

# **Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India**



Government of India

**Department of Biotechnology**

Ministry of Science & Technology

**Central Drugs Standard Control Organization**

Ministry of Health & Family Welfare

**2012**



# **Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India**

**MEMBERS OF THE TASK FORCE SET UP BY DCGI AND SUB-COMMITTEE OF RCGM OF DBT FOR PREPARATION OF THE GUIDELINES**

<b>Chairpersons</b> Dr. G.N. Singh, Drugs Controller General (India), New Delhi	<b>Coordinators/Member Secretaries</b> Shri Satyapal Shani, Deputy Drugs Controller (I), Central Drugs Standard Control Organization
Dr. V.P. Kamboj, Chairman, RCGM and Ex-Director, Central Drug Research of Institute and Honorary Scientist, INSA	Dr. K.K. Tripathi, Adviser, Department of Biotechnology, Ministry of Science & Technology
<b>Members</b> Dr. Bikas Mendi, Department of Pharmacology, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh	<b>Industry members</b> Shri K. V. Subramanian, Chief Executive Officer, Reliance Life Sciences Pvt. Ltd.
Dr. C. D. Tripathi, Head, Dept. of Pharmacology, Vardhman Medical College, New Delhi.	Dr. G. L. Telang, Vice Chairman and Managing Director, Roche Scientific Company (India) Pvt. Ltd.
Dr. Anurag S. Rathore, Associate Professor, Dept. of Chemical Engineering, Indian Institute of Technology (IIT) Delhi	Dr. Sanjay Singh, Chief Executive Officer, Gennova Biopharmaceuticals Ltd.
Dr. B. Sesikeran, Director, National Institute of Nutrition (NIN), Hyderabad	Dr. Cartikeya Reddy, Sr. Vice President, Dr. Reddy's Laboratories
Dr. J. Nagaraju, Staff Scientist & Chief, Laboratory of Molecular Genetics, Centre for DNA Fingerprinting & Diagnostics, Hyderabad	Dr. Sriram Akundi, Associate Vice President (Quality and Regulatory Affairs), Biocon India Ltd.
Dr. A.K. Kondapi, Professor, Laboratory for Molecular Therapeutics, Dept. of Biotechnology, School of Life Sciences, University of Hyderabad	Dr. Alpna Seth, Managing Director, Biogen Idec Biotech India
Dr. Anjali A. Karande, Professor, Department of Biochemistry, Indian Institute of Science, Bangalore	Dr. Samir C. Sangitrao, General Manager (Regulatory Affairs), Cadila Healthcare Ltd.
Dr. A.K. Panda, Staff Scientist VI, Product Development Cell, National Institute of Immunology	
Shri Arvind Kukrety, Assistant Drugs Controller (I), Central Drugs Standard Control Organization	

**Drafting Committee**

Dr. K.K. Tripathi, Adviser, Department of Biotechnology, Ministry of Science & Technology  
Shri Satyapal Shani, Deputy Drugs Controller (I), Central Drugs Standard Control Organization  
Dr. Anurag S. Rathore, Associate Professor, Dept. of Chemical Engineering, Indian Institute of Technology (IIT) Delhi  
Shri Arvind Kukrety, Assistant Drugs Controller (I), Central Drugs Standard Control Organization  
Dr. Vibha Ahuja, General Manager, Biotech Consortium India Limited

**Assisted by**

Ms. Rajalakshmi Muralidharan, Scientist-E, DBT  
Dr. Nitin K Jain, Scientist-D, DBT  
Dr. Amit Parikh, Scientist-C, DBT  
Dr. Anjali Nagpal, Biogen Idec Biotech India

Ms. Meenu Batolar, Biogen Idec Biotech India  
Dr. L. Praveen Kumar, Dr. Reddy's Laboratories Ltd.  
Dr. S. Harinarayana Rao, Reliance Life Sciences Pvt. Ltd.  
Mr. Vivek Veerbhan, Biotech Consortium India Limited

**For further information please contact**

Department of Biotechnology,  
Ministry of Science & Technology  
Block-2, CGO Complex, Lodi Road,  
New Delhi-110003

Central Drugs Standard Control Organization  
Directorate General of Health Services  
Ministry of Health and Family Welfare  
Government of India  
FDA Bhavan, ITO, Kotla Road, New Delhi -110002



# Content

Message	
Foreword	
1. Introduction	1
2. Background & Objectives	1
3. Applicable Regulations and Guidelines	2
4. Competent Authorities	3
5. Scope	4
6. Principles for Development of Similar Biologics	4
6.1 Selection of Reference Biologic	5
6.2 Manufacturing Process	6
6.3 Quality Consideration of Similar Biologics	8
6.4 Quality Comparability Study	11
7. Data Requirements for Preclinical Studies	12
7.1 Prerequisite before Conducting Preclinical Studies	12
7.2 Preclinical Studies (Pharmacodynamic and Toxicology Studies)	13
7.3 Immune Responses in Animals	17
8. Data Requirements for Clinical Trial Application	17
8.1 Pharmacokinetic Studies	18
8.2 Pharmacodynamic Studies	19

8.3	Confirmatory Safety and Efficacy Study	20
8.4	Safety and Immunogenicity Data	21
8.5	Extrapolation of Efficacy and Safety Data to other Indications	22
9.	Data Requirements for Market Authorization Application	22
10.	Post-Market Data for Similar Biologics	23
10.1	Pharmacovigilance Plan	23
10.2	Adverse Drug Reaction (ADR) Reporting	23
10.3	Post Marketing Studies (Pms)	23
11.	Application Forms	25
12.	Archiving of Data	25
13.	Glossary	26
14.	References	29

Annexes:

1:	Protocols on Regulatory Pathway for Recombinant Pharma Products Adopted from Mashelkar Report	30
2:	Requirement of Physicochemical and Biological Characterization of	
2a:	Nucleic Acid Based Recombinant Products	35
2b:	Therapeutic Proteins	37
2c:	Therapeutic Enzymes	39
2d:	Antibodies	41



सत्यमेव जयते



MINISTRY OF  
SCIENCE & TECHNOLOGY

सचिव  
भारत सरकार  
विज्ञान और प्रौद्योगिकी मंत्रालय  
बायोटेक्नोलॉजी विभाग  
ब्लाक-2, 7 वां तल, सी० जी० ओ० कम्प्लेक्स  
लोदी रोड, नई दिल्ली-110003

SECRETARY  
GOVERNMENT OF INDIA  
MINISTRY OF SCIENCE & TECHNOLOGY  
DEPARTMENT OF BIOTECHNOLOGY  
Block-2, (7th Floor) C.G.O. Complex  
Lodi Road, New Delhi-110003

डा० एम० के० भान  
Dr. M. K. Bhan

## MESSAGE

Biotechnology innovation has made dramatic contributions in the field of healthcare with more than 200 biologic medicines and vaccines benefitting millions of patients worldwide and more than 600 products under development. These products can now also be produced by manufacturers other than the innovator, with the expiry of some of patents. These new biotechnological medicines commonly referred to as similar biologics offer a major opportunity to provide greater access to affordable healthcare for several life saving medicines.

India has emerged as one of the leading contributors to the world market for similar biologics with the continuous growth. In fact similar biologics are expected to become the most important economic and therapeutic component of the pharmaceutical market in India. With several companies venturing into this area, a strong need was felt to streamline the regulatory process through a well defined set of guidelines.

I am extremely pleased to note that the two agencies involved in the regulation of similar biologics in India have joined together to prepare "Guidelines on similar biologics: Regulatory requirements for market authorization in India". These guidelines clearly outline the data requirements for production process, characterization, preclinical studies and clinical trials.

I congratulate Dr. G.N. Singh, Drug Controller General of India and his colleagues for joining hands with the Department of Biotechnology (DBT) for preparing the guidelines through a consultative process with stakeholders. I express my appreciation for sincere efforts by Dr. V.P. Kamboj, Chairman, RCGM and Dr. K.K. Tripathi, Adviser, DBT and Member Secretary, RCGM for preparation of these guidelines. I also wish to place on record the valuable inputs provided by the members of two committees set up by DBT and DCGI for the purpose of preparation of these guidelines. The support provided by Biotech Consortium India Limited in managing the consultative process is also acknowledged.

I am confident that these guidelines would be of immense help to industry to become globally competitive and also provide safe and affordable similar biologics in the country.

  
(M.K. Bhan)



## **FOREWORD**

The Central Drugs Standard Control Organization (CDSCO), being the apex regulatory authority for approval of drugs in India, is committed to safeguard and enhance the Public Health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices.

As a consequence of biopharmaceuticals reaching the end of their patent life, there has been great demand in this new field of development for similar biologics since past few years. The concept of similar biologics has the potential to produce affordable biotech medicines, a need was felt to address issues and challenges particularly with respect to products that qualify as similar biologics, similarity with innovative products and establishing appropriate regulatory pathways to ensure cost effective production of these products.

We are pleased to note that CDSCO team has worked in collaboration with the Department of Biotechnology (DBT) to develop "Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India", as these products are regulated jointly by both the agencies. I express my gratitude to Dr. M.K. Bhan, Secretary, DBT and Dr. V.P. Kamboj, Chairman, RCGM for their guidance and interest in shaping up these guidelines.

