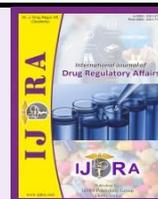


Available online on 15 June 2019 at <https://ijdra.com/index.php/journal>**International Journal of Drug Regulatory Affairs**Open Access to Pharmaceutical and Medical Research
Associated with Delhi Pharmaceutical Sciences & Research University

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Review Article

**A comprehensive study of Regulatory compliance for Biosimilars in US, EU and India**

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Abstract

The biopharmaceutical industry has gained significant interest in the last decade as the numbers of blockbuster biologic products are losing their patent rights. The regulatory authority is also providing marketing approval for Biosimilar products. Biological medicines are biotechnology developed drugs having large molecule which is complex in nature and are very sensitive to manufacturing conditions and parameters. Even a minor change in manufacturing conditions alters the quality and safety aspects of end product owing to increased risk for immune response. Biopharmaceutical companies use information technology such as molecular modelling and statistical data for drug development. Biosimilar drugs have moderate marketing cost which is alluring and generally 40 to 50 % less to that of originator drug product. Biosimilars are also known as “follow on biologics” or “similar biologics”. The following points needs consideration such as global harmonization, extrapolation studies, interchangeability study, long term post marketing studies to gain physician confidence in biosimilars.

Keywords: Biopharmaceuticals, Biosimilars, United states Food and Drug Administration (US FDA), European Medical Agency (EMA), Biologics License Application (BLA)

Article Info: Received 16 Apr. 2019; Review Completed 20 May 2019; Accepted 23 May 2019

**Cite this article as:**

Bansal A, Shukla VK, Chauhan S. A comprehensive study of Regulatory compliance for Biosimilars in US, EU and India. International Journal of Drug Regulatory Affairs [Internet]. 15 Jun 2019 [cited 15 Jun 2019]; 7(2):17-34. Available from:

<http://ijdra.com/index.php/journal/article/view/313>

DOI: [10.22270/ijdra.v7i2.313](https://doi.org/10.22270/ijdra.v7i2.313)

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1. Introduction

Biosimilars are biological products manufactured after patent expiry of innovator biologics and these are also called as Follow-on biologics, Similar biologics, Follow-on protein products and these biologics proposed to have the same mechanism of action for the similar diseases as the innovator biological drug product. The term “bio-generic” is ambiguous, as no two biological products could be same, because of complexity in their manufacturing process and method. Therefore, the common terms used to exemplify such products are “Follow-on biologics” and “Biosimilars”(1).

Unlike small chemical molecules, with defined and entirely reproducible structure, proteins are more complex and unlikely to be structurally identical to a reference product. Many potential differences in protein structure can arise. Even minor structural differences (changes in glycosylation patterns) can

significantly affect a protein’s safety and effectiveness and hence it is important to evaluate these differences.

Since biosimilars are not “generic medicines”, many characteristics associated with the authorization process do not apply. Manufacturing biosimilars are highly complex and expensive apart from the unique knowledge required to establish the relevant cell clone expressing the protein. The current analytical methodology may not be able to detect all relevant structural and functional differences between two protein products. Also, there may be an incomplete understanding of the relationship between a product’s structural attributes and its clinical performance.

The data derived from analytical studies, animal studies, and clinical studies are required to demonstrate bio-similarity because bioavailability/bioequivalence studies alone would not conclude the bio-similarity is owing to the complex nature of the biotechnology-derived products.

Whether the 'biosimilar' approach would be applicable to an individual biological medicinal product depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences, e.g. as regards the possibility to identify comparability margins, availability of sensitive clinical endpoints and model conditions etc.

The posology and route of administration of the biosimilar should be similar to the reference medicinal product. Deviations from the reference product as regards formulation or excipients require justification or further studies unlike small chemical molecules, with defined and entirely reproducible structure; proteins are more complex and unlikely to be structurally identical to a reference product. Many potential differences in protein structure can arise. Even minor structural differences (changes in glycosylation patterns) can significantly affect a protein's safety and effectiveness and hence it is important to evaluate these differences.

