GUIDELINES ON SIMILAR BIOLOGICS:

Regulatory Requirements for Marketing Authorization in India, 2016

Department of Biotechnology
Ministry of Science & Technology,
Government of India

Central Drugs Standard Control Organization
Ministry of Health & Family Welfare
Government of India

Effective: 15th August 2016

Content

सत्यमेव जयते
के. विजयराघवन
K. VijayRaghavan

सचिव
भारत सरकार
विज्ञान और प्रौद्योगिकी मंत्रालय
बायोटेक्नोलॉजी विभाग
ब्लाक-2, 7 वां तल, सी. जी. ओ. कम्पलेक्स
लोदी रोड़, 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

MESSAGE

The world market for biosimilars is estimated to reach $6.22 Billion by 2020 from $2.29 Billion in 2015. The growth is driven by factors such as growing pressure for affordable product development, advances in biochemical and molecular biology instrumentation, growing demand for biosimilar drugs particularly in developing and emerging countries like India to address ever growing chronic diseases, increasing number of off-patented therapeutics and monoclonals along with organised system for clinical trials.

India has become an important destination for world class R&D and expertise in Biopharma. In biosimilars, it has emerged as leading player following the publishing of similar biologics guidelines in 2012. The Indian capacity in chemical and molecular characterisation in industry and public sector institutions is robust enough to compete further. Therefore, a revision in the guidelines in meeting the ever changing global standards for further growth has become essential.

It is noteworthy to appreciate the synergy and efforts of two ministries involved in the regulation of Similar Biologics in India in preparation of "Guidelines on Similar Biologics: Regulatory requirements for market authorization in India 2016". Although case- by -case examination is important, these guidelines provide required clarity and essentiality of data requirements for proving the similarity, physico-chemical characterization, preclinical studies and clinical trials.

I congratulate Dr. G. N. Singh, Drugs Controller General of India and his colleagues from Biological Division CDSCO 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. S. R. Rao, Member Secretary, RCGM and Adviser, DBT, Govt. of India for preparation of these guidelines.

I also wish to place on record the valuable inputs of joint committee set up by DBT and DCGI for the purpose of preparation of these guidelines. We thank all stakeholders including representatives of industry associations, academic and RCGM experts for their valuable inputs. Although these guidelines are stringent and contemporary covering latest standards of safety and efficacy on similar biologics, I am positive that these guidelines would facilitate Indian and global industry to become competitive internationally.

K. VijayRaghava

(K.VijayRaghavan)

Tele : 24362950/24362881 Fax : 011-24360747 E-mail : vijay.dbt@nic.in

Dr. G. N. Singh
Drug Controller General (India)
Tel. : (011) 23236965
Fax : (011) 23236973

स्वास्थ्य सेवा महानिदेशालय
सी. डी. एस. सी. ओ. (एच. क्यू.)
एफ. डी. ए. भवन, कोटला रोड़
नई दिल्ली–110002
DIRECTORATE GENERAL OF HEALTH SERVICES
CENTRAL DRUG STANDARD CONTROL ORGANISATION
CDSCO (H.Q.)
F.D.A. BHAVAN, KOTLA ROAD,
NEW DELHI-110002

3rd August, 2016.

FOREWORD

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

The revision of the 2012 DBT-CDSCO guidance document for the development and approval of Similar Biologics utilizes an approach that will rely on strong scientific in vitro and in vivo drug evaluation and comparability. The assessment process aims to establish similarity of Biologicals based on a founding principle consisting of five essential elements that systematically and progressively reduces the risk of uncertainty associated with safety and efficacy of Similar Biologic drugs.

We are pleased to note that CDSCO Biological Division has examined and reviewed the 2012 guidelines in collaboration with the Department of Biotechnology (DBT) to revise the same to make it at par with latest standards providing more clarity. This will ensure robust and clear regulatory pathway for approval of Similar Biologics. Regulatory Requirements for Marketing Authorization in India, as these products are regulated jointly by both the agencies. I express my gratitude to Prof. K. Vijay Raghavan, Secretary, DBT 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 similar biologics. We sincerely thank the members of both the committees for their valuable inputs. We are pleased that the guidelines have been revised through a consultative process with the involvement of various stakeholders, ABLE, industry associations, premier scientific Institutions, Laboratories as well as series of consultations and public review process.

We are of the firm opinion that this revised guidelines 2016 will go a long way in providing guidance and documentary support to both applicants and regulators for the development, approval and post marketing evaluation of safety and efficacy of Similar Biologics in the country and provide access to affordable bio-therapeutics to the patients across the globe.

(Dr. G.N. Singh)

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.

A Similar Biologic product is that which is similar in terms of quality, safety and efficacy to an approved Reference Biological product based on comparability.

These guidelines address the regulatory pathway regarding manufacturing process and safety, efficacy 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.

These guidelines are for the guidance of all stakeholders and are not meant to substitute or rephrase the Rules made under Drugs and Cosmetics Act, 1940 or any other relevant Acts and are subject to being in conformity with the Drugs and Cosmetics Act and Rules as may be amended from time to time**.**

2. Background & Objectives

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

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 the 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 market 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:
    - Submission of Clinical Trial Application for Evaluating Safety and Efficacy
    - Requirement for permission of New Drug Approval
    - Post approval changes in Biological products: Quality, Safety and Efficacy Documents
    - Preparation of Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
- Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011.
- Guidelines on Similar Biologics: Regulatory Requirements for Marketing authorization in India 2012.

4. Competent Authorities

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

Institutional BioSafety Committee (IBSC)

IBSC is required to be constituted by any person including research institutions handling hazardous microorganisms and/ or genetically engineered organisms. IBSC is responsible for ensuring biosafety on-site, along with initial review of applications to be recommended to RCGM. IBSC is also assigned with the responsibility to review and authorize firm for exchange of aforesaid organisms for the purpose of research.

Review Committee on Genetic Manipulation (RCGM)[1]

RCGM is functioning from the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India. In the context of Similar Biologics, RCGM is responsible for authorizing the conduct of research and development, exchange of genetically engineered cell banks for the purpose of research and development and review of data up to preclinical evaluation.

Genetic Engineering Appraisal Committee (GEAC)[1]

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

([1] RCGM and GEAC are statutory committees set up as per provisions of Rules, 1989)

Central Drugs Standard Control Organization (CDSCO)[2]

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 clinical trials as well as new drugs. In the context of Similar Biologics, CDSCO is responsible for clinical trial approval (also grants permission for import of drugs for clinical trial and export of clinical samples for biochemical and immunological analysis) and permission for manufacturing and marketing.

Zonal offices of CDSCO are responsible for authorizing import of drugs for examination, test and analysis for research and development.

([2] 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 Biologics can only be developed against the 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 approved / licensed and marketed in an ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) country.

Any product can be considered as a 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 Similar Biologic is demonstrated in quality to a Reference Biologic.

These guidelines are applicable for Similar Biologics to be developed in India or imported into the country for marketing authorization. Detailed regulatory pathways for indigenously developed and imported products[3] are given in Annexure I.