These guidelines have been developed by joint efforts of members of a task force set up by CDSCO and sub-committee of RCGM to ensure that consistent science based and data driven standards are applied in the regulatory process keeping in view the principles of safety, efficacy and quality of biologics products. We sincerely thank the members of both the committees for their valuable inputs. I appreciate the efforts of Shri Satyapal Shani, Deputy Drugs Controller (India) and Dr. K.K. Tripathi, Adviser, DBT for coordinating the whole process besides other subject experts and institutions. We are pleased that the guidelines have been made through a consultative process with the involvement of various stakeholders including industry representatives through membership in the task force as well as series of consultations and public review process. We also appreciate efforts of Biotech Consortium India Limited in coordinating the consultative process on behalf of CDSCO and DBT.

We are of the firm opinion that this important guideline will go a long way in providing guidance and documentary support to both applicants and regulators for the development of similar biologics in the country and provide affordable medicines for the Indian Population.

  
(Dr. G.N. Singh)  
Drugs Controller General (I)





# Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India

## 1. Introduction

The “Guidelines on Similar Biologics” prepared by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) lay down the regulatory pathway for a similar biologic claiming to be similar to an already authorized reference biologic .

The guidelines address the regulatory pathway regarding manufacturing process and quality aspects for similar biologics.

These guidelines also address the pre-market regulatory requirements including comparability exercise for quality, preclinical and clinical studies and post market regulatory requirements for similar biologics.

## 2. Background & Objectives

The CDSCO is the national regulatory authority in India that evaluates safety, efficacy and quality of drugs in the country. The DBT through Review Committee on Genetic Manipulation (RCGM) is responsible for overseeing the development and preclinical evaluation of recombinant biologics.

Presently, several organizations are actively engaged in manufacturing and marketing similar biologics in India. So far, these similar biologics were approved by RCGM and CDSCO using an abbreviated version of the pathway applicable to new drugs on a case by case basis. Since there are several such products under development in India, both regulatory agencies considered the need to publish a clear regulatory pathway outlining the requirements to ensure comparable





safety, efficacy and quality of a similar biologic to an authorized reference biologic. Based on demonstration of similarity in the comparative assessment, a similar biologic may require reduced preclinical and clinical data package as part of submission for market authorization.

The objective of this document is to provide guidelines to applicants to enable them to understand and comply with the regulatory requirements for the authorization of similar biologics in India.

### **3. Applicable Regulations And Guidelines**

The similar biologics are regulated as per the Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (as amended from time to time) and Rules for the manufacture, use, import, export and storage of hazardous microorganisms/genetically engineered organisms or cells, 1989 (Rules, 1989) notified under the Environment (Protection) Act, 1986. Various applicable guidelines are as follows:

- Recombinant DNA Safety Guidelines, 1990
- Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other biologicals, 1999
- CDSCO guidance for industry, 2008:
  - o Submission of Clinical Trial Application for Evaluating Safety and Efficacy
  - o Requirements for permission of New Drugs Approval
  - o Post approval changes in biological products: Quality, Safety and Efficacy Documents
  - o Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
- Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011



## 4. Competent Authorities

The competent authorities involved in the approval process are as follows:

### Review Committee on Genetic Manipulation (RCGM)<sup>1</sup>

RCGM functions in the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India. In the context of similar biologics, RCGM is responsible for authorizing import/export for research and development and review of data up to preclinical evaluation.

### Genetic Engineering Appraisal Committee (GEAC)<sup>1</sup>

GEAC functions under the Ministry of Environment and Forests (MoEF) as statutory body for review and approval of activities involving large scale use of genetically engineered organisms (also referred as living modified organisms) and products thereof in research and development, industrial production, environmental release and field applications.

### Central Drugs Standard Control Organization (CDSCO)<sup>2</sup>

CDSCO, headed by the Drug Controller General of India (DCGI) is the apex regulatory body under Ministry of Health & Family Welfare (MoHFW), Government of India which is responsible for the approval of new drugs. In the context of similar biologics, CDSCO is responsible for grant of import/export license, clinical trial approval and permission for marketing and manufacturing. State Food and Drug Administration (FDA) works with CDSCO in each state and is responsible for issuance of license to manufacture similar biologics in India.

---

<sup>1</sup>RCGM and GEAC are statutory committees set up as per provisions of Rules, 1989

<sup>2</sup>CDSCO functions as per the provisions of the Drugs and Cosmetics Act, 1940



## 5. Scope

These guidelines apply to similar biologics that contain well characterized proteins as their active substance, derived through modern biotechnological methods such as use of recombinant DNA technology. The demonstration of similarity depends upon detailed and comprehensive product characterization, preclinical and clinical studies carried out in comparison with a reference biologic.

Similar biologic can only be developed against an authorized reference biologic that has been approved using a complete data package in India. In case the reference biologic is not authorized in India, it should have been licensed and marketed for at least 4 years with significant safety and efficacy data. In case of no medicine or only palliative therapy is available or in national healthcare emergency, this period of 4 years may be reduced or waived off.

Any product can be considered as similar biologic only if it is proven to be similar using extensive quality characterization against the reference biologic. Further product development should only be considered once the similarity of the product / molecule is demonstrated in quality.

The guidelines are applicable for similar biologics developed in India or imported into the country. Detailed regulatory pathways for indigenously developed and imported products<sup>3</sup> are given in Annexure 1.

## 6. Principles for Development of Similar Biologics

Similar biologics are developed through sequential process to demonstrate the similarity by extensive characterization studies revealing the molecular and quality attributes with regard to the reference biologic.

Although the extent of testing of the similar biologic is likely to be less than that required for the reference biologic, it is essential that the testing of the similar biologic be sufficient to ensure that the product meets acceptable levels of safety, efficacy and quality to ensure public health.

Generally, a reduction in data requirements is possible for preclinical and / or clinical components of the development program by demonstration of comparability of product (similarity to authorized reference biologic) and the consistency in production process, which may vary depending on the characteristics of the already authorized reference biologic.

---

<sup>3</sup>Adopted from Report of the Task Force on Recombinant Pharma , 2005, chaired by Dr. R.A. Mashelkar, DG, CSIR (commonly referred as Mashelkar Report)



Identification of any significant differences in safety, efficacy and quality studies would mean the need for a more extensive preclinical and clinical evaluation and the product will not qualify as a similar biologic.

In case the reference biologic is used for more than one indication, the efficacy and safety of the similar biologic has to be justified and if necessary demonstrated separately for each of the claimed indications. Justification will depend on clinical experience, available literature data and whether or not the same mechanism of action is involved in specific indications.

### 6.1 Selection of Reference Biologic

Reference biologic which is authorized using complete dossier is critical for the development of similar biologic. The rationale for the choice of the reference biologic should be provided by the manufacturer of the similar biologic in the submissions to the DBT and CDSCO.

The reference biologic has to be used in all the comparability exercise with respect to quality, preclinical and clinical considerations. The following factors should be considered for selection of the reference biologic:

- The reference biologic should be licensed in India and should be innovator product. The reference biologic should be licensed based on a full safety, efficacy and quality data. Therefore another similar biologic cannot be considered as a choice for reference biologic.
- In case the reference biologic is not marketed in India, the reference biologic should have been licensed and widely marketed for 4 years post approval in innovator jurisdiction in a country with well established regulatory framework. In case no medicine or only palliative therapy is available or in national healthcare emergency, this period of 4 years may be reduced or waived off.
- The same reference biologic should be used throughout the studies supporting the safety, efficacy and quality of the product (i.e. in the development programme for the similar biologic)
- The dosage form, strength and route of administration of the similar biologic should be the same as that of the reference biologic.
- The active substance (active ingredient) of the reference biologic and that of the similar biologic must be shown to be similar

The acceptance of an innovator product as a reference biologic for evaluation of similar biologic does not imply approval for its use in India.



## 6.2 Manufacturing Process

The manufacturing process for similar biologic should be highly consistent and robust. If the host cell line used for the production of reference biologic is disclosed, it is desired to use the same cell line as the reference biologic. Alternatively any cell line that is adequately characterized and appropriate for intended use can be used to develop a similar biologic, with appropriate justification in order to minimize the potential for significant changes in critical quality attributes of the product and to avoid introduction of certain types of process related impurities that could impact clinical outcomes and immunogenicity. For the establishment and characterization of the cell banks, the guidelines issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (referred to as ICH) viz. Q5A<sup>4</sup>, Q5B<sup>5</sup> and Q5D<sup>6</sup> should be referred for guidance.

The data requirements for review of manufacturing process at preclinical submission stage include a complete description of the manufacturing process from development and characterization of cell banks, stability of clone, cell culture/ fermentation, harvest, excipients, formulation, purification, primary packaging interactions (if different from reference biologic), etc. and the consequences on product characteristics as indicated below:

### 6.2.1 Molecular Biology Considerations

The details regarding host cell cultures (including viral clearance), vectors, gene sequences, promoters etc. used in the production of similar biologics should be provided with appropriate drawings/figures. The details of post-translational modifications if any (glycosylation, oxidation, deamidation, phosphorylation etc.) should be explained.

