

Regulations for biosimilars

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What are Biosimilars?

- Biosimilars are often called follow-on biologics, generic biologics or follow-on proteins.
- Biosimilars are new versions of existing trade-name biological products whose patents have expired.
- Highly similar biosimilars are not “identical” to the reference product.
- They do not utilize the same living cell line, production process, or raw material as the innovator drug

How are Biopharmaceuticals Made?

- Upstream & Downstream

Introduction

- Biological medicines are derived from living cells or organisms and consist of large, highly complex molecular entities which may be difficult to characterize.
- Due to the variability of the biological system and the manufacturing process, biological medicines may show a certain degree of variation, even between batches of the same product.
- A biosimilar medicine is a biological medicine that is developed to be highly similar and clinically equivalent to an existing biological medicine.
- A biosimilar contains a version of an active substance of an already approved biological medicine, which is referred to as the 'reference medicine' or 'originator medicine'.
- Similarity to the reference medicine in terms of quality, structural characteristics, biological activity, safety and efficacy must be established based on a comprehensive scientific comparability exercise such that they do not have any clinically meaningful differences from the reference medicine in terms of quality, safety and efficacy

What is Biologic Medicines ?

- A large Protein molecule typically derived from living cells and used in the treatment or prevention of disease.
- Include therapeutic proteins, DNA, monoclonal antibodies and fusion proteins.
- Often 200 to 1,000 times the size of a small molecule drug and far more complex structurally.
- Examples:
 - Human Growth hormone
 - Human insulin
 - Erythropoietin
 - Vaccines
 - Monoclonal antibodies

Overview of USFDA Guidelines for Biosimilars Integration of Information to Biosimilarity

- General Regulatory Approach for Assessment.
- A risk-based, totality-of-the-evidence approach to evaluate all data and information provided by a sponsor to support a demonstration of biosimilarity.
- Sponsors must use a stepwise approach in their development of biosimilar products.
- The type and amount of analyses and testing required to demonstrate biosimilarity will be on a product-specific basis.
- General scientific principles in conducting comparative analyses will be followed by US FDA.
- Recombinant protein production: sources of variation between manufacturers.

- Reasons of Biosimilars' heterogeneity (~ potential differences between the biosimilar and the innovator drug):
 - Biological therapeutics are a complex mixture consisting of the parent drug, multimers, truncated fragments.
 - The components may or may not exhibit biological activity, post-translational modifications of the parent and/or truncated fragments, host cell proteins as well as process related impurities.
 - Any one of these can cause differences in the way these drugs behave in the immunoassay, bioassay and electrophoresis

- The General Requirements are:
 - Analytical studies demonstrating that the biological product is “highly similar” to the reference product.
 - Animal studies (including the assessment of toxicity); and
 - Clinical studies
 - assessment of immunogenicity and pharmacokinetics (PK)
 - PD studies or RCTs to demonstrate
 - efficacy & safety
 - purity, and potency
 - in 1 or more appropriate conditions of use for which the reference product is licensed.
 - Overall Guiding Principles requirement for approval

Differences between chemical generics & biosimilars

1. Heavier Unlike structurally well-defined, low molecular weight chemical drugs, biopharmaceuticals are:
 - High molecular weight compounds with complex three-dimensional structure
 - For example, the molecular weight of Aspirin is 180 Da whereas Interferon- β is 19,000 Da
2. Larger
 - Typical biologic drug is 100 to 1000 times larger than small molecule chemical drugs.
 - Possesses fragile three-dimensional structure as compared to well-characterized one-dimensional structure of chemical drug.
3. Difficult to define structure
 - Small Molecule drugs \rightarrow easy to reproduce & specify by mass spectroscopy & other techniques.
 - Lack of appropriate investigative tools to define composite structure of large proteins
4. Complex manufacturing processes
 - Manufacturers of biosimilar products will not have access to manufacturing process of innovator products \rightarrow Proprietary knowledge
 - Impossible to accurately duplicate any protein product
 - Different manufacturing processes use different cell lines, protein sources & extraction & purification techniques \rightarrow heterogeneity of biopharmaceuticals
 - Versatile cell lines used to produce the proteins have an impact on the gross structure of the protein
 - Such alterations may significantly impact: Receptor binding, Stability, Pharmacokinetics & Safety
 - Immunogenic potential of therapeutic proteins \rightarrow Unique safety issue \rightarrow Not observed with chemical generics

Benefits of Biosimilars

- “The development of biosimilars allows for wider and, as important, earlier access to these agents because of their lower cost and consequently greater affordability”
- “lower cost is expected not only to improve cost- efficacy ratios, but also to improve drug access.