[3] Adopted from Report of the Task Force on Recombinant Pharma, 2005, chaired by Dr R.A. Mashelkar, DG, CSIR)

6. Principles for Development of Similar Biologics

Similar Biologics are developed through a 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 preclinical and clinical evaluation 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 in accordance with international guidelines (WHO 2013).

Generally, abbreviated data requirements are only possible for preclinical and /or clinical components of the development program but not for the quality components by demonstration of comparability of product (*Similarity* established to the Reference Biologic).

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 Similar Biologic also qualifies for all the indications only if it is justified and if meets the conditions set forth in the section “Extrapolation of Efficacy and Safety Data to other Indications”. Justification for extrapolation of indication shall be based on comparability in quality, preclinical and clinical studies, 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 is an innovator's product approved after evaluation of complete dossier is critical for the development of Similar Biologic.

The Reference Biologic has to be used in all the comparability exercises 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 / approved in India or ICH countries and should be the innovator's 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 in any ICH countries. The Reference Biologic product can be imported for developing the Similar Biologic for quality, pre-clinical and clinical comparability.
- 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 drug substance (active ingredient) of the reference biologic and that of Similar Biologic must 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 Similar Biologics manufacturer should develop the manufacturing process to yield a comparable quality product in terms of identity, purity and potency to the Reference Biologic. The manufacturing process for Similar Biologics should be validated and demonstrated to 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 host cell line for manufacturing Similar Biologics. 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 quality attributes (QAs) 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 ICH viz. Q5A[4], Q5B[5] and Q5D[6] should be referred for guidance.

4 ICHQ5A(R1): Viral Safety Evaluation of Biotechnology products derived from cell lines of Human or Animal Origin

5 ICHQ5B: Quality of Biotechnological Products: Analysis of the expression construct in cells used for production of R-DNA derived protein products

6 ICH Q5D: Derivation and characterization of cell substrates used for production of Biotechnological/Biological products)

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 detail of post-translational modifications (glycosylation, oxidation, deamidation, phosphorylation etc.), if any should be explained.

6.2.2 Upstream Process Development

- Upstream process should be described in detail including media components used for cell growth.
- At least three batches of reproducible fermentation data at pilot scale (batch size adequate to give enough purified product to generate preclinical data).
- Upstream process should be well controlled and monitored.
- Details of upstream process kinetics data from consistency batches 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 upstream batches.
- Demonstrate that the overall productivity is reproducible and scalable.

6.2.3 Downstream Process Development

- Detail description of the methods followed for the cell harvesting and extraction of the protein.
- 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 three consecutive batches of purification from three independent batches of cell culture/ fermentation.
- Describe post translational variation, if any.
- Details of removal of impurities like product related variants & impurities, and host cell & process related impurities considered to pose a risk of Immunogenicity (EMEA 1997).
- Virus clearance validation studies.

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

- Detailed description of the drug substance and drug product processes
- Critical and key 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[7], Q5C[8], Q6B[9]), as appropriate.

The characterization studies should include samples of the applicant's r-DNA derived 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 three 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 r-DNA derived products are given in Annexure II. It may be noted that this Annexure II is suggestive but not limited to the specified method and the requirements may vary on case by case.

([7] ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology
[8] ICH Q5C: Stability testing of Biotechnological/Biological Products
[9] ICHQ6B: Specifications: test Procedures and Acceptance criteria for Biotechnological/Biological Products)

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 drug substance and 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. Biological assays should be validated 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 Similar 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 a 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 (for drug substance and drug product) are established around quality attributes (QAs) with the intent of ensuring consistency in product quality and comparability to Reference Biologic according to relevant guideline (ICH Q6B). Methods used for setting specifications may or may not be the 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, which must be in line with international norms.

6.3.4 Stability

The shelf-life and storage condition of drug substance and drug product should be assigned based on real-time stability studies. 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 Q1 A(R2), ICH Q5C, WHO TRS 822). Side-by side accelerated and stressed stability 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 active drug product level. It is required to assure that the molecular structure of active drug substance present in the Similar Biologic is comparable to active drug substance present in Reference Biologic. However, in cases where the required analyses of quality attributes of the active substance of the Reference Biologic can be made at the finished product stage, testing of the isolated active ingredient may not be needed. 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 may be there. However, 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 be governed by Quality Attributes (QAs), which employ state-of-the-art high resolution analytical techniques and methods that are sensitive enough to detect the possibilities of changes to the product. From the perspective of establishing Similarity, Quality Attributes of a Similar Biologic may be considered in two categories; Critical Quality Attributes (CQA) and Key Quality Attributes (KQA):

1) Critical Quality Attributes (CQA) are those Quality Attributes which have direct impact on the clinical safety or efficacy. All attributes that directly impact the known mechanism(s) of action of the molecule fall in this category. CQAs must be controlled within limits that need to be established based on the Reference Biologic.

2) Key Quality Attributes (KQA) are those Quality Attributes which are not known to impact clinical safety and efficacy but are considered relevant from a product and process consistency perspective. Attributes that do not impact the known mechanism(s) of action of the molecule fall in this category. KQAs must necessarily be controlled within acceptable limits; however it may acceptable to have slight differences in comparison to the Reference Biologic.

The list of routine analytical tests to be included for a comprehensive quality comparability exercise of Critical and Key Quality Attributes is given in Annexure-II.

This is intended as guidance, and proposes a framework to establish analytical similarity that incorporates molecular structure, function and heterogeneity. It may be noted that is only indicative and a specific determination will need to be made for each biologic molecule.

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 Biologics

- 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, cartridge, vial

The application to RCGM should be accompanied by approval of Institutional BioSafety Committee (IBSC) of the developer (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, dose, 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 Similar Biologic and Reference Biologic should be established by *in vitro* cell based bioassay (e.g. cell proliferation assays /cytotoxicity / neutralizing / 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, as applicable.

7.2.2 Toxicological Studies

In case of in vivo toxicity studies, at least one repeat dose toxicity study in a pharmacologically relevant species is required to be conducted with an intended route of administration.

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 pharmacologically relevant animal species is not available and has been appropriately justified, toxicity studies need to be undertaken either in rodent or non-rodent species as per requirements of Schedule Y with due permission from RCGM.

Regarding route of administration either in pharmacologically relevant or pharmacologically non-relevant animal model the route of administration would include only the intended route as per schedule Y.

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.

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 repeated-dose toxicity studies. In the toxicity study the Similar Biologic should be compared with Reference Biologic at least at 1X of human equivalent dose (HED). Any difference in the levels of doses should be justified and 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. This evaluation, if feasible may be performed as a part of above mentioned repeated-dose toxicity study.

Accordingly, the study groups of animals in repeated-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 repeated-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 centre
- 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 standalone 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 repeated-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.

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 repeated-dose toxicological studies.

Based on the successful evaluation of preclinical study reports including demonstration of consistency of the process and product, product characterization, product specifications and comparison of similar biologics to reference Biologic, RCGM will recommend the DCG(I) to allow the sponsor to conduct appropriate phase of clinical trial as per the CDSCO requirements. The applicant may submit parallel application to RCGM and office of DCG (I) seeking approval to conduct clinical trial. However, office of DCG (I) shall complete the scrutiny of application and issue permission, only after RCGM recommendation was received.