---

<sup>4</sup>ICH Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

<sup>5</sup>ICH Q5B: Quality of Biotechnological Products: Analysis of The Expression Construct In Cells Used for Production of R-DNA Derived Protein Products

<sup>6</sup>ICH Q5D: Derivation and Characterization of Cell Substrates used for Production of Biotechnological/Biological Products



### 6.2.2 Fermentation Process Development

- At least three batches of reproducible fermentation data at pilot scale (batch size adequate to give enough purified product to generate preclinical data).
- Fermentation process should be carried out in controlled and monitored environment.
- Details of fermentation kinetics data from a representative batch indicating cell growth, product formation, pH, temperature, dissolved oxygen, major nutrient consumption pattern and agitation rate.
- Concentration to be defined in terms of product/litre, yield and volumetric productivity.
- Data to verify that the specific protein yield (amount of protein per unit cell mass) remains constant for all fermentation batches.
- Demonstrate that the overall productivity is reproducible and scalable.

### 6.2.3 Downstream Process Development

- Steps involved in purification of protein.
- Batch size for protein purification.
- Description of each unit operation step during purification and recovery of protein along with quantitative recovery of product at each stage.
- Describe the quality of the refolded protein if the starting material is aggregated or from inclusion bodies and include details of the refolding process, specific activity at different doses, dose response curve, stability data and confirmation of solubility and absence of aggregation.
- Consistency of recovery in 3 consecutive batches of purification from 3 independent batches of fermentation



For clinical trial application, additional requirements are applicable as per CDSCO guidelines. A well-defined manufacturing process with its associated process controls assure that an acceptable product is produced on a consistent basis in accordance with Good Manufacturing Practice (GMP). Data for submission should include:

- Detailed description of the drug substance and drug product processes
- Critical quality attributes of the product
- Manufacturing process controls
- Critical process parameters
- Stability data
- Comparability of product manufactured at clinical scale against reference biologic
- Data from consistency batches and/or process validation batches as applicable

### 6.3 Quality Based Considerations for Similar Biologics

#### 6.3.1 Analytical Methods

The analytical methods should be chosen for establishing product comparability as per the critical quality attributes of the product. For certain attributes (e.g. product aggregation) it is customary to use multiple, orthogonal methods for characterization. Extensive state of the art analytical methods should be applied to detect even “slight differences” in all relevant quality attributes. Indian Pharmacopoeia monograph should be followed, if available.

The measurement of quality attributes in characterization should entail the use of appropriately qualified assays, which are reproducible and reliable. The methods used to measure quality attributes for batch release, stability studies and in-process controls should be validated in accordance with ICH guidelines (ICH Q2<sup>7</sup>, Q5C<sup>8</sup>, Q6B<sup>9</sup>), as appropriate.

---

<sup>7</sup>ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology

<sup>8</sup>ICH Q5C: Stability Testing of Biotechnological/Biological Products

<sup>9</sup>ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products





The characterization studies should include samples of the applicant's recombinant product, reference biologic as control, known positive standard and negative control, wherever relevant. To ensure the statistical analysis, each quantitative experiment should be done at least 3 times and data should be represented in terms of mean and standard deviation. Appropriate statistical significance should be represented throughout the characterization data. Physicochemical and biological characterization methods to be used for various categories of products viz. recombinant proteins, therapeutic enzyme, monoclonal antibodies etc. are given in Annexure 2 (2A-2D). It may be noted that these Annexures are suggestive but not limited to the specified method and the requirements may vary on case by case.

### **6.3.2 Product Characterization**

Characterization studies for similar biologics include physicochemical properties, biological activity, immunological properties, functional assays, purity (process- and product-related impurities etc.), contamination, strength, and content. Principles outlined in the ICH Q6B guideline should be followed. Indian Pharmacopoeia Monograph should be followed, if available.

- i. **Structural and Physicochemical Properties:** The analysis of physicochemical characteristic should include determination of primary and higher order structure of the product along with other significant physicochemical properties. The target amino acid sequence of the similar biologic should be confirmed and is expected to be the same as for the reference biologic. Analytical methods that are used (including biological and functional assays) should have acceptable precision and accuracy. In cases, where post translational modifications are taking place, these modifications need to be identified and quantified.

In case any significant differences are found, these should be scientifically justified and critically examined in preclinical studies and clinical trials.

- ii. **Biological Activity:** Biological products may have multiple biological activities. In such cases, appropriate biological assays will be required to characterize the activity and establish the product's mechanism of action



and clinical effects (in units of activity). The data from biological assays will supplement the physicochemical characterization of the product as described in the section 6.3.1.

Assays should be calibrated against an international or national reference standard, where available and appropriate. If no such standards are available, an internal reference standard must be established as per the ICH guidelines. If the methods of bioassay(s) are documented in the specification, test(s) can be conducted accordingly.

- iii. Immunological Properties: The manufacturing process of recombinant biologics is known to affect the level of process related impurities and post translational modifications of the product. These characteristics may affect the immunogenicity of the product. Hence evaluation by characterization (antibody or antibody-derived product); comparison to reference biologic with respect to specificity, affinity, binding strength and Fc function; and evaluation by animal studies should be performed.
- iv. Purity and Impurities: Characterization of similar biologic requires evaluation of the following via a combination of analytical procedures:
  - Product related variants (e.g., glycoforms, isomers etc.)
  - Product related impurities (e.g., aggregated, oxidized or deamidated product)
  - Host cell related impurities (e.g., host cell protein, host cell DNA etc.)
  - Process related impurities (residual media components, resin leachates etc.)

Differences observed in the purity and impurity profiles of the similar biologic relative to the reference biologic should be evaluated to assess their potential impact on safety and efficacy. Where the similar biologic exhibits different impurities, those impurities should be identified and characterized when possible. Depending on type and amount of the impurity, conduct of preclinical and clinical studies will help to confirm that there is no adverse impact on safety and efficacy of the similar biologic.



### 6.3.3 Specifications

Specifications of similar biologics are established around critical quality attributes of the product with the intent of ensuring consistency in product quality and comparability to reference biologic. Methods used for setting specifications may or may not be same as the analytical methods used for product characterization and for establishing product comparability. Acceptance limits should be set based on reference biologic data and data from sufficient number of batches from preclinical or clinical batches.

### 6.3.4 Stability

To set a shelf-life and storage condition of drug product and drug substance, its real time stability test should be conducted. Stability studies on drug substance and drug product should be carried out using containers and conditions that are representative of the actual storage containers and conditions, according to relevant guidelines (e.g. ICH Q5C<sup>10</sup>, WHO TRS 822<sup>11</sup>).

Side-by-side accelerated and stressed studies comparing the similar biologic to the reference biologic will be of value in determining the similarity of the products by showing comparable degradation profiles.

## 6.4 Quality Comparability Study

The quality comparison between similar biologic and reference biologic is essential. The applicant should submit a full quality dossier as per CDSCO guidance for industry, 2008 including the results of comparability exercise for the similar biologic with the reference biologic before the applicant proposes to take the similar biologic to clinical development. First three consecutive standardized batches which have been used to demonstrate consistency of the manufacturing process should be used.

Head-to-head characterization studies are required to compare the similar biologic and the reference biologic at both levels of drug substance and drug

---

<sup>10</sup> ICH Q5C: Stability Testing of Biotechnological/Biological Products

<sup>11</sup> Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization, Forty-second report, Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 822).



product. In case the isolation of the drug substance is not possible, comparability can be demonstrated at the drug product level with appropriate scientific justification. Differences between the similar biologic and the reference biologic should be evaluated for their potential impact on safety and efficacy of the similar biologic and additional characterization studies may be necessary.

Minor differences between similar biologic and reference biologic in each quality component can be there. Appropriate data should be submitted to verify that these differences do not impact on the safety and efficacy.

The quality comparison between the similar biologic and the reference biologic should employ state-of-the-art analytical techniques, including the analytical methods that are sensitive enough to detect the possibilities of changes to the product. The list of routine analytical tests to be included for quality comparability exercise is given in Annexure-2 (2A-2D).

## 7. Data Requirements for Preclinical Studies

### 7.1 Prerequisite before Conducting Preclinical Studies

The applicant has to comply with the RCGM requirements like demonstration of consistency of the process and product, product characterization and product specifications. The applicant should submit the data generated along with the following basic clinical information and preclinical study protocols to RCGM for obtaining permission. The toxicology studies should be initiated after the approval of RCGM. The basic information about the reference biologic and similar biologic may include the following:

#### **Basic information about the reference biologic**

- Information about the drug, route of administration, absorption and elimination rate, therapeutic index, dose, vehicle, mode of administration, dose response etc.
- Bioequivalence range, if available.
- Tissue-specific localization , if available.
- Available toxicity data on reference biologic.
- Mode of action.



### **Basic information about the similar biologic**

- Known / proposed clinical use
- Target population (Age, sex, pregnancy, lactating, children etc.)
- Dosage (frequency and intervals) –units
- Route / alternate routes of administration
- Final formulation + adjuvants, additives etc. - Toxicology data of adjuvants
- Diluents
- Presentation e.g. pre filled syringe

The application to RCGM should be accompanied by approval by the Institutional Biosafety Committee (IBSC) of the applicant (copy of the minutes should be submitted), and approval of Institutional Animal Ethics Committee (IAEC), if available. The applicant should also provide details of the proposed site for conduct of toxicity testing and personnel to be involved e.g. study director, principal investigator, pathologist, other Investigators and quality assurance officer at the site. Status of GLP certification of proposed facility should also be provided.

