Guidelines on Similar Biologic: Regulatory Requirements for Marketing Authorization in India
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Guidelines on Similar Biologic: Regulatory Requirements for Marketing Authorization in India

1. Introduction

The “Guidelines on Similar Biologic” 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.

The 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 & Cosmetics Act, 1940 or any other relevant Acts and are subject to being in conformity with the Drugs & 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 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:
  - Submission of Clinical Trial Application for Evaluating Safety and Efficacy
  - Requirements for permission of New Drugs Approval
  - Post approval changes in Biological products: Quality, Safety and Efficacy Documents
  - Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
- 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
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 marketing and manufacturing.

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

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

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 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 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 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.

The 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 Biologic

Similar Biologic is 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 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 in accordance with international guidelines. (WHO 2013).

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.

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 which is an innovator product approved after evaluation of 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 / approved in India or ICH countries and should be the 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 in any ICH country. 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 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 Biologic 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 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 for manufacturing Similar 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 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
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.

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 3 consecutive batches of purification from 3 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)

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 Biologic

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 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 recombinant therapeutic protein 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
\(^9\)ICH Q6B: Specifications: test Procedures and Acceptance criteria for Biotechnological/Biological Products
6.3.2 Product Characterization

Characterization studies for Similar Biologic 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 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 posttranslational 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 Biologic (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 product and drug substance should be assigned based on real-time stability data. 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 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 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 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 is 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 a 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 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, 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 test 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 pharmacologically relevant animal model should be conducted to ensure and confirm the potential toxicity (including toxicokinetics) of the molecule. 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 pharmacologically 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 with due permission from the RCGM.

Regarding the route of administration, in cases when the pharmacologically 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. 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. 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 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 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.

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.

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 DCG (I) seeking approval to conduct clinical trial. However, DCG (I) shall complete the scrutiny of application and issue permission, only after RCGM clearance 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

Given that the Similar Biologic would be established to be same 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

The NHV study can be performed as a parallel study to 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 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 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 Reference Biologic and Similar Biologic. If a 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. 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 Biologic in these settings.
In order to discharge any residual risk, a comparative phase III clinical trial may also be required in order to establish the comparability with respect to clinical safety and efficacy.

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. 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 is 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 be based on safety data from a sufficient number of patients treated for an acceptable period of time and 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 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 and has preferentially been done in an in-patient setting with safety measurement (including immunogenicity) 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.

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 and validated PD marker.

8.3.2 Non-comparative safety and efficacy study:

For a product which is found Similar in pre-clinical, in-vitro characterisation 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. Phase III clinical trials of such a Similar Biologics product may be waived as noted above or, where considered necessary, an appropriate single arm study in at least 100 evaluable subjects may be carried out in the most sensitive indication to address any residual uncertainty.

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 reduced 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 need 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.

The package insert of the Similar Biologic shall be based on data generated by the manufacturer or from verifiable publicly available data.

10. Post-Market Data for Similar Biologic

Although Similar Biologics are not new drug products and their risk is expected to be Similar to the Reference Biologic, since a Similar Biologic is authorized based on a reduced preclinical and clinical data package, 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. The risk management plan should consist of the following:

10.1 Pharmacovigilance Plan

The clinical studies done on Similar Biologic 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 within 15 days of initial receipt of the information by the applicant as per Schedule Y.

10.3 Post Marketing studies (Phase IV Study)

Finally, in order to further reduce the residual risk of the Similar Biologic, 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 product. 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 Biologic 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.

Exceptions:
In the case of Similar Biologic 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:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Agency involved</th>
<th>Application</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing License for test, analysis and examination (After CDSCO NOC)</td>
<td>State FDA</td>
<td>Form 30</td>
<td>Form 29</td>
</tr>
<tr>
<td>Import license for test, analysis and examination</td>
<td>CDSCO -zonal</td>
<td>Form 12</td>
<td>Form 11</td>
</tr>
<tr>
<td>Cell bank import / export / transfer / received</td>
<td>RCGM</td>
<td>Form B1/B3/B5/B7</td>
<td></td>
</tr>
<tr>
<td>Carrying out Research and Development</td>
<td>RCGM</td>
<td>Form C1</td>
<td></td>
</tr>
<tr>
<td>Preclinical studies permission</td>
<td>RCGM</td>
<td>Form C3a</td>
<td></td>
</tr>
<tr>
<td>Submission of Preclinical study report</td>
<td>RCGM</td>
<td>Form C5a</td>
<td></td>
</tr>
<tr>
<td>Clinical Trial</td>
<td>CDSCO</td>
<td>Form 44</td>
<td>CT Permission letter</td>
</tr>
<tr>
<td>Import /Manufacturing and marketing permission</td>
<td>CDSCO</td>
<td>Form 44 (separate for DS and DP)</td>
<td>Form 45A/46A (bulk product and</td>
</tr>
</tbody>
</table>
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 D&C act 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. Reference Biologic

A Reference product is used as the comparator for 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.

j. Pharmacovigilance

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

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)


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)


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


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 I

![Diagram showing the protocol for the development, manufacture, and marketing of pharmaceutical products derived from LMOs but not being an LMO itself.]
Guidelines on Similar Biologic: Regulatory Requirements for Marketing Authorization in India

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

Application

DCGI (Examination of complete dossier including human clinical trials data. Accord approval for Human CT and protocols.)

HUMAN CT conducted

DCGI (Approves market authorization under Drugs & Cosmetics Rules based on clinical trials data)

DCGI (Post Release Monitoring)
Annexure II 2A,2B,2C,2D