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 indicate that there are no differences in Critical Quality Attributes (CQAs), and that all Key Quality Attributes (KQAs) are well controlled in order to allow the initiation of clinical evaluation.

8.1 Pharmacokinetic (PK) Studies

The PK data should support the subsequent Phase III clinical development given that the purported Similar Biologic would be established to be similar as the Reference Biologic product. After completion of extensive characterization comparability on quality attributes, a PK study of the Similar Biologic in comparison with the Reference Biologic product may be performed in an appropriate number of:

a. Normal Healthy Volunteers (NHV) and / or

b. Patients

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 include:

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

In sequential development approach, the Normal Healthy Volunteers (NHV) study is performed before the Phase III safety and efficacy study.

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 study is more appropriate for Similar 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 required 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 Similar Biologic and Reference Biologic. If a PD marker is available in healthy volunteers, PD in healthy volunteers can be done, unless considered unethical due to expected adverse events and toxicity e.g. oncology drugs.

Comparative PD studies are recommended when the PD properties of the Reference Biologic are well characterized with at least one PD marker validated for a clinical outcome 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. If PD marker is not available and the PK can be done in patients then the PK study can be combined with phase III clinical study. The PD study can also be a part of Phase III clinical trials wherever applicable.

8.3 Confirmatory Safety and Efficacy Study

The establishment of in-vitro, pre-clinical and PK/PD Similarity as described in earlier section is important as robust, high quality processes, a comprehensive quality comparison and comparative preclinical and PK/PD studies help in demonstrating the Similarity of the Similar Biologics in these settings.

In order to eliminate any residual risk, a comparative phase III clinical trial may also be required to establish the comparability with respect to clinical safety and efficacy. Only in exceptional cases i.e. if there are no residual uncertainties left after comparing Similar Biologic and Reference Biologic at the analytical, non-clinical and PK/PD level, an additional comparative safety and efficacy trial is not needed.

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 study should be conducted in a sensitive and homogenous patient population with appropriate sensitive primary end points as per requirement of a Phase III clinical trial. The design of the studies and the clinical comparability of the primary efficacy endpoints are important and should be given careful consideration and should be scientifically justified on clinical grounds. Equivalence, non-inferiority or comparability Phase III clinical trials may be conducted based on comparability established during physicochemical characterization, preclinical and PK/PD studies, after approval of design and protocol by CDSCO. However, the comparability Phase III clinical trials intended for seeking marketing approval of Similar Biologics falling under the category of new drugs as per Drugs and Cosmetics Rules, 1945 shall be conducted in accordance with the Indian Good Clinical Practice (GCP) guidelines, generally in not less than hundred evaluable patients in test arm to evaluate the safety, efficacy and comparability. Based on the results of such Clinical trials, the marketing approval may be considered if safety, efficacy and comparability are established. Further, Phase IV clinical trials may be required to be conducted, generally in more than two hundred patients in continuation of comparability clinical trials.

The nature, severity and frequency of adverse events should be compared between the Similar Biologic and Reference Biologic and should also be based on safety data and efforts 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 as per the protocol.

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 preclinical evaluations conducted and /or the PK/PD studies have not demonstrated comparability.

8.3.1 Waiver of safety and efficacy study

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 of PD markers validated for clinical outcome and has preferentially been done in an *in-patient* setting with safety measurement (including meaningful immunogenicity assessment) for adequate period justified by the applicant and efficacy/PD 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 especially for large molecular weight biologics like Monoclonal antibodies. In case, the safety and efficacy study is waived all the indications approved for reference product may be granted based on comparable quality, non-clinical as well as convincing PK/PD data.

Wherever the phase III trial is waived, the immunogenicity should have been gathered in the PK/PD study and will also need to be generated during post- approval Phase IV study.

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

For a product which is found Similar in pre-clinical, in-vitro characterization having established PK methods and a PD marker that is surrogate of efficacy, the residual risk is significantly reduced in the Phase I study if equivalence is demonstrated for both PK and PD. In such cases clinical trials may be waived.

8.4 Safety and Immunogenicity Data

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

From a safety and Immunogenicity perspective, if the firm conducts pre-approval studies that included more than 100 patients on the proposed Similar Biologic drug, the number of patients in phase IV study can be modified accordingly so that the safety data (from both Phase III and IV) is derived from a minimum of 300 patients treated with the Similar Biologics.

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.
- However, new indications not mentioned by innovator will needs to 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

It is important to establish a formal Risk Management Plan to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the Similar Biologic since authorization is based on a reduced preclinical and clinical data package. 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 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 as per Schedule Y.

10.3 Post Marketing Studies (Phase IV Study)

Finally, in order to further reduce the residual risk of the Similar Biologics, additional safety data may need to be collected after market approval through a pre-defined single arm study of generally, more than 200 evaluable patients and compared to historical data of the Reference Biologic. The study should be completed preferably within 2 years of the marketing permission / manufacturing license unless otherwise justified.

The primary aim of the post marketing phase IV study is safety and hence following parameters should be considered for the post marketing phase IV study protocol:

- Primary endpoint: Safety
- Secondary endpoint: Efficacy and Immunogenicity

The phase IV protocol should be submitted along with marketing authorization application for approval.

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 regard to the therapeutic consequences of unwanted immunogenicity.

It is not mandatory to carry out additional non-comparative immunogenicity studies in post marketing studies, if immunogenicity is evaluated in clinical studies. The immunogenicity of the Similar Biologics 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 in pre-approval clinical studies or post-approval clinical studies), the impact of the antibodies on the PK/PD parameters of the Similar Biologics 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 Biologics should be conducted.

Exceptions:

In the case of Similar Biologics that can be evaluated for rare diseases, the clinical trial population size can be reduced as per the rarity and severity of the disease as well as the limitation of access to therapeutic options.

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 (After CDSCO NOC)	State FDA	Form 30	Form 29
Import license for test, analysis and examination	CDSCO -zonal	Form 12	Form 11
Cell bank import / export / transfer / received	RCGM	Form B1/B3/ B5/B7	
Carrying out Research and Development	RCGM	Form C1	
Preclinical studies permission	RCGM	Form C3a	
Submission of Preclinical study report	RCGM	Form C5a	
Clinical Trial	CDSCO	Form 44	CT Permission Letter
Import /Manufacturing and marketing permission	CDSCO	Form 44 (separate for DS and DP)	Form 45A/ 46A (bulk product) and Form 5/46 (Finished product)
Manufacturing License	State FDA/ CDSCO (counter signature)	Form 27 D	Form 28 D
Registration certificate for import	CDSCO	Form 40 (with schedule DI and DII) / Form 44	Form 41 / Form 45
Marketing permission / License for imported product	CDSCO	Form 8 & 9	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. Refer Drugs and Cosmetic Act, 1940 and Rules 1945 for the application format.

12. Archiving of Data / Retention of Samples:

The manufacturer should establish the SOP for data archival as well as sample retention. The applicant should archive all the data (quality, preclinical and clinical documentation) for a period of at least five years after marketing approval by competent authority in India. Important samples such as test substance, vehicle, plasma / serum, tissues, paraffin blocks, microscope slides, electronic material, etc., should be retained till the period 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 data archival and sample retention SOP.