### **7.2 Preclinical Studies (Pharmacodynamic and Toxicology Studies)**

The preclinical studies should be conducted prior to the initiation of any clinical studies. These preclinical studies should be comparative in nature and designed to detect differences if any, between the similar biologic and reference biologic. The preclinical study design may vary depending upon the clinical parameters such as therapeutic index, the type and number of indications applied. The approach adopted should be fully justified in the preclinical overview. Preclinical studies should be conducted with the final formulation of the similar biologic intended for clinical use and for the reference biologic unless otherwise justified. The dosage form, strength and route of administration of the similar biologic should be the same as that of the reference biologic and in case of any differences in these parameters, it should be justified.

The following studies are required for preclinical evaluation:



### 7.2.1 Pharmacodynamic Studies

- i. *In vitro* studies: Comparability of test and reference biologic should be established by *in vitro* cell based bioassay (e.g. cell proliferation assays or receptor binding assays).
- ii. *In vivo* studies: *In vivo* evaluation of biological/ pharmacodynamic activity may be dispensable if *in vitro* assays are available, which are known to reliably reflect the clinically relevant pharmacodynamic activity of the reference biologic. In cases where the *in-vitro* assays do not reflect the pharmacodynamics, *In vivo* studies should be performed.

### 7.2.2 Toxicological Studies

In case of *in vivo* toxicity studies, at least one repeat dose toxicity study in a relevant species is required to be conducted. The duration of the study would be generally not less than 28 days with 14 days recovery period. However the duration may vary depending on the dosage and other parameters on case by case basis.

Regarding the animal models to be used, the applicant should provide the scientific justification for the choice of animal model(s) based on the data available in scientific literature. However if the relevant animal species is not available and has been appropriately justified, the toxicity studies need to be undertaken in two species i.e. one rodent and other non rodent species, as per the requirements of Schedule Y<sup>12</sup> with due permission from the RCGM.

Regarding the route of administration, in cases when the relevant animal model is used, the route of administration would include only the intended route, whereas in all other cases, Schedule Y should be followed.

The dose should be calculated based on the therapeutic dose of the reference biologic. If required a pilot dose response study should be conducted prior to initiating the toxicity studies. Generally there would be three levels of doses (viz. low, medium and high) used in the animal toxicology studies corresponding to 1X, 2X and 5X of human equivalent dose or higher test dose for repeat dose toxicity studies. Any difference in the levels of doses should be justified and

---

<sup>12</sup>Schedule Y: Requirements and Guidelines for Permission to Import and / or Manufacture of New Drugs for Sale or to Undertake Clinical Trials notified as per G.S.R. 32(E), dt. 20.01.2005 under the Drugs and Cosmetics Rules, 1945



approved prior to the studies. Regarding the schedule of administration, the therapeutic schedules may be used as the basis.

Depending on the route of administration, local tolerance should be evaluated. If feasible, this evaluation may be performed as a part of above mentioned repeat dose toxicity study.

Accordingly the study groups of animals in repeat dose toxicity testing will consist of :

- i. Historical Control (Optional)
- ii. Vehicle Control
- iii. Vehicle Control for recovery group
- iv. Formulation without protein (for vaccines) if multiple adjuvants - each to be checked independently
- v. 1X similar biologic for study duration ( lowest dose)
- vi. 1X Reference biologic for study duration
- vii. 2X Medium dose similar biologic
- viii. 5X High dose similar biologic
- ix. Similar biologic with a recovery group going beyond the end of study period for 7 to 14 days

The protocols and the study reports should provide complete details of various steps in the toxicity testing as indicated below:

- Procedures prior to euthanasia e.g. blood drawing, body weight, etc.
- Events immediately after euthanasia, necropsy, gross – description, organ weights and organs sampled for histopathology.
- Biochemical parameters – Equipment and methods used - units of measurement and expression.
- Haematology procedures and parameters – method to be used (automated or manual).
- Statistical methods used.
- Bone marrow either examined as an aspirate /smear or on histopathology section.





In case of histopathological observations, the applicants should consider the following points:

- Every observation considered as deviation from described normal histology needs to be documented and the incidence of each of these in the different groups should be denoted
- Whether such a feature is significant or not can be decided on review of statistical significance or dose response or if it is within or outside the normal range of values in case of biochemical and haematological observations.
- If all organs from all animals were not examined e.g. in 5 animals only 4 livers were examined, the reason for the 1 liver not being examined should be documented.
- In case of premature death or morbidity the proposed course of action is to be included in the protocol.

Other toxicity studies, including safety pharmacology, reproductive toxicity, mutagenicity and carcinogenicity studies are not generally required for evaluation of a similar biologic unless warranted by the results from the repeat dose toxicological studies.

The final report of the study should reflect all the aspects approved in the protocol and the following additional sections/documents:

- RCGM approval of protocol and test center
- IBSC approval of report
- IAEC approval for animal use and for the procedures
- QA statement
- Signatures of study director and all investigators who were involved in the study
- All quality analytical reports on the test material and vehicle
- Animal feed and animal health certifications



- Protocol deviations if any
- Discussion on the results
- Individual animal data, summary data and any other data like computer analysis outputs etc
- Conclusion

### 7.3 Immune Responses in Animals

Antibody response to the similar biologic should be compared to that generated by the reference biologic in suitable animal model. The test serum samples should be tested for reaction to host cell proteins.

For evaluating immune toxicity of the similar biologic under study, the results of local tolerance (part of repeat dose or stand alone test) should be analyzed with the observations regarding immunogenicity in sub-chronic study. Therefore, the immunogenicity testing should be included as part of the sub-chronic repeat dose study while developing the protocols.

The other parameters for evaluating immune toxicity include immune complexes in targeted tissues may be considered while evaluating histopathology observations, etc.

After completion of preclinical studies the reports are submitted to RCGM for review and consideration.

Based on the successful evaluation of preclinical study reports including demonstration of consistency of the process and product, product characterization, product specifications and similarity to reference biologic, RCGM will recommend the applicant to approach DCG(I) to conduct appropriate phase of clinical trial as per the CDSCO requirements.

## 8. Data Requirements for Clinical Trial Application

Besides the information submitted in the preclinical application, the applicant has to submit application for conduct of clinical trial as per the CDSCO guidance for industry, 2008. The quality data submitted should establish comparability of similar biologic manufactured at clinical scale against reference biologic.



## 8.1 Pharmacokinetic Studies

Comparative pharmacokinetic (PK) studies should be performed in healthy volunteers or patients to demonstrate the similarities in pharmacokinetic characteristics between similar biologic and reference biologic on case to case basis.

The design of comparative pharmacokinetic studies should take the following factors into consideration.

- Half life
- Linearity of PK parameters
- Endogenous levels and diurnal variations of similar biologic under study (where applicable)
- Conditions and diseases to be treated
- Route(s) of administration, and
- Indications

Appropriate design considerations can be combined into single dose or multiple dose studies with adequate justification. These design considerations include:

- Single dose, comparative, PK studies
- Parallel arm or
- Cross over
- Multiple dose, comparative parallel arm steady state PK studies

### 8.1.1 Single Dose Comparative PK Studies

Dosage in the PK study should be within the therapeutic dose range of reference biologic. Appropriate rationale for dose selection should be provided. The route of administration should be the one where the sensitivity to detect differences is the largest. Sample size should have statistical rationale (i.e. statistically justified) and comparability limits should be defined and justified prior to conducting the study.



The analytical method should be validated to have satisfactory specificity, sensitivity and a range of qualification with adequate accuracy and precision. It should have capability to detect and follow the time course of the similar biologic (the parent molecule and / or degradation products) in a complex biological matrix that contains many other proteins.

Differences in elimination kinetics between similar biologic and reference biologic e.g. clearance and elimination half life should be explored. Similarity in terms of absorption / bioavailability should not be the only parameters of interest.

A parallel arm design is more appropriate for biologics with a long half life or for proteins for which formation of antibodies is likely or if study is being done in patients. In case of short half life, cross over design may be considered with a scientific justification.

### **8.1.2 Multiple Dose Comparative PK Studies**

Multiple-dose, comparative, parallel arm steady state PK studies are required for a similar biologic that is used in a multiple dose regimen, where markedly higher or lower concentrations are expected at steady state than that expected from single dose data PK measurements, and where time-dependence and dose-dependence of PK parameters cannot be ruled out.

In case multi-dose comparative PK studies are not done adequate justification should be provided.

## **8.2 Pharmacodynamic Studies**

As for the PK studies in the similar biologic clinical development program, the pharmacodynamic (PD) studies should also be comparative in nature.

Comparative, parallel arm or cross-over, PD study in most relevant population (patients or healthy volunteers) is required for detecting differences between reference biologic and similar biologic. If PD marker is available in healthy volunteers, PD in healthy volunteers can be done.

Comparative PD studies are recommended when the PD properties of the reference biologic are well characterized with at least one PD marker being linked to the efficacy of the molecule. The relationship between dose / exposure, the



relevant PD marker(s) and response / efficacy of the reference biologic should be well established and used to justify the design. The acceptance ranges for the demonstration of similarity in PD parameters should be predefined and appropriately justified.