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Unlike small chemical molecules, with defined and entirely reproducible structure, Biosimilars are more complex and unlikely to be structurally same to a reference innovator product. Several potential

differences in biosimilar structure can arise, even minor difference scan suggestively affect the safety and effectiveness of the biosimilar product and hence it is necessary to evaluate these differences. Many characteristics of Biosimilars are not associated with the market authorization process and hence Biosimilars are not considered as "generic Medicines". Manufacturing Biosimilars are highly complex and expensive apart from the unique knowledge necessary to establish the relevant cell clone expressing the protein. The existing analytical methods are not able to detect all the structural and functional differences between two products that is reference and purposed product. Also, there is inadequate knowledge of the relationship between the structure of biosimilar product and its clinical performance. The data resulting from animal studies, clinical and analytical studies are essential to demonstrate bio-similarity because bioavailability/bioequivalence studies alone would not conclude the bio-similarity is owing to the complex nature of the biotechnology derived products. The posology and route of administration of the similar biologic should be same to the reference biologic product. Any change in the reference product about formulation or excipients needs explanation and additional studies.

Classification of biological product

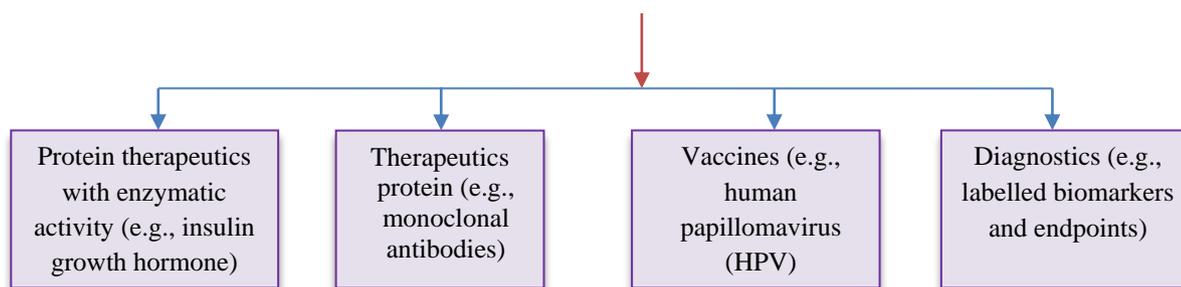


Figure 1. Classification of biological product

Biosimilar Segment review

The market for biosimilar reached to a value of 2.9 Billion US\$ in 2017. There are several factors affecting biosimilar market such as patent expiry of biological blockbuster drugs, rising occurrence of chronic diseases and drug price control initiatives from governments. Affecting by such factors, the biosimilar market is further expected to reach 15.6 Billion US\$ by 2023, at a CAGR of 30% for the next five years

Analysis studies of currently approved biologic drugs and global pipeline shows that the global biosimilar market will be worth of 240 Billion dollar and Indian biosimilar market is expected to cross 40 billion dollars by 2030. Growth is mainly driven by increased market opportunity in Europe, favorable environment for regulatory approvals in US and more clinical demand across ROW markets.

Manufacturers and pharmaceutical companies are concentrating on the development and growth of novel pharmaceuticals, specifically for the blockbuster drugs. Though, patent protections and intellectual rights are one

of the big concerns for stakeholders in development of these products. In such state, development of biosimilar is the focus for the pharmaceutical manufacturers (figure-2).

At Global level the biosimilar market is categorized into Monoclonal antibody, Human growth hormone, Erythropoietin, Insulin, Granulocyte colony stimulating factor, interferon and other biosimilar (Figure-3).

Biosimilars Market Key Segments

By Applications

- Oncology diseases
- Growth hormone deficiencies
- Chronic and autoimmune diseases
- Blood disorders
- Others

By Types

- Erythropoietin
- Insulin

- Interferon
- Granulocyte-Colony Stimulating Factor
- Human growth hormone
- Monoclonal antibodies
- Others