Emerging Role of Biosimilars

- Countries around the world- growing, aging population ---> ↑ in chronic disease.
- Expanding demand for good-quality healthcare ---> challenge of controlling healthcare expenditure.
- The safe and regulated introduction of biosimilars into the market has been forecasted to increase access to much needed biologic medicines and reduce costs.

Concerns with Biosimilars

- The two biosimilar products have different origin.
- The two biosimilars may have same therapeutic effect.
- They may have different side effect and toxicology. Hence Biosimilars require thorough testing.
- Similarity between a biosimilar and its reference bio-therapeutic product should be evaluated in all respects (quality, safety and efficacy).
- Surported copies of bio-therapeutic medicines that have not undergone head-to-head comparisons with an appropriate reference product put patient safety at risk and should not be licensed via biosimilar pathways.

Issues of concern with use of biosimilars

1. Efficacy issues

- Differences between the bioactivity of the biosimilars & their innovator products
 - Example:
 - 11 epoetin-alfa products from 4 different countries (Korea, Argentina, China, India)
 - Significant diversions from specification for in vivo bioactivity
 - Ranged from 71-226%

2. Safety issues Concerns regarding immunogenicity

- Example:
- ↑ in no. of cases of Pure Red Cell Aplasia associated with specific formulation of epoetin α
- Caused by the production of neutralizing antibodies against endogenous epoetin

3. Pharmacovigilance

- Due to limited clinical database at the time of approval → Vigorous Pharmacovigilance required
- Immunogenicity is a unique safety issue
- Adverse drug reactions monitoring data should be exhaustive
- Type of adverse event & data about drug such as: Proprietary name, International nonproprietary name (INN) & dosage

4. Substitution

- Allows dispensing of generic drugs in place of prescribed IP
- Rationale for generics → Original drugs & their generics are identical & have the same therapeutic effect
- Produce cost savings

- Same substitution rules should not be applied:
 - Decrease the safety of therapy or cause therapeutic failure
 - Uncontrolled substitution → confounds accurate Pharmacovigilance
 - Adverse event emerges after switching from IP to its biosimilar without documentation → event will not be associated to a specific product or it will be described to a wrong product
- Naming and labeling
 - Generic adaptation of chemical medicines is assigned the same name → identical copies of the reference products
 - Biosimilars require unique INNs, as this would facilitate:
 - Prescribing & dispensing of biopharmaceuticals:
 - Precise Pharmacovigilance
 - Need for Comprehensive labeling of biosimilars including deviations from IP & unique safety & efficacy data
 - Assist the physician & pharmacist in making informed decisions

Regulation of Biosimilars

WHO regulations for Biosimilars

- In 2009 the World Health Organization developed a set of globally accepted standards to assure the safety, efficacy and quality of biosimilar medicines.
- These have been developed in the wake of increased interest in biosimilars by local regulatory authorities seeking to develop national standards.

What is biosimilarity?

- “Biosimilarity” is the regulatory term used to denote the comparability between a biosimilar and its reference medicinal product.
- Regulatory bodies across the world including India, recommends a stepwise approach to demonstrate biosimilarity between a proposed medicine and the original biologic
- The aim is to demonstrate no clinically meaningful difference in terms of safety, potency and purity

Regulation of biosimilar in India

INTRODUCTION

- A biosimilar is a biological medicine that is similar, but not identical, to an already registered reference bio therapeutic product in terms of quality, safety, and efficacy.
- These drugs may be also called as biosimilar products.
- **India (CDSCO) Definition:** Similar biologics- A biological product/ drug produced by genetic engineering techniques and claimed to be “similar” in terms of safety, efficacy and quality to a reference biologic, which has been granted a marketing authorization in India by DCGI on the basis of a complete dossier, and with a history of safe use in India

- A biosimilar is a biological medicine that is similar, but not identical, to an already registered reference biopharmaceutical product in terms of quality, safety, and efficacy and intended to have the same mechanism of action for the same diseases as the innovator biopharmaceutical drugs .
- These drugs may be also called as biosimilar products , follow-on protein products and subsequent-entry biologics.
- Biosimilar are generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes, starting material and method of control.
- Biosimilar are biologic medical products whose active drug substance are made by a living organism or derived from a living organism by recombinant DNA or controlled gene expression methods.

