from the completed Module *3.2.1.4]* The Drug Substance standard declared by the company responsible for routine testing: [Insert the declared drug substance standard from the completed Module *3.2.1.4*]
1.3.2	Container Closure system (name, manufacture)	Information on container and closure system from Module 3.2.1.6.
1.3.3	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 *3.2.1.7*]

2	DRUG PRODUCT (NAME, DOSAGE FORM)	
2.1	**Manufacture (name, dosage form)**	**Module 3.2.2.3**
2.1.1	Composition	Information on the product composition from 3.2.2.1
	Manufacturer(s) (name, dosage form)	Information on the manufacturer(s): [Insert the completed Module 3.2.2.3.]
2.1.2	Batch Formula (name, dosage form)	Information on the batch formula: [Insert the tabulated summary on the batch formula from the completed Module 3.2.2.3.2]
2.1.3	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 3.2.2.3.3]
2.1.4	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 3.2.2.3.4, 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 3.2.2.3.4. under Intermediates.]
2.2	**Control of Excipients (name, dosage form)**	**Module 3.2.2.4**
2.2.1	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 3.2.2.4.]
2.3	**Control of Drug Product (name, dosage form)**	**Module 3.2.2.5**

2.3.1	Specification(s) (name, dosage form)	Specification(s) for the drug product: [Insert the specification(s) for the drug product from the completed Module 3.2.2.5.1] 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 3.2.2.5.1]
2.3.2	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 3.2.2.7]
2.4	**Stability (name, dosage form)**	**Module 3.2.2.8**
2.4.1	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 3.2.2.8.1]
2.4.2	*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 *3.2.2.8.3*]

3	**APPENDICES**	**Module 3.2.3**
3.1	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 3.2.3.1.]
3.2	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 3.2.3.2, 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 3.2.3.2, under *Viral Clearance Studies*.]

Annexure C to Module 1

SUMMARY OF PRODUCT CHARACTERISTICS

Doc. No. SPC/032024 Ver.1.2

Annexure C to Module 1

1. NAME OF THE MEDICINAL PRODUCT (GENERIC NAME)

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Excipient(s):>

Give full list of excipients

3. PHARMACEUTICAL FORM (DOSAGE FORM AND STRENGTH)

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

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 (Drug Interactions)

<No interaction studies have been performed.>

<Interaction studies have only been performed in adults>

4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.) (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 Mechanism of action

5.2 Pharmacodynamic properties

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

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

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

<This medicinal product has been authorized 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.

5.3 Pharmacokinetic properties

6. PRECLINICAL SAFETY DATA (NON-CLINICAL PROPERTIES)

6.1 Animal Toxicology or Pharmacology

<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:>

7. DESCRIPTION

8. PHARMACEUTICAL PARTICULARS

8.1 List of Excipients

8.2 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.>

8.3 Shelf-Life

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

9. NATURE AND CONTENTS OF CONTAINER (PACKAGING INFORMATION)

<Not all pack sizes may be marketed.>

9.1 Storage and Handling Instructions

9.1.1 Special precautions for storage

9.1.2 Special precautions for disposal

<For storage conditions of the <reconstituted> <diluted> medicinal product.

<Any unused product or waste material should be disposed of in accordance with local requirements.>

<No special requirements>

10. PATIENT COUNCELLING INFORMATION

11. MARKETING AUTHORISATION HOLDER (DETAILS OF MANUFACTURER)

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

12. DETAILS OF MARKETING AUTHORISATION NUMBER(S) (DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE)

13. DATE OF REVISION

<{DD/MM/YYYY}><{DD month YYYY}>

d{MM/YYYY}

Annexure D to Module 1

Summary of Drugs Substance:

S. No.	Description	Information
1	Name of the Drug substance & Composition (as per label claim)	
2	History, Source, Strain details	
3	Brief description of manufacturing process of Drug substance	
4	Pharmacopoeial compliance (Consistency and analysis of 3 batches)	
5	Stability of Drug substance (3 batches) • Real time Stability Data • Accelerated Stability Data	

Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products

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3.2.1.2 DRUG SUBSTANCE (NAME, MANUFACTURER)

Manufacture (name, manufacture)

Information on the manufacturer(s): [Insert the completed Module 3.2.1.2]

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 3.2.1.2]

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 3.2.1.2]

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

3.2.1.3 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 3.2.1.3]

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 3.2.1.4]

The drug substance standard declared by the company responsible for routine testing: [Insert the declared drug substance standard from the completed Module 3.2.1.4.1]

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 3.2.1.7]

3.2.2 DRUG PRODUCT (NAME, DOSAGE FORM)

Manufacture (name, dosage form)

Manufacturer(s) (name, dosage form)

Information on the manufacturer(s): [Insert the completed Module 3.2.2.3]

Batch Formula (name, dosage form)

Information on the batch formula: [Insert the tabulated summary on the batch formula from the completed Module 3.2.2.3]

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 3.2.2.3.]