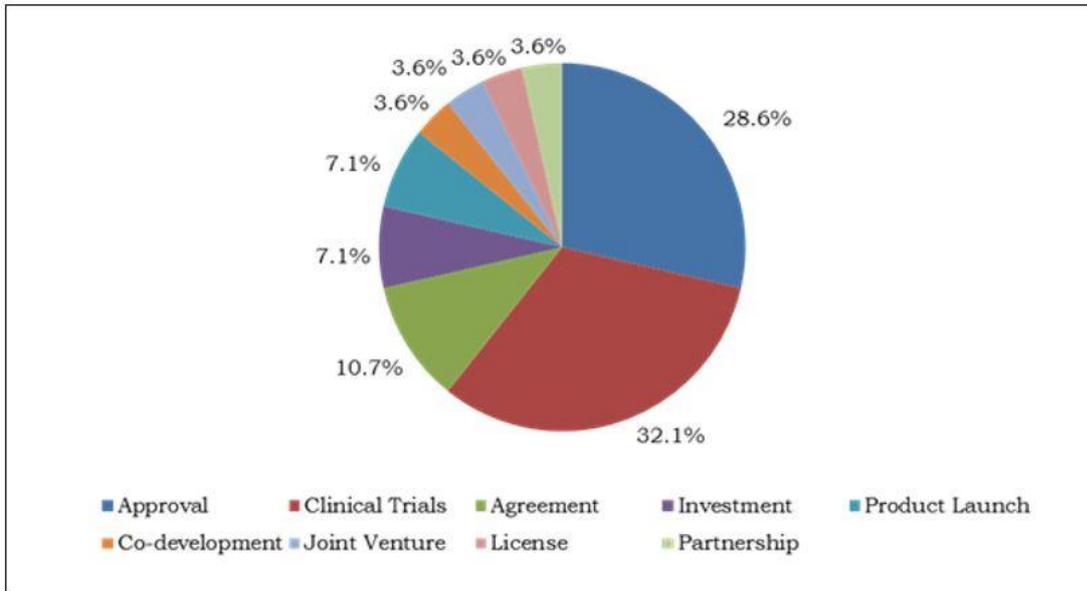


Figure 2. Biosimilar products under development (2)

By Geography

- Europe
- LAMEA
- North America
- Asia-Pacific

A similar step-by-step development process for biosimilar followed across geographies(3),(4)

The biosimilar development includes stepwise comparability exercises beginning with an evaluation of the biosimilar quality characteristics as well as of

reference biological product. Establishing similarity between biosimilar and reference biological requires comparison of quality characteristics that will lead to the reduced clinical and non-clinical data required for the approval process. For the approval and market authorization of biosimilar product, a more comprehensive clinical and non-clinical data is required, if any difference is found in the quality characteristics affecting safety and efficacy will not likely to qualify as biosimilar.

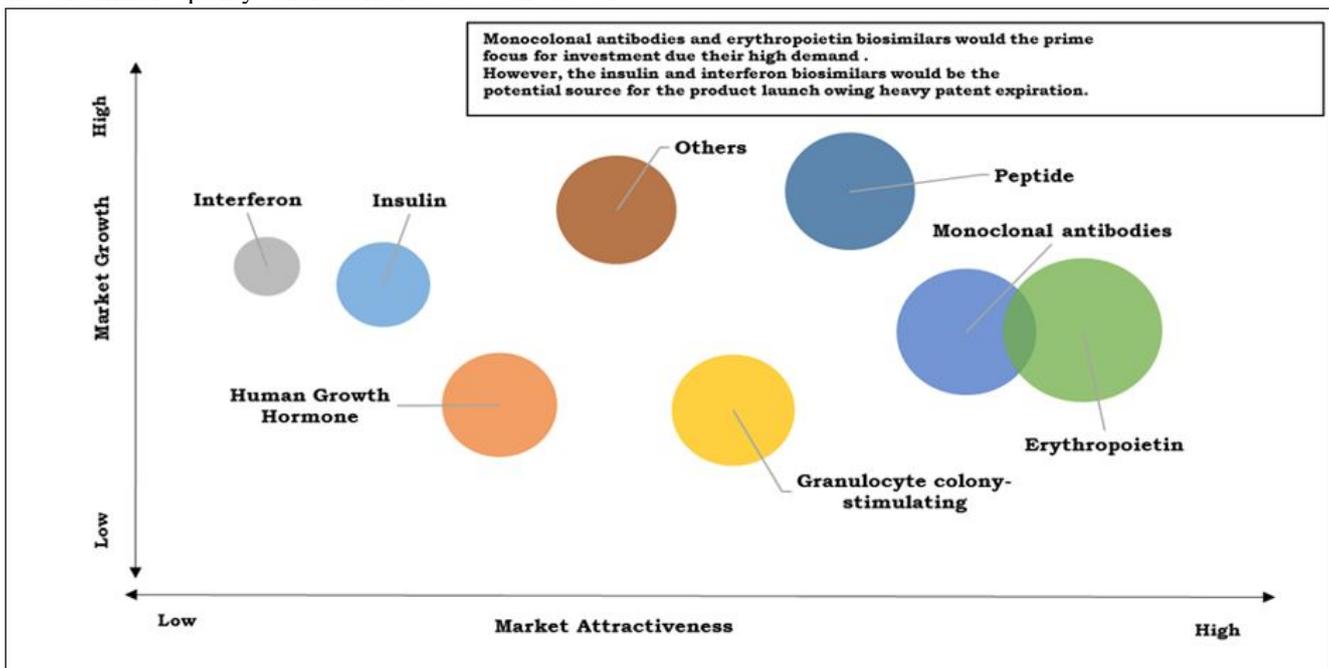


Figure 3. Top Investment Pockets (4)