Regulatory Framework in India Central Drugs Standard Control Organization (CDSCO)

- 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.
- CDSCO proposed guideline addresses the requirements regarding manufacturing process, quality aspects, and pre-market regulatory requirements including comparability exercise for quality, non-clinical and clinical studies and post market regulatory requirements

- Three other competent authorities are involved in the approval process of biosimilar or Similar Biologics products (SBPs).
 - 1. Review Committee on Genetic Manipulation (RCGM), which works under Department of Biotechnology (DBT), Ministry of Science and Technology.
 - 2. Institutional Bio Safety Committee (IBSC)
 - 3. Genetic Engineering Approval Committee (GEAC), which functions under the Department of Environment (DoE).

Application Regulation 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)
- 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.
- 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:
 - Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011.
 - Guidelines on Similar Biologics: Regulatory Requirements for Marketing authorization in India 2012.
 - Guidelines on Good Distribution Practice for Biological Products.
 - Pharmacovigilance Requirement for Biological Products

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:
 1. The Reference Biologic should be licensed / approved in India or ICH countries and should be the innovator's product.
 2. In case the Reference Biologic is not marketed in India, the Biologic should have been licensed in an ICH country.

3. The Reference Biologic product can be imported for developing the Similar Biologic for quality , pre-clinical and clinical comparability.
4. 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).
5. The dosage form, strength and route of administration of the Similar biologic should be the same as that of the Reference Biologic.
6. The active drug substance (active ingredient) of the reference biologic and that of similar Biologic must shown to be similar.

Preclinical Studies

- The preclinical studies should be conducted prior to the initiation of any clinical 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.
- 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:
 1. Pharmacodynamic Studies
 2. Toxicological Studies
 3. Immune Response in Animals

Pharmacodynamic Studies

- In vitro studies: Comparability of test and reference biologic should be established by in vitro cell based bioassay (e.g. cell proliferation assays or receptor binding assays).
- 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 pharmacodynamic, in vivo studies should be performed.

Toxicological Studies

- In case of in vivo toxicity studies, at least one repeat dose toxicity study in a relevant species is required to be conducted.
- The duration of the study would be generally not less than 28 days with 14 days recovery period.
- Regarding the animal models to be used, the applicant should provide the scientific justification for the choice of animal model(s) based on the data available in scientific literature.
- However if the relevant animal species is not available and has been appropriately justified, the toxicity studies need to be undertaken in two species i.e. one rodent and other non rodent species, as per the requirements of Schedule Y.

Immune Response 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 Biologics 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 DCGI 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 DCGI seeking approval to conduct clinical trial.
- The office of DCGI shall complete the scrutiny of application and issue permission, only after RCGM recommendation was received.

Data Requirement 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.
- **Critical Quality Attributes(CQR):**
 - 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.
- **Key Quality Attributes(KQA):**
 - 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.

- In Guidelines by CDSCO have established have different protocols for approval of biosimilar.
- These protocols are as follow

Protocol I:

- Indigenous product development, manufacture and marketing of pharmaceutical products derived from live modified organisms (LMOs), where the end product is not an LMO

Protocol II:

- Indigenous product development, manufacture and marketing of pharmaceutical products.

Protocol III:

- Import and marketing of pharmaceutical products in finished formulations.

Protocol IV:

- Import and marketing of pharmaceutical products in bulk for making finished formulations.

Protocol V:

- Import and marketing of pharmaceutical products derived from LMOs in bulk and/or finished formulations

- **Protocol 1** : Indigenous product development, manufacture and marketing of pharmaceutical products derived from live modified organisms (LMOs), where the end product is not an LMO
- **Protocol 2** : Indigenous product development, manufacture and marketing of pharmaceutical products where the end product is not an LMO
- **Protocol 3** : Import and marketing of Pharma Products in Finished Formulations where the End Product is a LMO

Biosimilar Pathway in India

- Waiver of safety and efficacy study
- The confirmatory clinical safety and efficacy study can be waived If all the below mentioned conditions are met:
 - 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.
 - The Similar Biologic is comparable to Reference Biologic in all preclinical evaluations conducted.
 - 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.
 - A comprehensive post-marketing risk management plan that has been presented to regulatory Body , which 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

Conclusion

- With lapse of the patent of biological product , biosimilar will make healthcare treatment more accessible.
- Accessibility of the biosimilar product in the business sector will lead to cost reduction.
- It is the worldwide need instead of the economy improvement.
- Biosimilar are bigger and more intricate than the chemical drugs. As they are not the generics, the generic approach won't be suitable for the biosimilar product.
- Biosimilar maker needs to face extraordinary difficulties in the development, clinical improvement, manufacturing, registration and product marketing contrasted with customary generics.