The parameters investigated in PD studies should be clinically relevant and surrogate markers should be clinically validated. PD studies may be combined with PK studies, in which case the PK/PD relationship should be characterized.

PD study can also be a part of Phase III clinical trials wherever applicable.

### **8.3 Confirmatory Safety and Efficacy Study**

Information to establish comparative safety and efficacy in relevant patient population is mandatory for all similar biologics.

Comparative clinical trials are critical to demonstrate the similarity in safety and efficacy profiles between the similar biologic and reference biologic with few exceptions (e.g. recombinant human soluble insulin products for which only comparative clinical safety study is required). The design of the studies and the clinical comparability margins of the primary efficacy endpoints are important and should be given careful consideration and should be justified on clinical grounds. In line with the principle of similarity, equivalence trials with equivalence designs (requiring lower and upper comparability margins) are preferred. If non-inferiority trials are required they must be clearly justified and applicants are advised to consult with CDSCO prior to study initiation. Sample sizes should have statistical rationale and comparability limits should be defined and justified prior to conducting the study.

The nature, severity and frequency of adverse events should be compared between the similar biologic and reference biologic and should be based on safety data from a sufficient number of patients treated for an acceptable period of time. Efforts should be made to ensure that comparative clinical studies have a sufficient number of patients treated for acceptable period of time in order to allow detection of significant differences in safety between similar biologic and reference biologic.



One or more adequately powered, randomized, parallel group, blinded confirmatory clinical safety and efficacy trials are desirable based on the comparability established during preclinical and PK / PD studies. More than one safety and efficacy study may be required and the similar biologic will be treated as a “stand-alone product” if the similar biologic is not comparable to reference biologic in all preclinical evaluations conducted and /or the PK/PD studies have not demonstrated comparability.

The confirmatory clinical safety and efficacy study can be waived if all the below mentioned conditions are met:

- i. Structural and functional comparability of similar biologic and reference biologic can be characterized to a high degree of confidence by physicochemical and *in vitro* techniques
- ii. The similar biologic is comparable to reference biologic in all preclinical evaluations conducted
- iii. PK / PD study has demonstrated comparability and has preferentially been done in an in-patient setting with safety measurement (including immunogenicity) for adequate period justified by the applicant and efficacy measurements
- iv. A comprehensive post-marketing risk management plan has been presented that will gather additional safety data with a specific emphasis on gathering immunogenicity data

The confirmatory clinical safety and efficacy study cannot be waived if there is no reliable and validated PD marker.

#### **8.4 Safety and Immunogenicity Data**

Both pre-approval and post-approval assessment of safety is desired to be conducted for similar biologic.

Regarding pre-approval safety assessment, comparative pre-approval safety data including the immunogenicity data is required for all similar biologics including those for which confirmatory clinical trials have been waived. This pre-approval safety data is primarily intended to provide assurance of the absence of any unexpected safety concerns.



Comparative safety data based on adequate patient exposure (both numbers and time) must, in conjunction with the published data on the reference biologic provide assurance of absence of any unexpected safety concerns and in conjunction with the proposed non-comparative post-marketing study provide a comprehensive approach to the evaluation of safety of the similar biologic.

Post approval safety data requirements are elaborated in section 10.3.

### **8.5 Extrapolation of Efficacy and Safety Data to Other Indications**

Extrapolation of the safety and efficacy data of a particular clinical indication (for which clinical studies has been done) of a similar biologic to other clinical indications may be possible if following conditions are met:

- Similarity with respect to quality has been proven to reference biologic
- Similarity with respect to preclinical assessment has been proven to reference biologic
- Clinical safety and efficacy is proven in one indication
- Mechanism of action is same for other clinical indications
- Involved receptor(s) are same for other clinical indications

New indication not mentioned by innovator will be covered by a separate application.

## **9. Data Requirements for Market Authorization Application**

The applicant should submit application for market authorization as per CDSCO guidance document for industry, 2008 . For cases where commercial manufacturing is performed either at a different scale and/or with a different process as compared to that used for manufacturing phase III clinical trial batches, then information on comparability of quality needs to be additionally submitted with appropriate justification and will be dealt with on a case to case basis.





## 10. Post-Market Data for Similar Biologics

Though similar biologics are not new drug products and their risk will be similar to reference biologic; however as similar biologics are authorized based on a reduced preclinical and clinical data package, it is important to submit the Risk Management Plan to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the similar biologics. The reference biologic shall be maintained throughout the life cycle of the product.

The risk management plan should consist of the following:

### 10.1 Pharmacovigilance Plan

The clinical studies done on similar biologics prior to market authorization are limited in nature so the rare adverse events are unlikely to be encountered. Hence a comprehensive pharmacovigilance plan should be prepared by manufacturer to further evaluate the clinical safety in all the approved indications in the post-marketing phase. The pharmacovigilance plan should include the submission of periodic safety update reports (PSURs). The PSURs shall be submitted every six months for the first two years after approval of the similar biologic is granted to the applicant. For subsequent two years the PSURs need to be submitted annually to DCGI office as per the Schedule Y.

### 10.2 Adverse Drug Reaction (ADR) Reporting

All cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant as per Schedule Y.

### 10.3 Post Marketing Studies (PMS)

The clinical studies done on similar biologics prior to market authorization are limited in nature so post marketing studies should be conducted and the reports be submitted to DCGI. The plan of post market studies should be captured in Pharmacovigilance plan and update on the studies should be submitted to the CDSCO.



Regarding post-marketing safety and immunogenicity study at least one non-comparative post-marketing clinical study with focus on safety and immunogenicity (on case by case basis) should be performed. This study must be designed to confirm that the similar biologic does not have any concerns with regards to the therapeutic consequences of unwanted immunogenicity. If immunogenicity is evaluated in clinical studies, it is not mandatory to carry out additional non-comparative immunogenicity studies in post marketing studies.

The immunogenicity of the similar biologic should be evaluated using appropriately designed studies with state-of-the-art methods, taking into consideration the potential impact on both safety and efficacy.

Rationale on the strategy for testing immunogenicity should be provided. Assay methods should be validated and should be able to characterize antibody content (concentration or titer) as well as the type of antibodies formed. Of most concern are those antibodies that have potentially serious impact on safety and efficacy, such as neutralizing antibodies and antibodies with cross reactivity. When neutralizing antibodies are detected in patients in clinical studies (either pre-approval clinical studies or post-approval clinical studies), the impact of the antibodies on the PK/PD parameters of the similar biologic should be analyzed, where the data is available. Furthermore an assessment of the impact of the neutralizing antibodies and cross-reacting antibodies (if applicable) on the overall safety and efficacy of the similar biologic should be conducted.



## 11. Application Forms

Various application forms for submitting request to regulatory agencies are as under:

Stage	Agency involved	Application	Approval
Manufacturing License for test, analysis and examination	State FDA / CDSCO	Form 30	Form 29
Preclinical studies permission	RCGM	Form C3	Form C4
Submission of Preclinical study report	RCGM	Form C5	Form C6
Clinical Trial	CDSCO	Form 44	Permission letter
Manufacturing and Marketing permission	CDSCO	Form 44	Form 45/46 (Finished product)
Form 46A (Bulk product)			
Manufacturing License	State FDA/ CDSCO	Form 27 D	Form 28 D
Registration and Import License	CDSCO	Form 40/ Form 8	Form 41/Form 10

*The applicant should comply with the established pharmacopoeia requirements while testing the excipients and as well as biological product for which monograph is available in Indian Pharmacopoeia.*

## 12. Archiving of Data

The applicant should archive all the data upto clinical evaluation for a period of at least five years after marketing approval by competent authority in India. The site of archiving should be indicated in the study protocols and reports. The material that needs to be archived should also be mentioned. These may include test substance, vehicle, plasma / serum, tissues, paraffin blocks, microscope slides, documents, electronic material etc and the individual durations (e.g. test material until date of expiry). The designated authority, which will be responsible for archiving and can be approached for inspection or retrieval if required, should be indicated in the study report by the applicant.



## 13. Glossary

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

- a. **Comparability exercise:** Comparison of a similar biologic with a reference biologic with the goal to establish similarity in safety, efficacy and quality.
- b. **Drug:** Drug includes (as defined in Drugs and Cosmetics Act, 1940).
  - (i) all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes;
  - (ii) such substances (other than food) intended to affect the structure or any function of human body or intended to be used for the destruction of (vermin) or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette;
  - (iii) all substances intended for use as components of a drug including empty gelatine capsules; and
  - (iv) such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette, after consultation with the Board.

### c. Drug substance

The active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product. It may be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain other components such as buffers.



**d. Drug product**

A pharmaceutical product type that contains a drug substance, generally in association with excipients.

**e. Equivalent**

Similar or virtually identical in the parameter of interest. Equivalent efficacy of two medicinal products means they have similar (no better and no worse) efficacy and any observed differences are of no clinical relevance.

**f. Genetic engineering**

The technique by which heritable material, which does not usually occur or will not occur naturally in the organism or cell concerned, generated outside the organism or the cell is inserted into said cell or organism. It shall also mean the formation of new combinations of genetic material by incorporation of a cell into a host cell, where they occur naturally (self cloning) as well as modification of an organism or in a cell by deletion and removal of parts of the heritable material (Rules, 1989).