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

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

d. Drug product

The dosage form in the final immediate packaging intended for marketing. A pharmaceutical product type that contains a drug substance, generally in association with excipients.

e. 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).

f. 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).

g. 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.

h. 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.

i. Pharmacovigilance

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

j. Reference Biologic

A Reference Biologic is used as the comparator for comparability studies with the Similar Biologic in order to show Similarity in terms of safety, efficacy and quality. The Reference Biologic should be licensed / approved in India or ICH countries and should be the innovator's 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.

k. Similar

Absence of a relevant difference in the parameter of interest.

l. Similar Biologic

A Similar Biologic product is that which is similar in terms of quality, safety and efficacy to an approved Reference Biological product based on comparability.

14. References

I. EMA guideline on Similar Biological medicinal products, London, 2014 (CHMP/437/04 Rev 1)

II. EMA Guideline on Similar Biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, London, 2014 (EMEA/CHMP/BMWP/42832/2005 Rev1)

III. EMA guideline on Similar Biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues. London, 2006 (CHMP/BMWP/42832)

IV. EMA guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins London, 2007 (CHMP/BMWP/14327)

V. ICH guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals (S6), 1997 and addendum, 2011

VI. Guideline for Safety Study of Biological Products, (KFDA, 2010)

VII. World Health Organization (WHO) Guidelines on Evaluation of Similar Biotherapeutic Products (SBP), 2009

VIII. World Health Organization (WHO), Guidelines on the quality, safety and efficacy of bio-therapeutic protein products prepared by recombinant DNA technology, 2013

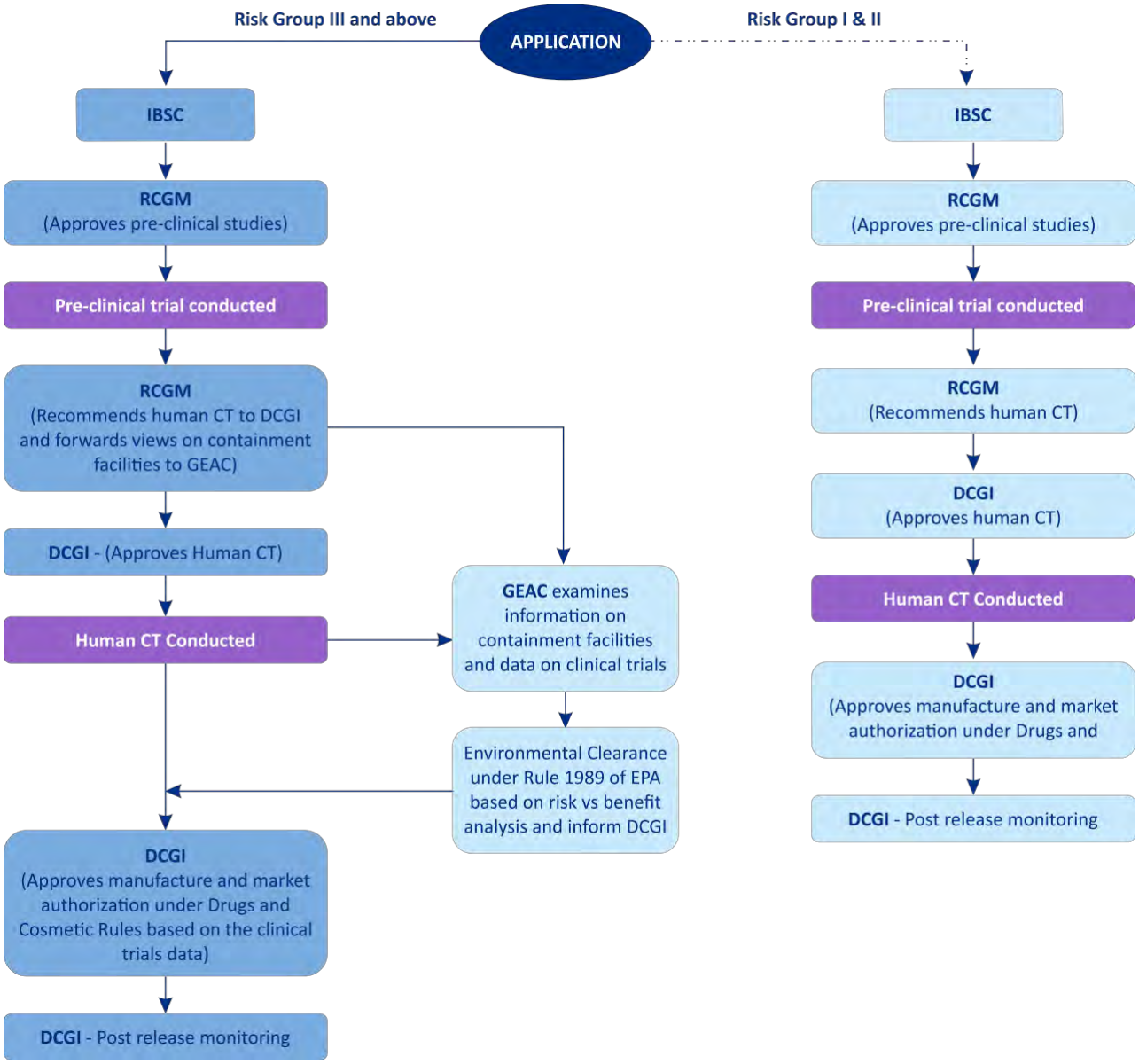
IX. EMA- DNA and Host cell protein impurities routine testing versus validation studies, 1997

X. ICH Q1 A(R2)- Stability Testing of New Drug Substances and Products, 2003

Annexure 1:

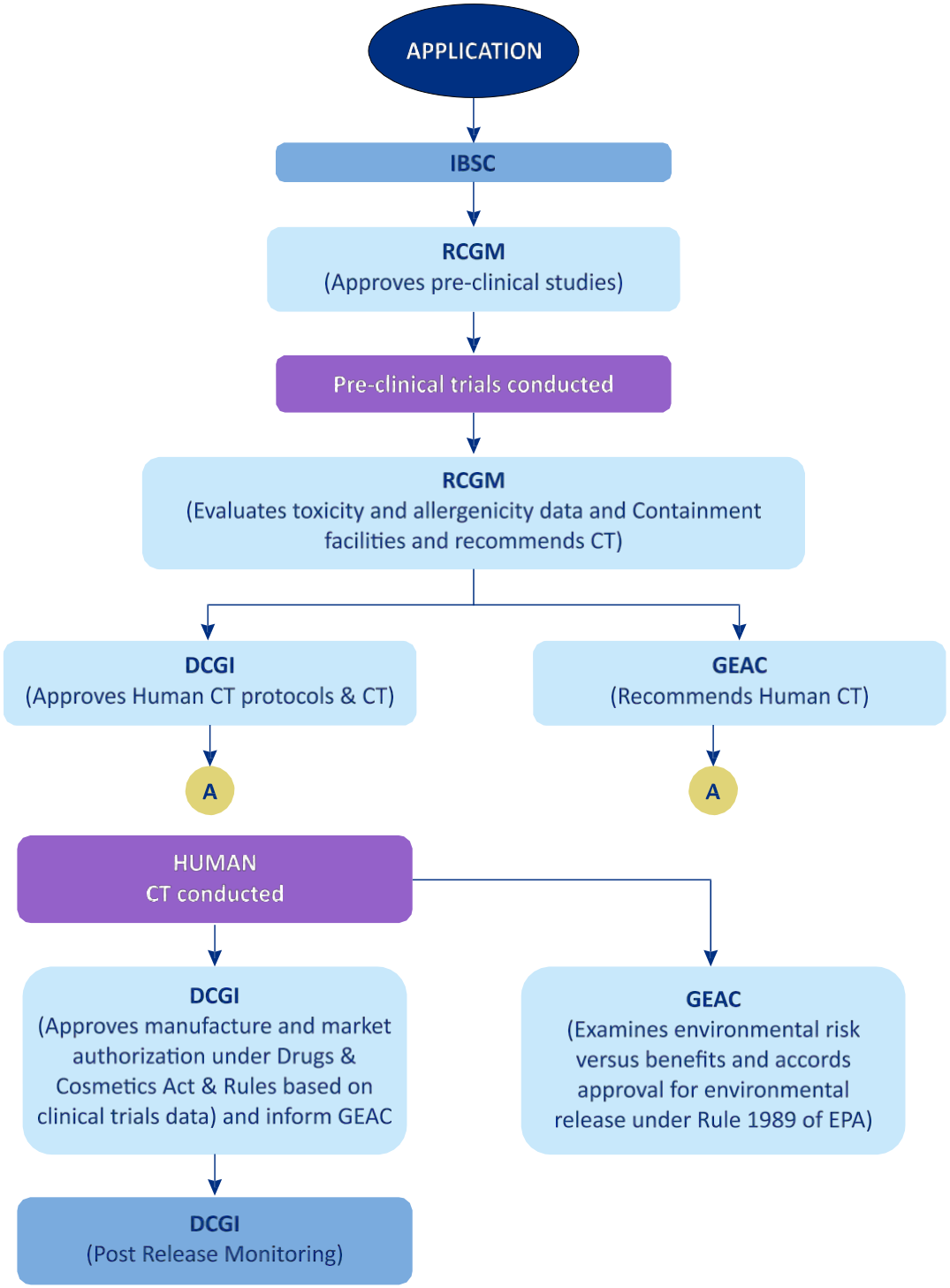
Protocols on Regulatory Pathway for Recombinant Pharma Products Adopted from Mashelkar Report.

PROTOCOL – I
Indigenous product development, manufacture and marketing of pharmaceutical products derived from LMOs but the end product is not a LMOs