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 3.2.2.3.4, 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 3.2.2.3.4]

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 3.2.2.4]

3.2.2.5 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 3.2.2.5.1]

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 3.2.2.5.1]

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 3.2.2.7]

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 3.2.2.8]

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 3.2.2.8.3]

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 3.2.3.1.]

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 3.2.3.2, 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

3.2.1 DRUG SUBSTANCE (NAME, MANUFACTURER)

Information must be provided for each Drug Substance

3.2.1.1 General Information (name, manufacturer)

3.2.1.1.1 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.

3.2.1.1.2 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.

3.2.1.1.3 Description and Characterization of drug substance

3.2.1.1.4 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.

3.2.1.1.4.1 Strain/cell substrate

3.2.1.1.4.2 System of seed, Master, Working bank

3.2.1.1.4.3 Embryonated egg and other cell substrate

3.2.1.1.5 General description of raw materials

3.2.1.1.6 Analytical certificates signed by the manufacturer and the applicant for registration

3.2.1.2 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 a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.

Rather than 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.

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study (ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided.

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.

3.2.1.3 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”.

3.2.1.3.1 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 sulfhydryl reagents, urea, residual host cell 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.

3.2.1.3.2 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.

3.2.1.3.3 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									

3.2.1.4 Quality control of Drug substance (name, manufacturer)

3.2.1.4.1 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.

3.2.1.4.2 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.

3.2.1.4.3 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).

3.2.1.4.4 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)

3.2.1.4.5 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.

3.2.1.5 Reference Standards or Materials (name, manufacturer)

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

3.2.1.6 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.

3.2.1.7 Stability (name, manufacturer)

3.2.1.7.1 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.

3.2.1.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

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

3.2.1.7.3 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.

3.2.2 DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.2.1 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.

3.2.2.2 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.

3.2.2.2.1 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.

3.2.2.2.2 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

3.2.2.2.3 Justification of final qualitative/quantitative formula should be provided.

3.2.2.2.4 Manufacturing Process Development (name, dosage form)

The selection and optimization of the manufacturing process in particular its critical aspects, should be explained. Where relevant, the method of sterilization 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

3.2.2.2.5 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 Pharmacopoeial tests for elastomeric components and plastics,

and maintenance of pH, should be included. The results from the suitability and compatibility studies should be provided.

3.2.2.3 Manufacture of Drug Product (name, dosage form)

3.2.2.3.1 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.

3.2.2.3.2 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)		

3.2.2.3.3 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.

3.2.2.3.4 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.

3.2.2.3.5 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.

3.2.2.3.6 A brief description of batch identification of system should be provided.

3.2.2.4 Control of Excipients (name, dosage form)

3.2.2.4.1 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 guidance's and/or regulatory authorities for additional guidance.

3.2.2.4.2 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.

3.2.2.4.3 Validation of Analytical Procedure

Description of validation of analytical procedure should be provided.

3.2.2.4.4 Justification of Specifications (name, dosage form)

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

3.2.2.4.5 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.

3.2.2.4.6 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.

3.2.2.5 Control of Drug Product (name, dosage form)

3.2.2.5.1 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.

3.2.2.5.2 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).

3.2.2.5.3 Analytical certificates signed by manufacturer and applicant for registration should be provided.

3.2.2.5.4 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 characterization of impurities and a summary of the justification of the drug product specification should be provided.

3.2.2.5.5 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)

3.2.2.5.6 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 characterization of impurities should also be provided. Validation of analytical procedures and a summary of the justification of the drug product specification should be provided.

3.2.2.5.7 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.

3.2.2.6 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.

3.2.2.7 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.

3.2.2.8 Stability (name, dosage form)

3.2.2.8.1 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.

3.2.2.8.2 Freeze dried products: stability testing of freeze dried materials, diluents and re-constituted products, thermo stability, where applicable

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

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

3.2.2.8.4 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.

3.2.3 APPENDICES

3.2.3.1 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.

3.2.3.2 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) non-compendial 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

References:

1. New Drugs and Clinical Trials Rules, 2019 under Drugs and Cosmetics Act, 1940.
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 (ICMR), New Delhi.
4. The Common Technical Document for the registration of pharmaceuticals for human use: Quality – M4Q(R1); Quality Overall Summary of Module 2 Module 3 : Quality

Central Drugs Standard Control Organization, Ministry of Health and Family Welfare| Govt. of India