**g. Head-to-head comparison**

Direct comparison of the properties of the similar biologic with the reference biologic in the same study.

**h. Immunogenicity**

The ability of a substance to trigger an immune response or reaction (e.g., development of specific antibodies, T cell response, allergic or anaphylactic reaction).

**i. Impurity**

Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or excipient including buffer components. It may be either process- or product-related.



**j. Manufacture**

“Manufacture” in relation to any drug includes any process or part of a process for producing, altering, ornamenting, finishing, packing, labelling, breaking up or otherwise treating or adopting any drug with a view to its sale or distribution but does not include the compounding or dispensing in the ordinary course of retail business; and “to manufacture” shall be construed accordingly.

**k. Non-inferior**

Not inferior to a comparator in the parameter studied. A non-inferiority clinical trial is one which has the primary objective of showing that the response to the investigational product is not clinically inferior to a comparator by a pre-specified margin.

**l. Innovator product**

A medicine which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e., the approved indication(s) for use were granted on the basis of full safety, efficacy and quality data.

**m. Pharmacovigilance**

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

**n. Reference Biologic**

A reference biologic is used as the comparator for head-to-head comparability studies with the similar biologic in order to show similarity in terms of safety, efficacy and quality. Only a product that was licensed on the basis of a full registration dossier can serve as reference biologic.

**o. Similar**

Absence of a relevant difference in the parameter of interest.



**p. Similar biologic**

A biological product/ drug produced by genetic engineering techniques and claimed to be “similar” in terms of safety, efficacy and quality to a reference biologic, which has been granted a marketing authorization in India by DCGI on the basis of a complete dossier, and with a history of safe use in India.

The products, where the reference biologic is not authorized in India shall be considered on a case by case basis if such products have been granted marketing approval in countries with well established regulatory systems such as US FDA, EMA etc. and have been in wider use for a minimum of four years.

Such products are also referred as biosimilars, similar biotherapeutic products, subsequent entry biologics or follow on biologics in various countries.

## 14. References

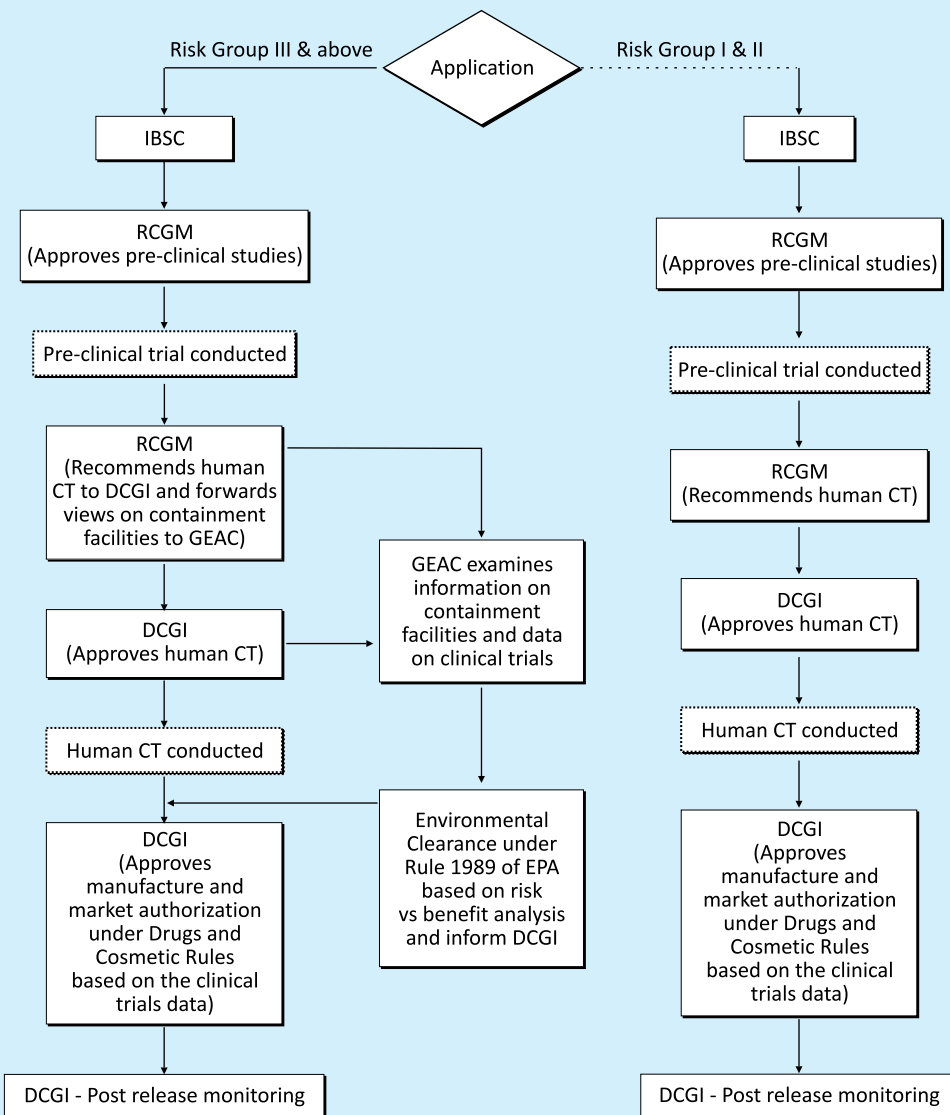
- i. EMEA guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues. London, 2006 (CHMP/BMWP/42832)
- ii. EMEA guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins London, 2007 (CHMP/BMWP/14327)
- iii. ICH guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals (S6), 1997
- iv. Guideline for Safety Study of Biological Products, (KFDA, 2010)
- v. World Health Organization (WHO) Guidelines on Evaluation of Similar Biotherapeutic Products (SBP), 2009





**PROTOCOL - I**

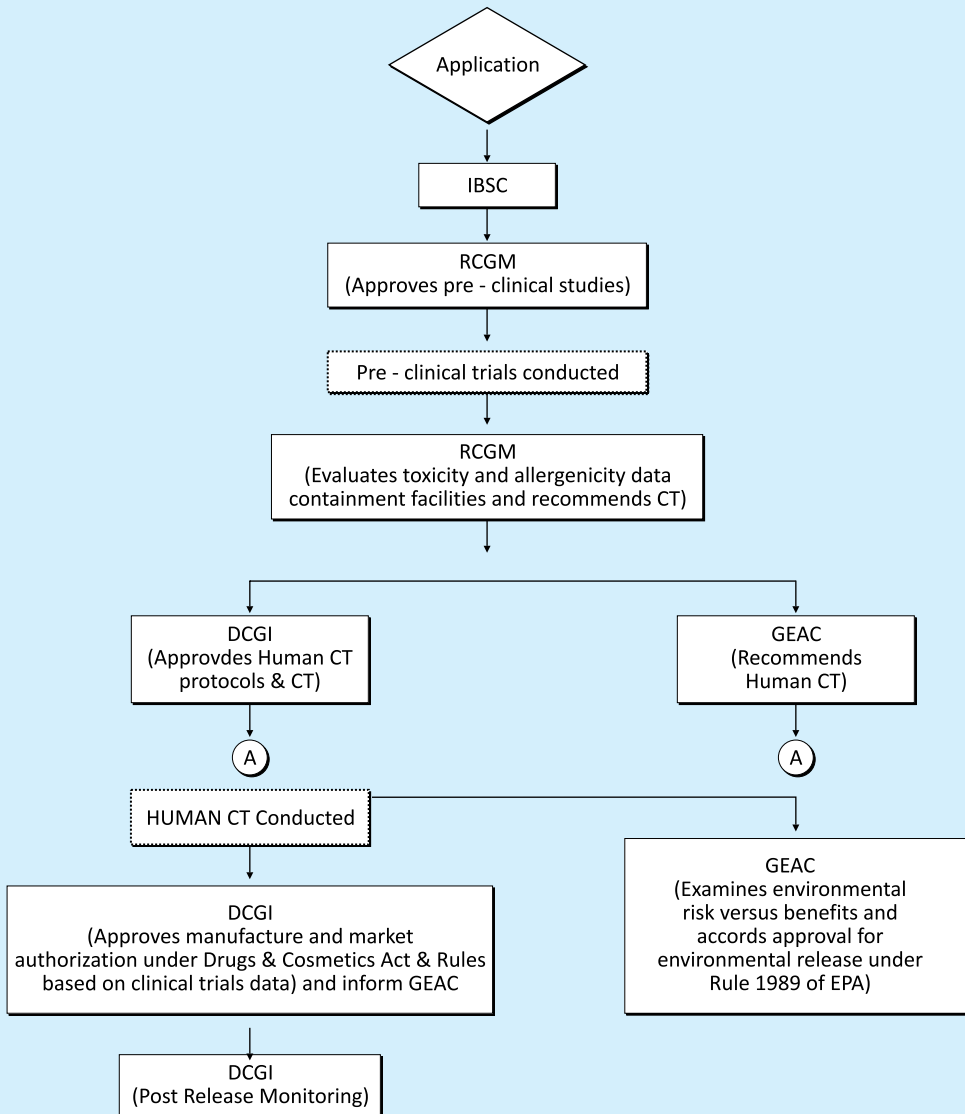
**Indigenous product development, manufacture and marketing of pharmaceutical products derived from LMOs but the end product is not an LMO**