Step-wise approach

- a. Analytical, quality comparison/characterization

- Manufacturing process
- Product characterization

- Quality comparability study
 - Structural and physicochemical properties
 - stability
 - Biological activity
 - Immunological properties
 - Purity and impurity
- b. Non-clinical Comparative studies
- In-vitro studies
 - In-vivo studies
- c. Comparative Clinical studies
- Pharmacokinetic study
 - Pharmacodynamics study
 - Confirmatory safety and efficacy study
 - Safety and immunogenicity data

2. Central Drug Standard Control Organization (CDSCO)

Relevant Guidelines related to Biosimilar (5)

The biosimilars are in harmony with the requirements of “Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945” and Guidelines for manufacture, export, import, use and storage of genetically engineered cells and tissue, notified under the “Environment Protection Act, 1986”. Various related guidelines are as follows:

- Recombinant DNA Safety Guidelines, 1990
- Guidelines for generating “Preclinical and clinical data for rDNA vaccines, diagnostics and other Biologicals”, 1999
- Regulatory guidance for Industry, 2008:
- “Guidelines and Handbook for Institutional Biosafety Committees (IBSCs)”, 2011
- Guidelines on Similar Biologics and marketing authorization in India, 2012

Authorities responsible for biosimilar medical products approval (6)

The concerned authorities in the approval procedure are as follows:

- Institutional Biosafety Committee (IBSC)
- Review Committee on Genetic Manipulation (RCGM)
- Genetic Engineering Appraisal Committee (GEAC)
- Central Drugs Standard Control Organization (CDSCO)

Development process of biosimilars(7-9)

Biosimilar development is a step wise approach to establish the Similarity by using wide spread characterization using various research methodologies, unfolding the molecular and excellent features with comparison to the Reference Biologic product. It is important that the biosimilar testing be sensitive enough to make sure that the product qualifies the satisfactory level of quality, efficacy and safety for the protection of public health.

Normally, a decrease in requirements of data is feasible for preclinical and clinical components of clinical trial program via comparability exercise of products. If any significant difference is found in quality, efficacy and safety, then you need to do an extra preclinical and clinical data evaluation for the biosimilar product approval.

Manufacturing Process

The manufacturing procedure of biosimilar should be tremendously reliable and consistent to yield a good quality pharmaceutical product in terms of safety, identification and purity comparable to the Reference Biologic. If the host cellular line is disclosed by the innovator of reference Biologic then, it's far anticipated to apply the same cellular line for production of Biosimilar. ICH issued various guidelines for quality of biotechnological product viz Q5A4, Q5B5 and Q5D6 for reference to guidance.

The information required for the evaluation of manufacturing process from pre-clinical to clinical submission shall consist of detailed description of development stage, screening, extraction, purification and so forth. The manufacturing process should include: Molecular Considerations, Upstream Process and Downstream Process

Selection of Reference Biologic

Innovator product (Reference Biologic) approved after complete assessment of whole dossier is critical for the improvement of Similar Biologic. The purpose for the selection of Reference Biologic must be justified by the manufacturer of the similar biologic.

Once the reference biologic is selected, it is used throughout the comparability exercise with respect to quality, safety and efficacy, preclinical and clinical studies. Factors considered for choice of the Reference Biologic:

- The selected Reference Biologic must be certified / approved in India or in any other country, which is a member of ICH nations and need to be the innovator product. Quality, safety and efficacy are one of the main parameters for the selection of reference biologic.
- The dosage form, route of administration and strength of the Biosimilar ought to be similar with that of Reference Biologic.

Biosimilarity demonstration and its Quality Consideration

A. Analytical Methods

Different analytical strategies should be selected/method depending on the essential quality attributes of the product to be compared. For characterization of different positive attributes, different methods may be use such as Extensive state of the art analytical techniques, to detect even “slight differences” in the quality attributes. Indian Pharmacopoeia (I.P) monograph shall be followed, if available.

Different techniques used to measure different quality attributes. ICH guidelines for Quality are universally accepted by all ICH member countries.

B. Product Characterization

Biosimilar characteristics include physicochemical properties, Biological activity, immunological properties, purity, strength, assays and contamination. ICH Q6B guidelines shall be followed. Active pharmaceutical ingredient and excipients shall be according to Indian Pharmacopoeia monograph.

C. Specifications

Biosimilar drug product specification for drug substance and drug product is documented with the motive of confirming consistency in product quality and comparison to international standards consistent with the guiding principle (ICH Q6B). Acceptance range of the specification should be same to that of Reference Biologic product and the preclinical and clinical data from enough number of batches, should meet the international standards and norms.