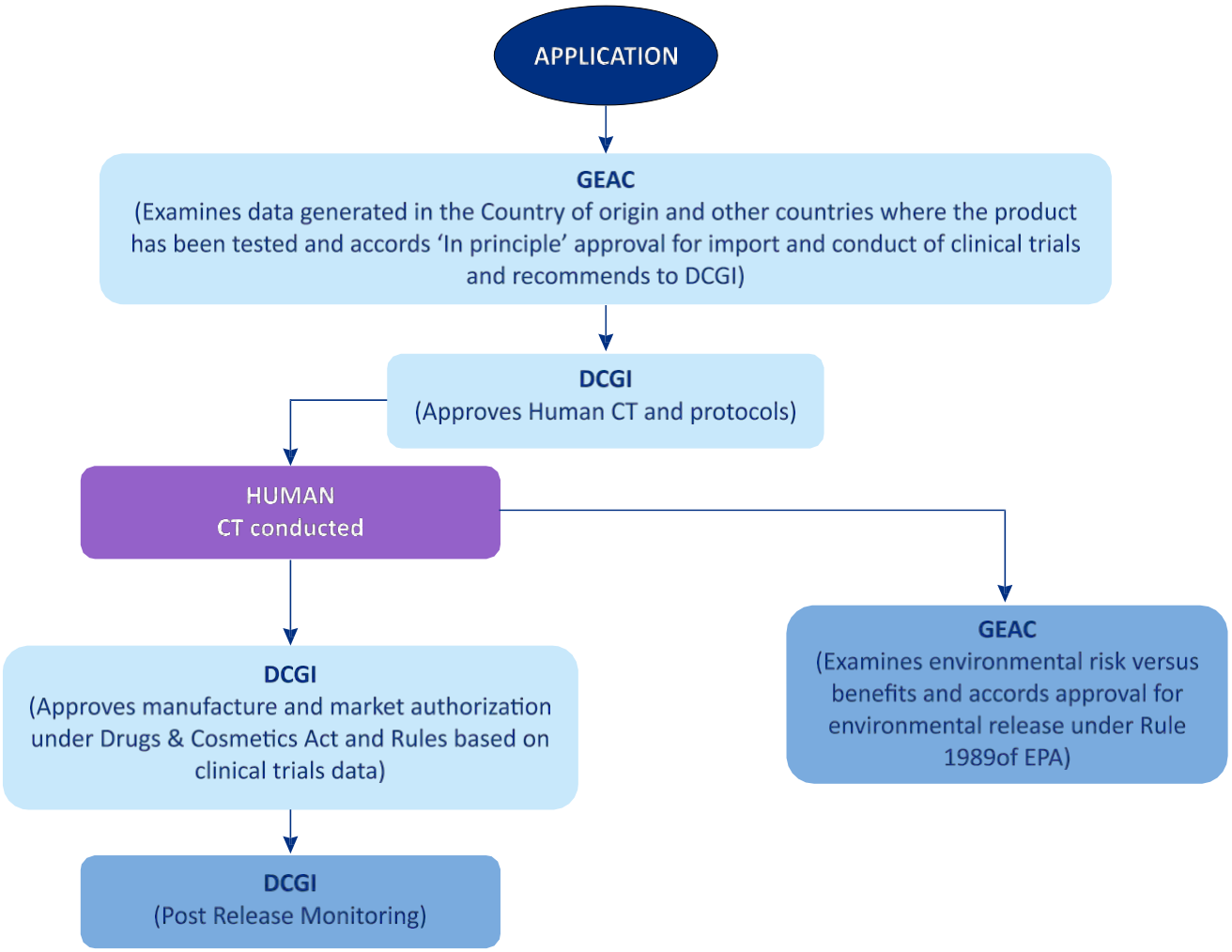


PROTOCOL – II

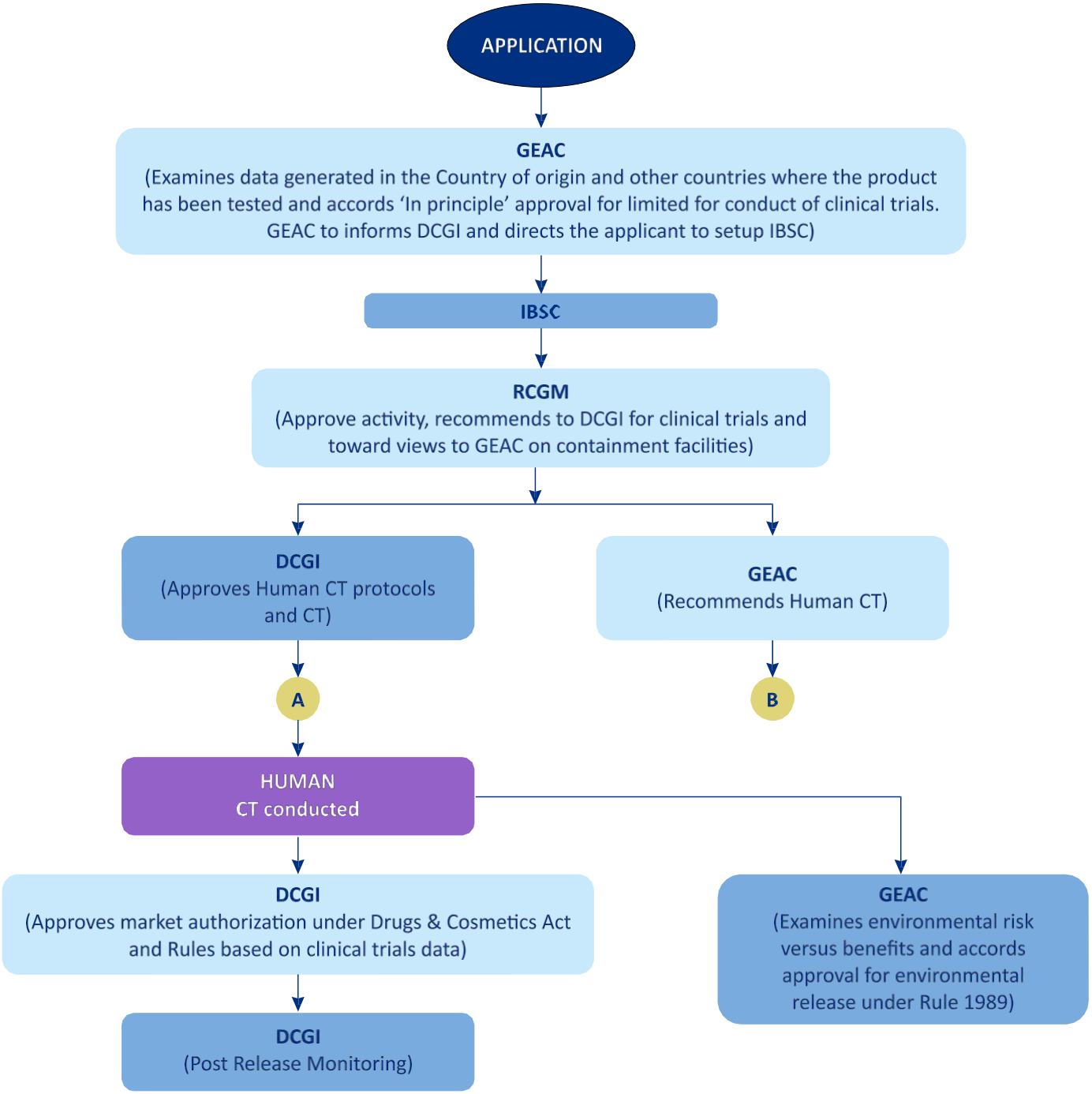
Indigenous product development, manufacture and marketing pharmaceutical products where the end product is a LMO



PROTOCOL – III
Import and marketing of Pharma Products in Finished Formulations where the End Product is a LMO

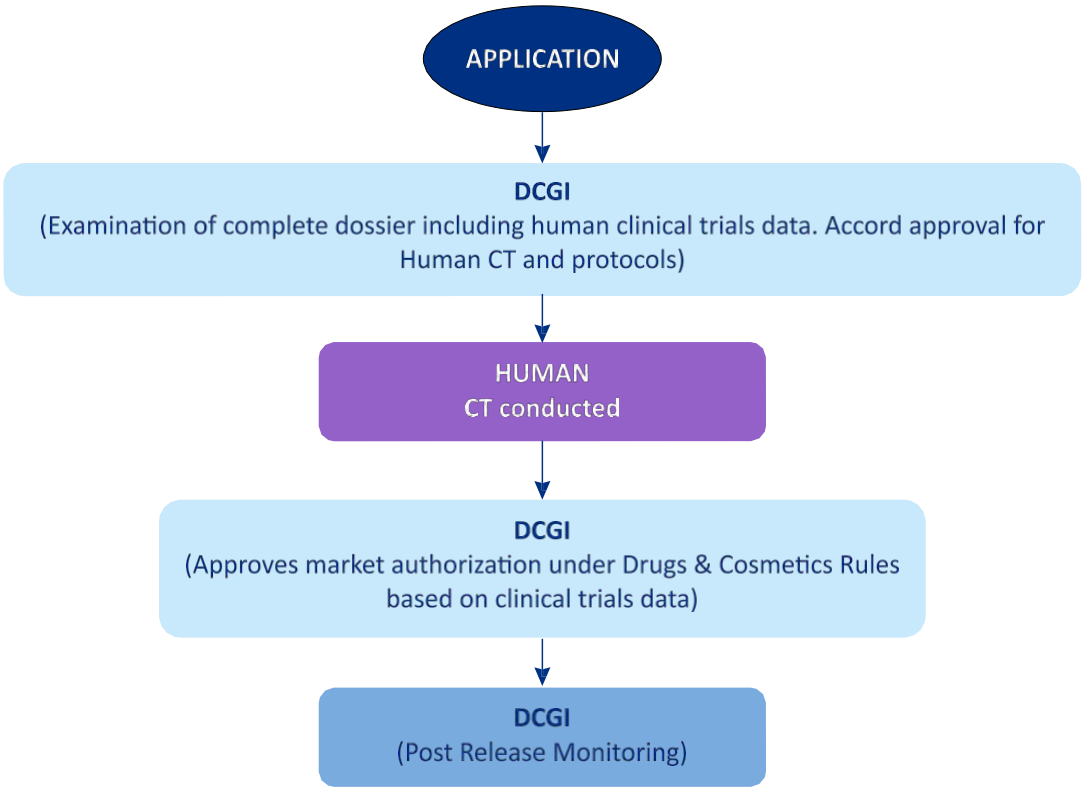


PROTOCOL – IV
Import and marketing of Pharma Products in Bulk for making Finished Formulation where the End Product is a LMO



PROTOCOL – V

Import and marketing of Pharma Products derived from LMOs in bulk and/or Finished Formulations where the end product is not a LMO



Annexure II:

Critical Quality Attributes (CQA) and Key Quality Attributes (KQA)

A. Physicochemical and biological characterization of nucleic acid based recombinant products (Vector for expression of recombinant protein, siRNA/ snRNA etc.)