## PROTOCOL - II

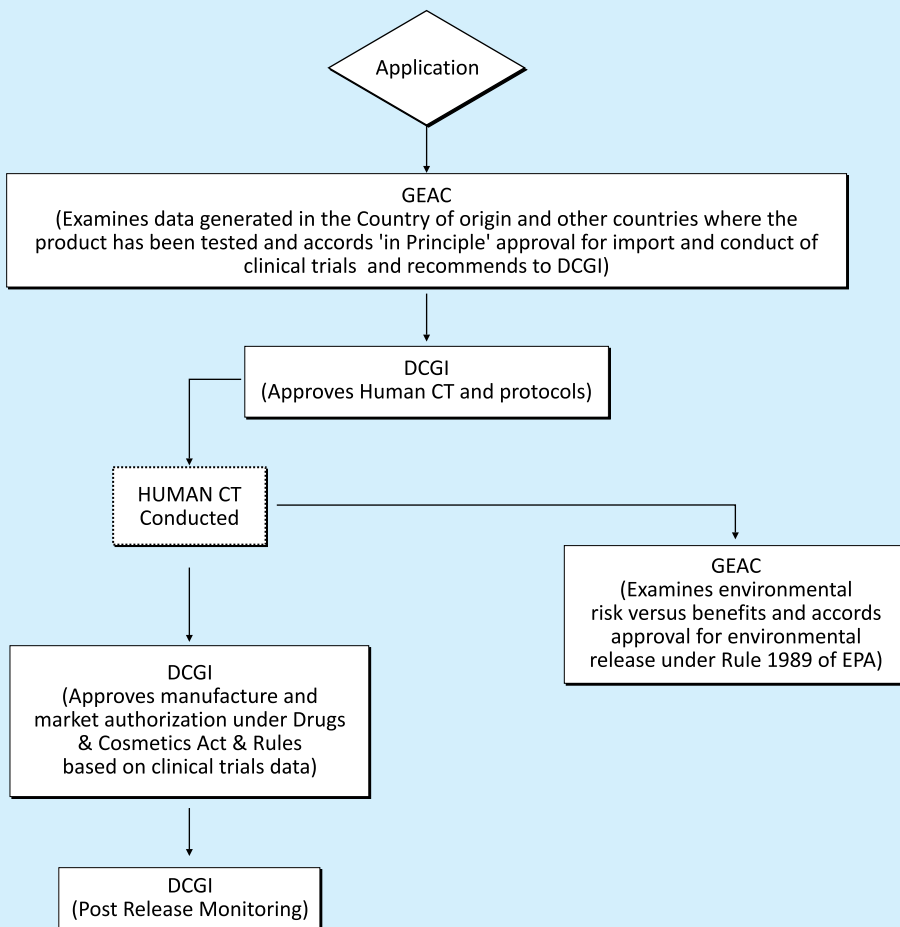
### Indigenous product development, manufacture and marketing of pharmaceutical products where the end product is not an LMO





### PROTOCOL - III

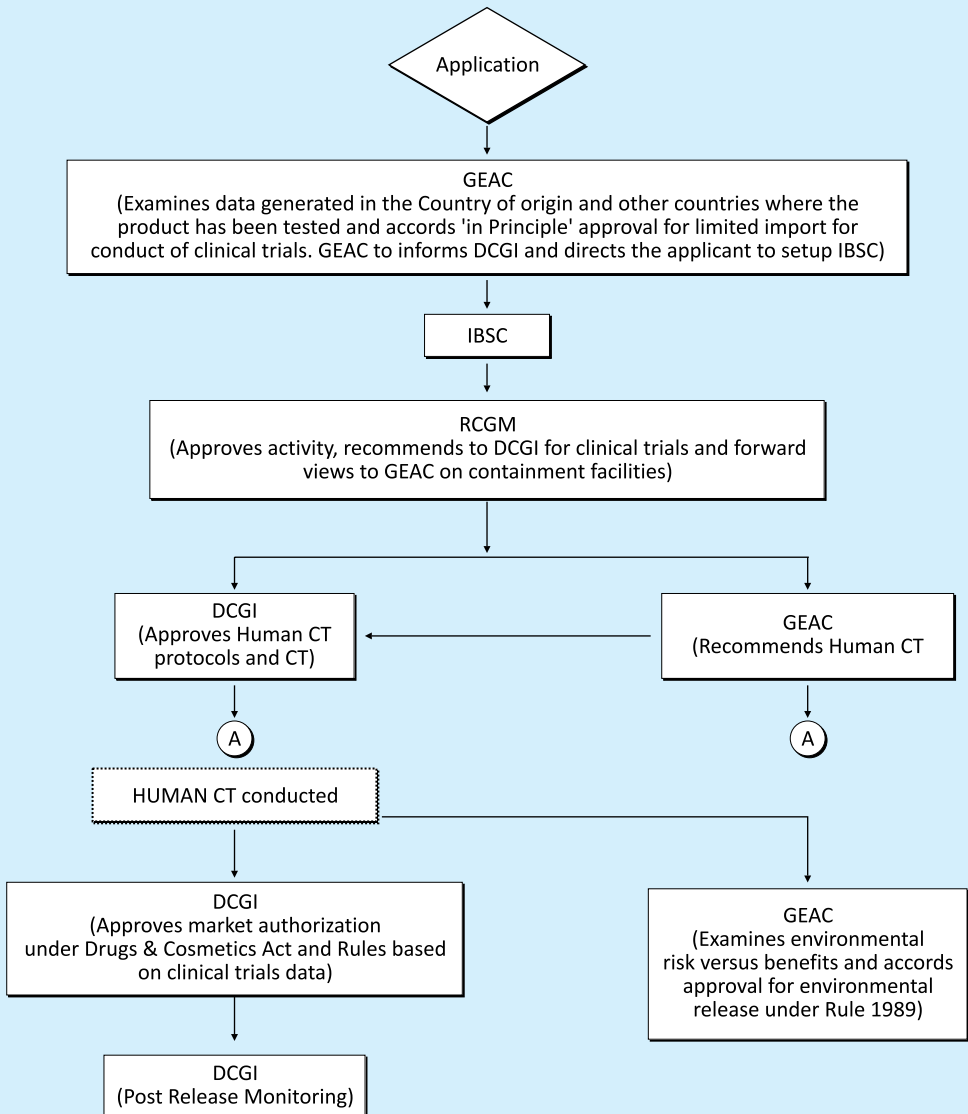
#### Import and marketing of pharma products in finished formulations where the end product is an LMO





### PROTOCOL - IV

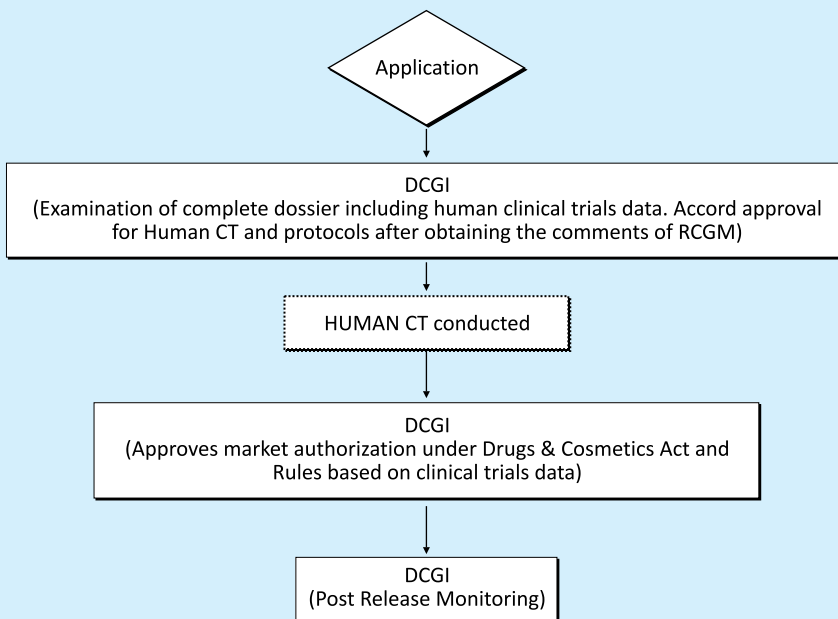
#### Import and marketing of pharma products in bulk for making finished formulation where the end product is an LMO





### PROTOCOL - V

**Import and marketing of pharma products derived from LMOs in bulk and / or finished formulations where end product is not an LMO**





Annexure 2

**2A. Physicochemical and biological characterization of nucleic acid based recombinant products**

Nucleic acid based recombinant products - Physicochemical	Nucleic acid based recombinant products - Biological
<p>Sequence (To prove if the sequence same as reference biologic).</p> <p>Restriction map for &gt;1000 bp (To check if secondary structure is same as reference biologic).</p> <p>Purity on HPLC (To check if any impurities are there).</p> <p>Gel electrophoresis (agarose/ acylamide/ urea page) (To check quality of sample).</p> <p>Southern/ Northern blot (Confirmation with reference biologic).</p>	<p><b>Vector for expression of recombinant protein</b></p> <ul style="list-style-type: none"> <li>• Expression pattern in actual target host cell (To compare efficiency of expression of similar biologic with reference biologic in the target cell) .</li> <li>• Expression pattern in closest animal species upon administration (along with vehicle as negative control) (To compare efficiency of expression of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell).</li> <li>• Kinetics of expression during the proposed therapeutic period of protection (To compare half life of the similar biologic with reference biologic).</li> <li>• Efficacy in appropriate disease/ infection model <i>in vitro</i> and/or <i>in vivo</i> (To compare therapeutic activity of the similar biologic with reference biologic).</li> </ul>