D. Stability

The shelf life and storage condition of biologic products based on real-time stability data. Stability studies should be performed based on relevant guidelines (e.g. ICH Q1A, ICH Q5C). For demonstration of similarity between standard and reference product, stressed and accelerated stability conditions are also performed on biologic products.

E. Quality Comparability Study

For evaluation of biosimilar head-to-head characterization is done and very comprehensive knowledge is required to assure that the active molecular structure of drug product is comparable to Reference Biologic drug product. However, in cases the desired quality analyses for the comparability data of the active substance can be done on the finished product level, and then the testing of the isolated active ingredient may not be essential.

Post-Market Data for Similar Biologic

Table 1 The timeline required by the regulatory authority for the approval of biosimilar (10)

Procedure	Timeline
Approval for pre-clinical studies by RCGM	45days
Approval for Human Clinical Trials protocol by DCGI	45days
Clinical trial data examination by DCGI	90days
GEAC and DCGI decisions	45days

Table 2 Forms required for approval process

Stage	Licensing authority	Application Made	Approval
Manufacturing License for examination, test or analysis	State licensing authority	Form no.30	Form no.29
License for (Examination, test or analysis)	Zonal office (CDSCO)	Form no.12	Form no.11
Import / export of Cellbank	RCGM	Form no. B1/B3/ B5/B7	
Research and Development	RCGM	Form no. C1	
Permission for preclinical studies	RCGM	Form no. C3A	

However biosimilar aren't new drug products but their safety and efficacy risk is very high, because of reduced preclinical and clinical studies, therefore it is necessary to create a Risk Management Plan to monitor safety issues and detect unknown safety signals:

A. Pharmacovigilance Plan

The clinical study completed on biosimilar is limited in nature, so the unfavorable activities maybe encountered. Hence Pharmacovigilance plan is required and prepared by manufacturer. The Pharmacovigilance plan ensures clinical safety and includes the submission of periodic safety update reports (PSURs). The PSURs should be reported every six months for the first two years and annually for the subsequent years to DCGI office as in keeping with the "New Drugs and Clinical Trials Rules 2019"

B. Adverse Drug Reaction (ADR) Reporting

All cases with unexpected adverse reactions must be reported to the licensing authority within 15 days of initial reporting of the case, with the help of the applicant as in keeping with "New drugs and clinical Trials Rules 2019".

C. Post Marketing studies (Phase IV Study)

Further to reduce the residual risk of the biosimilar product, additional studies need to be done to collect safety records after market approval of the product through a pre-defined single arm studies, compared to Reference biologic product. The study must be completed within 2 years of the manufacturing license issued.

Archiving of Data / Retention of Samples

The manufacturer ought to establish the SOP for sample retention and for data archival such as quality, preclinical and clinical documents for duration of minimum five years after authorization of biologic drug product by regulatory authority in India. Samples such as test substance, vehicle, and serum should be preserved till the period of expiry. The authority responsible for inspection/retrieval ought to be specified in the SOP.

Preclinical study submission	RCGM	Form no. C5A	
Conduction of Clinical Trial	Central licensing authority i.e CDSCO	Form 44	Permission for Clinical trial
Import for Manufacturing	Central licensing authority i.e CDSCO	Form 44	Form 45A/ 46A for API and Form 45/46 for Finished product
Manufacturing License	State and Central licensing Authority	Form 27D	Form 28D
Import Registration certificate	Central licensing authority i.e CDSCO	Form 40/Form 44	Form 41/ Form 45
Imported product licence	Central licensing authority i.e CDSCO	Form no. 8 & 9	Form no. 10