Physico-chemical Characterization	Biological Characterization
Structure of active substance **Identity analysis:** • Sequence (To prove if the bases sequence same as reference biologic). **(CQA)** **For Secondary Structure analysis:** • Restriction map for >1000 bp *(To check if secondary structure is same as reference biologic).* **(CQA)** • CD spectrum from 190 to 800 nm. **(CQA)** • Absorption spectrum from 190 to 800 nm. **(CQA)**	**Functional& Biological activity** Data from *in-vitro* and */ or in-vivo* potency assays reflecting the mechanism of action of the drug. • Expression pattern in actual target host cell. *(To compare efficiency of expression of similar biologic with reference biologic in the target cell).* **(CQA)** • 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*). **(CQA)** • Kinetics of expression during the proposed therapeutic period of protection *(To compare half-life with reference biologics).* **(CQA)** **Efficacy (*in vitro / in vivo*)** • Efficacy in appropriate disease/ infection model *in vitro* and/or *in vivo*). **(CQA)** • 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).* **(CQA)**
Isoforms of active substance • Gel electrophoresis (agarose/acrylamide/urea page). (**CQA)** • Southern/ Northern blot/ Hybridization to the target sequence. (**CQA)**	
Product related variants and impurities Depending on % content, activity level and understanding its potential for undesirable activity / immunogenicity would enable to justify its impact on safety and efficacy. • Estimation of RNA and DNA using nanodrop or reagent. **(KQA)** • Purity on HPLC *(To check if any impurities are there).* (**KQA)** • Tm profile. **(KQA)**	

Process related impurities Some process related impurities may not impact biological activity. Robust process controls to acceptable limits would enable to justify its low impact on safety. • Absence of interference of marker enzyme/antibiotic. (**KQA)**	**Vector for expression of siRNA/ snRNA etc.** • Expression pattern in actual target host cell *(To compare efficiency of expression of similar biologic with reference biologic in the target cell).* **(CQA)** • 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).* **(CQA)** • Kinetics of expression during the proposed therapeutic period of protection *(To compare half-life of the similar biologic with reference biologic).* **(CQA)** • Efficacy in appropriate disease/ infection model *in vitro* and/or *in vivo (To compare therapeutic activity of the similar biologic with reference biologic).* **(CQA)** • 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).* **(CQA)**

B. Physicochemical and biological characterization of recombinant therapeutic Proteins:

Physico-chemical Characterization	Biological Characterization
Structure of active substance **For Primary Structure analysis:** • Amino acid sequence (full as well as N and / or C terminal) (**CQA)** • Intact Mass assessment by LC-ESI-MS / MALDI-TOFMS (**CQA)** • Peptide map (**CQA)** **For Secondary Structure analysis:** • Far UV Circular Dichroism Spectrum/ FTIR Analysis (**CQA)** • Tryptic Peptide Map-1D and 2D *(To check if secondary structure is conserved)*(**CQA)** • Sulfhydryl groups(s) and disulphide bridges*(To check if secondary structure is conserved)*(**CQA)** **For Tertiary Structure analysis:** • Fluorescence spectrum (**CQA)** • Near UV Circular Dichroism (**CQA)** • UV-VIS spectroscopy (**CQA)**	**Functional& Biological activity** Data from *in-vitro and / or in-vivo* potency assays reflecting the mechanism of action of the drug, receptor binding analysis can be considered strongly supportive for establishing comparable safety and efficacy for the Similar Biologics and Reference Biologic: • Receptor Binding Assay (**CQA)** • In-vitro bioassay • Biological 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)* **(CQA)** Biological 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*) **(CQA)** • Kinetics of biological 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).* **(CQA)** • Efficacy in appropriate disease/ infection model *in vitro* and/or *in vivo* (if available) (proliferation / cytotoxicity / neutralizing) *(To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).* **(CQA)** • *In-vivo* bioassay (*if available*) (**KQA**)
Isoforms of active substance: Isoforms generated by glycosylation; phosphorylation; acetylation; myristoylation; PEGylation (if applicable), esterification (if applicable) aggregates and clipped products; N or C terminal truncation or modification; charge variants and non-polar variants are known to influence the target binding or other receptor binding activity and therefore can have direct impact on the function.	

• Glycoforms and other modifications like Phosohorylation, acetylation, myrsitoylation, PEGylation, esterification by HPLC & MALDI-TOF **(CQA)** • Isoforms and charge variants by Iso-electric focusing **(KQA)** • N-terminal sequence confirmation**(CQA)** • C-Terminal sequence confirmation **(CQA)** • Ion exchange chromatography for charge • heterogeneity **(KQA)**	
Host and Process related impurities Host cell proteins, Host cell DNA, protein A and Leachable etc., may not impact biological activity. Robust process controls to acceptable limits would enable to justify its low impact on safety. These tests fall under the category of KQAs. • Host cell protein analysis **(KQA)** • Host cell DNA analysis **(KQA)** • Pyrogen content **(KQA)** **Drug Product characteristics** The following quality attributes need to be tested to characterize the drug product. • Protein content **(CQA),** • Appearance **(KQA)** • pH (**KQA)** • Osmolarity (**KQA)** • Composition of key excipients including stabilizer *(if formulation is same)* (**KQA)** • Visible/ sub visible particles, (**KQA)** • Pyrogen content(**KQA)**	

C. Physicochemical and biological characterization of recombinant mAbs:

Physico-chemical Characterization	Biological Characterization
Structure of active substance **For Primary Structure analysis:** • Amino acid sequence (full as well as N and / or C terminal) (**CQA)** • Intact Mass assessment by LC-ESI-MS / MALDI-TOFMS (**CQA)** • Peptide map (**CQA)** **For Secondary Structure analysis:** • Far UV Circular Dichroism Spectrum/ FTIR Analysis (**CQA)** • Tryptic Peptide Map-1D and 2D *(To check if secondary structure is conserved)*(**CQA)** • Sulfhydryl groups(s) and disulphide bridges*(To check if secondary structure is conserved)*(**CQA)** **For Tertiary Structure analysis:** • Fluorescence spectrum (**CQA)** • Near UV Circular Dichroism (**CQA)** • UV-VIS spectroscopy (**CQA)**	**Functional& Biological activity** Data from *in-vitro and / or in-vivo* potency assays reflecting the mechanism of action of the drug, receptor binding analysis and Fc-receptor and C1q binding assays (for monoclonal antibodies with effector function) can be considered strongly supportive for establishing comparable safety and efficacy for the Similar Biologics and Reference Biologic: • Receptor Binding Assay (**CQA)** • In-vitro bioassay • Apoptosis assay, (*if applicable*) (**KQA**) • Neonatal Receptor (FcRn) Binding Assay (**CQA)** • For mAbs with effector function (for mAbs having established effector functions) the following quality attributes should be considered as **CQA**. a. Receptor binding bioassay (FcRs) b. CDC assay c. ADCC assay • Neutralizing Biological 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)* **(CQA)** • Neutralizing Biological 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*) **(CQA)**

Isoforms of active substance:

Isoforms generated by glycosylation; phosphorylation; acetylation; myristoylation, esterification (if applicable) aggregates and clipped products; N or C terminal truncation or modification; charge variants and non-polar variants are known to influence the target binding or other receptor binding activity and therefore can have direct impact on the function.