<p><b>Nucleic acid based recombinant products - Physicochemical</b></p>	<p><b>Nucleic acid based recombinant products - Physicochemical</b></p>
<p>Absorption spectrum from 190 to 800 nm (To check similarity to reference biologic).</p> <p>CD spectrum from 190 to 800 nm (To check secondary structural changes if any due to binding of impurities).</p> <p>Hybridization to the target sequence. (To confirm with reference biologic).</p> <p>T<sub>m</sub> profile (To check if any impurities are present).</p> <p>Estimation of RNA and DNA using nanodrop or reagent. (To check concentration and impurity, if any)</p>	<ul style="list-style-type: none"> <li>• Absence of interference of marker enzyme/antibiotic, if any (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).</li> </ul> <p><b>Vector for expression of siRNA/ snRNA etc.</b></p> <ul style="list-style-type: none"> <li>• Expression pattern in actual target host cell (To compare efficiency of expression of similar biologic with reference biologic in the target cell)</li> <li>• Expression pattern in closest animal species upon administration (along with vehicle as negative control) (To compare efficiency of expression of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell).</li> <li>• Kinetics of expression during the proposed therapeutic period of protection (To compare half life of the similar biologic with reference biologic)</li> <li>• Efficacy in appropriate disease/ infection model <i>in vitro</i> and/or <i>in vivo</i> (To compare therapeutic activity of the similar biologic with reference biologic).</li> <li>• Absence of interference of marker enzyme/antibiotic if any (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).</li> </ul>



## 2B. Physicochemical and biological characterization of therapeutic proteins

Therapeutic Proteins – Physicochemical	Therapeutic Proteins – Biological
<ul style="list-style-type: none"> <li>• Appearance, particulates, pH, osmolality, particle size (if applicable) (To check homogeneity).</li> <li>• MW, Sequence and amino acid composition (To check purity).</li> <li>• N terminal sequence (atleast 20 amino acid) (To check amino acid sequence and structure).</li> <li>• Glycosylation, Phosphorylation, Acetylation, and Myristoylation, if any (To check if active/ inactive form).</li> <li>• PEGylation, esterification, if applicable (To check if modification is appropriate).</li> <li>• Tryptic map (1D and 2D) (To check if secondary structure is conserved).</li> <li>• Sulfhydryl groups(s) and disulphide bridges (To check if secondary structure is conserved).</li> </ul>	<ul style="list-style-type: none"> <li>• Biological activity in actual target host cell (To compare activity of protein in similar biologic with reference biologic in the target cell).</li> <li>• Biological activity in closest animal species (if available) upon administration (along with vehicle as negative control) (To compare activity of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell).</li> <li>• Kinetics of biological activity during the proposed therapeutic period of protection (To compare half life of the similar biologic with reference biologic).</li> <li>• Efficacy in appropriate disease/ infection model <i>in vitro</i> and/or <i>in vivo</i> (If available) (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic)</li> </ul>





<p><b>Therapeutic Proteins – Physicochemical</b></p>	
<ul style="list-style-type: none"> <li>• Size and Purity on HPLC (RP, SEC, IEX )/ MALDI (To check if it is homogeneous and no impurities are present ).</li> <li>• Isoform pattern, if any (To check if secondary structure is conserved).</li> <li>• Gel electrophoresis (IEF, SDS PAGE and Native PAGE), Western blot (To qualitative check purity/ nativity).</li> <li>• Absorption spectrum from 190 to 800 nm (molar absorptivity) (To check purity).</li> <li>• CD spectrum from 190 to 800 nm (To check if secondary structure is conserved)</li> <li>• Fluorescence spectrum (To check if any impurities such as quenchers are present).</li> <li>• FTIR spectrum, if applicable (To check if any prosthetic group is present).</li> <li>• NMR spectrum, if applicable (To check if any prosthetic group is present).</li> <li>• Affinity to the target receptor (To check if required affinity to receptor is conserved).</li> <li>• Helix to Coil Transition profile (To verify if the preparation is stable and impurities or isofoms are affecting the stability).</li> </ul>	



## 2C. Physicochemical and biological characterization of therapeutic enzymes

Therapeutic Enzymes – Physicochemical	Therapeutic Enzymes – Biological
<ul style="list-style-type: none"> <li>• Appearance, particulates, pH, osmolality, particle size (if applicable) (To check homogeneity).</li> <li>• Sequence and amino acid composition (To check purity).</li> <li>• Glycosylation, phosphorylation, acetylation and myristoylation, if any (To check if active/ inactive form).</li> <li>• Pegylation, estrification, if applicable (To check if modification is appropriate).</li> <li>• Tryptic peptide map (1D and 2D) (To check if secondary structure is conserved).</li> <li>• Size and purity on HPLC (RP, SEC, IEX)/ MALDI (To check if secondary structure is conserved).</li> <li>• Gel electrophoresis (IEF, SDS PAGE and Native PAGE), Western blot (To qualitatively check purity/ nativity).</li> <li>• Enzyme activity in gel assay in the presence of chromogenic substrate (To check activity).</li> </ul>	<ul style="list-style-type: none"> <li>• Biological activity in actual target host cell (To compare activity of enzyme in similar biologic with reference biologic in the target cell).</li> <li>• Biological activity in closest animal species upon administration (along with vehicle as negative control) (To compare activity of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell).</li> <li>• Kinetics of biological activity during the proposed therapeutic period of protection (To compare half life of the similar biologic with reference biologic).</li> <li>• Efficacy in appropriate disease/ infection model <i>in vitro</i> and/or <i>in vivo</i> (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).</li> </ul>



<b>Therapeutic Enzymes – Physicochemical</b>	
<ul style="list-style-type: none"><li>• Absorption spectrum from 190 to 800 nm (To check purity)</li><li>• CD spectrum from 190 to 800 nm (To check if secondary structure is conserved).</li><li>• Helix to Coil Transition profile (To verify if the preparation is stable and impurities or isofoms are affecting the stability).</li><li>• Fluorescence spectrum (To check if any impurities such as quenchers are present).</li><li>• Km with natural substrate (To check homogeneity of biosim interaction with active site same as reference biologic with reference to known substrates).</li><li>• Ki with known inhibitors (1/2) (To check comparability of compititive biosim interaction with active site same as reference biologic with reference to known inhibitors).</li></ul>	



## 2D. Physicochemical and biological characterization of antibodies

Antibodies – Physicochemical	Antibodies – Biological
<ul style="list-style-type: none"> <li>• Sequence and amino acid composition (To check purity).</li> <li>• Tryptic map (1D and 2D) (To check if secondary structure is conserved).</li> <li>• Light and heavy chain separation (To check antigenic recognition motif).</li> <li>• IgG type (To check specificity of IgG in localization of specific tissues/ plasma).</li> <li>• Purity on HPLC (RP, SEC, IEX)/ MALDI (To check if preparation is free of any impurities).</li> <li>• Gel electrophoresis (IEF, SDS PAGE and Native PAGE), Western blot (To check qualitative purity difference).</li> <li>• Absorption spectrum from 190 to 800 nm (To check purity).</li> </ul>	<ul style="list-style-type: none"> <li>• Neutralizing activity in actual target host cell (at least one highly prevalent Indian variant/isolate should be used) (To compare activity of similar biologic with reference biologic in the target cell)</li> <li>• Neutralizing activity in closest animal species (if feasible) upon administration (along with vehicle as negative control) (at least one highly prevalent Indian variant/isolate should be used) (To compare activity of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector/ antibody location and promoter activity in target cell).</li> <li>• Kinetics of Neutralizing activity during the proposed therapeutic period of protection (at least one highly prevalent Indian variant/ isolate should be used) (To compare half life of the similar biologic with reference biologic)</li> <li>• Efficacy in appropriate disease/ infection model <i>in vitro</i> and/or <i>in vivo</i> (If available) (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic)</li> </ul>



---

## Antibodies - Physicochemical

---

- |   |  |
|---|--|
| <ul style="list-style-type: none"><li>• CD spectrum from 190 to 800 nm (To check if secondary structure is conserved).</li><li>• Helix to Coil Transition profiles (To verify if the preparation is stable and impurities or isoforms are affecting the stability).</li><li>• Epitopic mapping of the antibody binding to specific and non-specific epitopes with antigenic variant isolated from an Indian isolates (To check specificity profile of similar biologic with reference biologic in epitope recognition, particularly in recognition of Indian variant of a host cell protein or infectious agent coded protein).</li><li>• Anti-body dilution factors in neutralization (To check symbol with reference biologic in the neutralization strength of the antibody preparation)</li></ul> |  |
|---|--|







Government of India

**Department of Biotechnology**

Ministry of Science & Technology

**Central Drugs Standard Control Organization**

Ministry of Health & Family Welfare