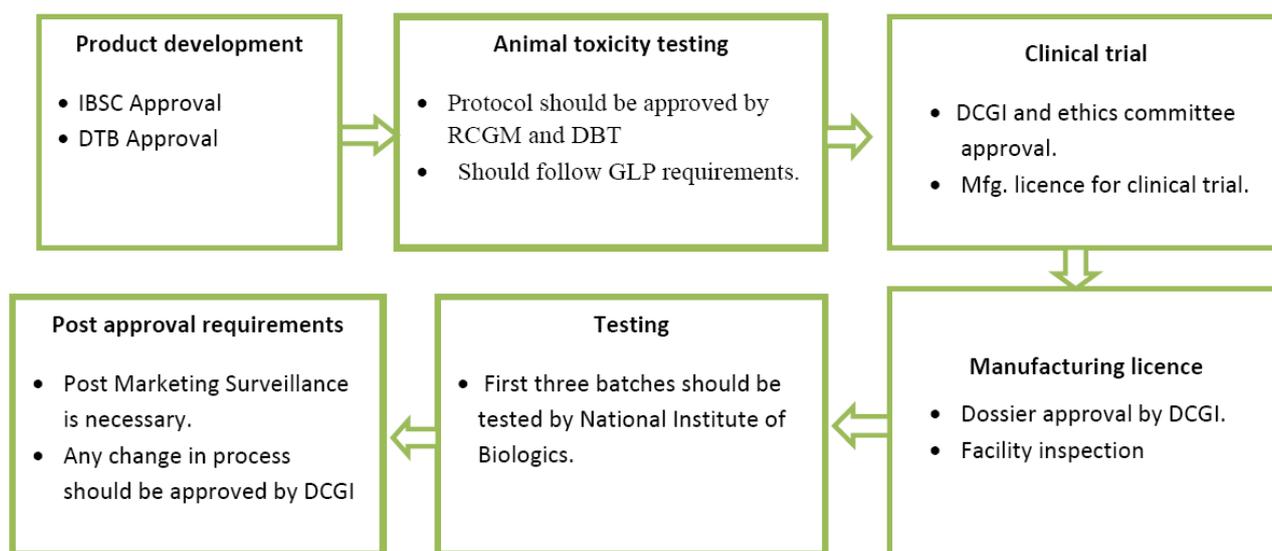


Figure 4. Flowchart: Approval pathway for biosimilar in India

3. United State Food and Drug Administration (USFDA)

Principles for Development of Biosimilars(11,12)

When designing the development program for biosimilar the sponsor, investigator should understand the complexity and scientific issues in manufacturing the biosimilar product.

A. Nature of biosimilar Products and Scientific issues

Proteins are generally more complex and are difficult to define its structure unlike small drug molecules and hence complex to prove its similarity to a reference product. Even a small difference in its structure can give rise to safety and efficacy issues.

In general, biosimilar proteins differ in following ways:

- (1) Primary amino acid sequence.
- (2) Modification to amino acids, sugar moieties or other side chains.
- (3) Complex structure such as protein folding and interactions.

B. Manufacturing Process Considerations

Different manufacturing processes of the biosimilar product affect the safety and effectiveness of the

product. Thus, the manufacturer must demonstrate similarity through different functional assays; analytical techniques in some cases animal studies are also conducted to collect the safety and efficacy data. The ICH guidance for industry (ICH Q5E) “Comparability of Biotechnological/ Biological Products” describes scientific principles for the comparability data for manufacturing changes.

Selection of Reference Biologic (13)

The applicant must demonstrate similarity to obtain marketing license of a proposed biosimilar product to a referenced biologic product that is already approved by FDA under section 351(k) of the PHS Act. A sponsor should submit comparability data such as analytical studies, clinical Pharmacokinetic study, and Pharmacodynamic study, to support the similarity of the product. However, a sponsor can use data resulting from animal or clinical studies comparing the biosimilar product to a non-US licensed reference product with scientific justification and ample data to establish a satisfactory bridge to the US licensed reference product. However, sponsors can take guidance from FDA during the development program, data for scientific justification and information regarding selection of licensed reference product.

Approaches and evidence to demonstrate biosimilarity (14, 15)

Stepwise approach is followed to demonstrate biosimilarity for the totality of the evidence submitted by the sponsor.

A. Using a Stepwise Approach to Demonstrate Biosimilarity

The stepwise approach starts with characterization of physiochemical properties which act as a foundation for product development plan for both proposed and reference biologic product. Negligible difference in structural and functional properties during comparability exercise of the proposed and reference product shall support the selective and targeted approach for animal and clinical testing for demonstration of biosimilarity. In-depth knowledge of the mechanism of action of drug, Pharmacodynamic parameters and other clinical understanding provide additional justification for selected and targeted approach to animal studies.

B. Totality-of-the-Evidence to Assess Biosimilarity

FDA considers risk-based approach and the totality of the data to demonstrate biosimilarity and evaluate the following:

1. Structural analysis,
2. Functional characterization,
3. Nonclinical studies,
4. Human Pharmacokinetic and Pharmacodynamic data,
5. Immunogenicity data, and
6. Comparative clinical studies.

Demonstrating Biosimilarity

To demonstrate biosimilarity the method of analysis and testing is determined on product specific basis (16).

A. Structural Analyses

The application submitted by the applicant for demonstration of biosimilarity include all data and information from physiochemical, biological and functional studies, may have some minor difference but not clinically meaningful active. Regulatory body expects the extensive characterization of the proposed product with state-of-the-art technology. The higher is the comprehensive characterization, the stronger will be the scientific justification.