- Glycoforms and other modifications like Phosphorylation, acetylation, myrsitoylation, esterification by HPLC & MALDI-TOF**(CQA)**
- Isoforms and charge variants by Iso-electric focusing **(KQA)**
- N-terminal sequence confirmation**(CQA)**
- C-Terminal sequence confirmation **(CQA)**
- Ion exchange chromatography for charge heterogeneity **(KQA)**

Product related variants and impurities

Depending on % content, activity level and understanding its potential for undesirable activity / immunogenicity would enable us to justify its impact on safety and efficacy

- RP-HPLC**(KQA)**
- SE-HPLC **(CQA)**
- IE- HPLC **(KQA)**
- Western Blot **(CQA)**
- SDS PAGE / CE –SDS**(KQA)**
- IEF/ CE-IEF **(KQA)**
- Light and heavy chain separation *(To check antigenic recognition motif)* **(KQA)**
- Helix to Coil Transition Profile *(To verify if the preparation is stable and impurities or isoforms are affecting the stability)* **(KQA)**

- Kinetics of neutralizing biological 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).* **(CQA)**
- Efficacy in appropriate disease/ infection model *in vitro* and/or *in vivo* (if available) (proliferation / cytotoxicity / neutralizing) *(To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).* **(CQA)**
- *In-vivo* bioassay (*if available*) (**KQA**)

Host and Process related impurities Host cell proteins, Host cell DNA, protein A and Leachable etc., may not impact biological activity. Robust process controls to acceptable limits would enable to justify its low impact on safety. These tests fall under the category of KQAs. • Host cell protein analysis**(KQA)** • Host cell DNA analysis**(KQA)** • Residual Protein A (if applicable) **(KQA)** • Pyrogen content **(KQA)**	
Drug Product characteristics The following quality attributes need to be tested to characterize the drug product. • Protein content **(CQA)** • Appearance **(KQA)** • pH (**KQA)** • Osmolarity (**KQA)** • Composition of keyexcipients including stabilizer *(if formulation is same)* (**KQA)** Visible/ sub visible particles, (**KQA)** Pyrogen content (**KQA)**	

D. Physicochemical and biological characterization of recombinant therapeutic Enzymes.

Physico-chemical Characterization	Biological Characterization
Structure of active substance **For Primary Structure analysis:** • Amino acid sequence (full as well as N terminal)**(CQA)** • Intact Mass assessment by LC-ESI-MS / MALDI-TOFMS **(CQA)** • Peptide map**(CQA)** **For Secondary Structure analysis:** • Circular Dichroism Spectrum/ FTIR Analysis (**CQA)** • Tryptic Peptide Map-1D and 2D *(To check if secondary* • *structure is conserved)*(**CQA)** **For Tertiary Structure analysis:** • Fluorescence spectrum**(CQA)** • Near UV-Circular Dichroism**(CQA)** • UV-VIS spectroscopy **(CQA)**	**Function & Biological activity** Data from *in-vitro* and */ or in-vivo* potency assays reflecting the mechanism of action of the drug, receptor binding analysis can be considered strongly supportive for establishing comparable safety and efficacy for the Similar Biologics and Reference Biologic: • Enzyme activity in gel assay in presence of chromogenic substrate *(To check activity).* **(CQA)** • Km with natural substrate**(CQA)** • Ki with known inhibitors**(CQA)** • Biological activity in actual target host cell *(to compare activity of enzyme in similar biologic with reference biologic in the target cell)* **(CQA)** • 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*

Isoforms of active substance Isoforms generated by glycosylation; phosphorylation; acetylation; myristoylation; aggregates and clipped products; N or C terminal truncation or modification; Chemical modifications are known to influence the target (substrate) binding activity and therefore can have direct impact on the function. • N-terminal sequence confirmation (**CQA)** • C-terminal sequence (**CQA)** • Glycosylation (**CQA)** • Phosphorylation (**CQA)** • Myristoylation, if any (**CQA)** • Pegylation, esterification (if applicable) (**CQA)**	*evaluate the efficiency of vector location and promoter activity in target cell*) **(CQA)** • Kinetics of biological activity during the proposed therapeutic period of protection *(To compare half-life of the similar biologic with reference biologic).* **(CQA)** • Efficacy in appropriate disease/infection model *in vitro* and/or *in vivo* (if available) (proliferation / cytotoxicity / neutralizing) *(To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).* **(CQA)** • Apoptosis assay, (*if applicable*) (**KQA**) *In-vivo* bioassay (*if available*) (**KQA)**

Product related variants and impurities

Depending on % content, activity level and understanding its potential for undesirable activity / immunogenicity would enable us to justify its impact on safety and efficacy

- RP-HPLC **(KQA)**
- SE-HPLC **(CQA)**
- IE- HPLC **(KQA)**
- Western Blot **(CQA)**
- SDS PAGE / CE –SDS **(KQA)**
- IEF/ CE-IEF **(KQA)**
- Light and heavy chain separation *(To check antigenic recognition motif)* **(KQA)**
- Helix to Coil Transition Profile *(To verify if the preparation is stable and impurities or isoforms are affecting the stability)* **(KQA)**

Process related impurities

Host cell proteins, Host cell DNA, protein A and Leachable etc., may not impact biological activity. Robust process controls to acceptable limits would enable to justify its low impact on safety.

- Host cell protein analysis**(KQA)**
- Host cell DNA analysis**(KQA)**
- Residual Protein A (if applicable) **(KQA)**
- Pyrogen content **(KQA)**

Drug product characteristics

The following quality attributes need to be tested to characterize the drug product.

- Protein content **(CQA),**
- Appearance **(KQA)**
- pH **(KQA)**
- Osmolarity **(KQA)**
- Quantitative composition of KQA excipients including stabilizer (if formulation is same) **(KQA)**
- Visible/ sub visible particles **(KQA)**
- Pyrogen content**(KQA)**

Acknowledgement:

These guidelines were prepared by the task force constituted by Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services, Ministry of Health and Family Welfare, Govt. of India and the experts from sub-committee of Review Committee of Genetic Manipulation (RCGM) of Department of Biotechnology (DBT), Ministry of Science & Technology, Govt. of India by revising the earlier guidelines on Similar Biologics published in year 2012.

CDSCO and DBT sincerely acknowledge the contribution of:

- **Chairperson:** Dr. G.N. Singh, Drugs Controller General (India), Central Drugs Standard Control Organization (CDSCO), New Delhi-110002
- **Co-chairperson:** Dr. S. R. Rao, Adviser, Department of Biotechnology (DBT), Ministry of Science & Technology, Govt. of India, New Delhi-110 003
- Department of Biotechnology (DBT), New Delhi
- National Institute of Biologicals (NIB), Noida
- Scientists from other esteemed institutions including Indian Pharmacopeia Commission (IPC), DBT-Biosafety Support Unit and other laboratories
- Representatives from Organization of Pharmaceutical Producers of India (OPPI), Association of Biotechnology Led Enterprises (ABLE), Federation of Indian Chambers of Commerce & Industry (FICCI), Confederation of Indian Industry (CII), Associated Chambers of Commerce of India (ASSOCHAM), Indian Pharmaceutical Association (IPA), Indian Drug Manufacturers' Association (IDMA) and other associations
- All participants who contributed on web based consultation
- Regulatory officials of Biological Division (Similar Biologics), CDSCO (HQ), New Delhi
- Coordinators: Dr. V. G. Somani, Joint Drugs Controller (India) & Dr. A. Ramkishan, Deputy Drugs Controller (India), Biological Division, CDSCO (HQ), New Delhi.

For further information please contact:

Department of Biotechnology Ministry of Science & Technology, Government of India, 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