B. Functional Assays

The functional assays are used to test the pharmacologic activity of biosimilar products using in-vitro and in-vivo methods. In vitro assays include, binding assays, biological assays and enzymatic assay. In vivo assay uses animal models to find out the functional effect on Pharmacodynamic and efficacy measures. A functional assay is necessary to support the demonstration of biosimilarity and used for selection of targeted approach for preclinical and clinical testing.

C. Animal Data

To support the biosimilarity, animal study data is also required including the evaluation of toxicity studies such

as Animal Toxicity Studies, Inclusion of Animal PK and PD Measures, Interpreting Animal Immunogenicity Results.

D. Clinical Studies – General Considerations (17)

The scope of the clinical studies depends on the left-over uncertainty about the proposed biosimilar product after evaluating comparability exercise. The assessment procedure for safety and efficacy for the reference product determine the conduction of clinical design and is justified by the sponsor.

FDA assumes to provide comparative human pharmacokinetic/Pharmacodynamic and immunogenic studies with no clinical meaningful difference, if any residual difference is found, additional clinical studies are to be done to collect safety and efficacy data.

Factors accessing the biosimilarity (18,19)

When assessing that similarity of the product we should consider the following factors:

A. Expression System

It is expected that the proposed and reference product will encode the same sequence (structure). Any change in the expression of the proposed and reference product should be carefully assessed because any difference the expression system will affect the product- and process-related impurities that may be present in the biosimilar product. However different expression systems will be assessed on a case-by-case basis.

B. Manufacturing Process

The manufacturer should have detailed understanding of the key and critical steps of the manufacturing process, its process controls and specification for the proposed product.

If the sponsor wants to make any changes in the manufacturing process after assessing the preliminary analytical similarity or clinical trials, then to support the filling application under 351(k) to the USFDA, sponsor needs to perform additional comparability exercise between pre and post changes in the proposed product and should submit supplementary analytical data for the changes made. The extent of tests done based on the changes made and on case to case basis.

C. Assessment of Physicochemical Properties

Physicochemical assessment of the biosimilar product includes: structural and functional properties; posttranslational modifications etc. The main objective of physicochemical assessment is to detect the potential differences in quality attributes between the reference and proposed product.

D. Functional Activities

The sponsor should have comprehensive knowledge about the suitable assays to carry out the functional tests for the proposed biosimilar product. The assay should be sensitive enough to find out the range of related activities and to detect the potential difference between the two biosimilar products.

E. Impurities

If any product or process-related impurities is identified during the comparability studies between the biosimilar and biologic drug product, a risk-based evaluation is done to identify the characteristics of impurities. If, the impurities are related at similar levels i.e. at physiochemical analysis between the two products, then pharmacological and toxicological studies may not deem to be necessary to demonstrate the biological activity. On the other hand, if the impurities identified are dissimilar in nature with that present in the reference biologic product, then supplementary analytical, clinical tests need to be performed to support the application.

F. Reference product and standards

Comprehensive structural, functional and biological properties of the reference product provide bundle of information to rely on existing scientific knowledge to develop the proposed biosimilar product. Enough justification should be provided to frame the similarity between proposed and reference biologic product.

Post Marketing Safety Monitoring Considerations

Post marketing safety monitoring is essential for ensuring the safety and efficacy of biosimilar products.

For post marketing safety monitoring of a drug product, sponsor should have a standard operating procedure to identify and differentiate the adverse event related to purposed biosimilar product and those that are not related to reference product. Rarely, but some potential safety risk such as immunogenicity may not be detected during developmental studies because of the limited sample size to assess rare adverse events. However, some features of post marketing safety monitoring are product-specific, and evaluated through post market surveillance.

4. European Medical Agency (EMA)

Principles for the development of Similar Biologic (20)

The development of biosimilar shall include two separate features:

- i. Molecular and Quality attributes (QA) of the purposed biosimilar product profile shall be comparable to the reference medicinal product,
- ii. There should be consistency in the product quality and performance, during the manufacturing process of the similar biologic.

It is not required that formulation of the similar biologic is supposed to be same as that of the reference medicinal product. Despite the formulation selected for the similar biologic, should be compatible, stable and active. If a dissimilar formulation is selected or preferred, suitable justified data and documents shall be given for its safety and efficacy as similar biologic have its own product lifecycle and when any change is done in active substance and finished formulation, a comparative assessment is performed (21).

Selection of Reference medicinal product (22, 23)

The sponsor should select the reference medicinal product carefully based on the conditions of use and treatment for the diseases and should have comprehensive knowledge while selecting the reference medicinal product.

The reference medicinal product should be clearly recognized as brand name, formulation, pharmaceutical dosage form etc. several different batches of multiple strengths of the reference product must be used during comparability exercise for quality profile. When establishing the targeted approach for quality, different batch number and lot number are used to demonstrate biosimilarity.

For demonstration of biosimilarity, European pharmacopoeia cannot be used as the reference for comparability exercise.

Data requirement for development of similar biologic (24)

A. Non-clinical studies

To demonstrate the biosimilarity, a correct stepwise approach is followed. Before conducting clinical studies, non-clinical ought to be performed such as in-vitro pharmacological/toxicological studies and analytical studies and then extent of in vivo work in animal studies should be decided.

It is significant to have a clear and obvious understanding of the characteristics of reference biosimilar product, to design a correct non-clinical study. Non-clinical study includes physiochemical, structural and biological properties should be assessed carefully as they play an important role in comparability exercise.

B. Clinical studies (25)

The clinical studies of biosimilar products is a stepwise procedure. It starts with PK/PD studies then followed by clinical safety and efficacy trials.

Extrapolation of safety and efficacy for more than one therapeutic indication

The reference biologic product may have many medicinal properties. When comparability exercise is done for one established use any indication, extrapolation studies for another clinical properties and uses of the reference product could be satisfactory but scientific justification is provided. If there is any uncertainty for safety and efficacy in one indication of use then for another condition of use, supplementary data need to be submitted for safety and efficacy. Extrapolation studies consist of totality of the data such as functional and biological properties as well as non-clinical and clinical data for that condition of use. Extra data is needed for specific situation (26).

- i. The reference biologic product as active substance that binds with several receptors resulting in an unfamiliar impact other than those of mentioned therapeutic indications.
- ii. There might be more than one active site present on the active substance itself giving

additional pharmacological effect other than the therapeutic dose.

Demonstrating Biosimilarity and its Quality Consideration (27, 28)

A. Biosimilar comparability exercise

For demonstration of similarity between reference and similar biologic, comparability exercise is mandatory, and it includes comprehensive and complete analyses using orthogonal and sensitive methods not only to establish similarities but also to find out any differences in the quality attributes.

B. Analytical considerations

It is the sponsor's responsibility to select the analytical methods for the biosimilar comparability exercise that would be sensitive enough to detect even slight differences. For several analytical methods and techniques, a side-by-side analysis of the reference and similar biologic may not be possible due to difference in manufacturing process and process originated impurities. Thus, finished product comparison is done and gives supportive data for documentation.

C. Physicochemical properties

The physicochemical characterization identifies the structure, composition, properties and parameters of product and impurities using suitable methods and technologies referred by the regulatory agency.

D. Biological activity

The biosimilar comparison data also include evaluation of the biological properties of the reference and similar biologic as an important footstep in demonstrating the broad characterization profile. The biological activity has specific mechanism of action to accomplish a defined therapeutic effect. Different biological assays and corresponding approaches should be considered such as enzymatic assays, ligand or receptor binding assays, functional assays and cell-based assays etc. depending on the different biological properties of the product.

E. Immunochemical properties

Immunological data is must for the determination of safety and efficacy of the biosimilar product. In case, if biosimilar products containing monoclonal antibodies,

Table 3 Assessment of the application

Day	Action
1	Start of procedure
80	Receiving assessment report from CHMP members and EMA. EMA sends this report to applicant to make it clear about the conclusion. This is called 80 days assessment period.
87	Pharmacovigilance Risk assessment committee (PRAC) circulate the Risk Management Plan (RMP) assessment report and list of Questions.
90	Adoption of Good Practice inspection report.
100	EMA receive comments
101-104	Pharmacovigilance Risk assessment committee adopts PRAC RMP overview report and advice.
115	Received draft of lot of questions and discussion with CHMP recommendations by its members and EMA. Dossier Module 3 (Quality) reviewed by Biotech Working Party (BWP).

immunological functions of monoclonal antibodies must be fully compared to give a comparison data for similarity of the products to the intended target.

F. Purity and impurities

The purity and impurity profiles of biosimilar product are compared using different analytical methods and assays with the reference product both quantitatively and qualitatively. The purity and impurity assay comparison specify different degradation pathways such as aggregation, oxidation and deamidation of the biosimilar medicinal product and possible post-translational modifications of the biosimilar products. The shelf life, quality profile, storage conditions, accelerated stability testing at different time points must be considered during comparison, it provides additional support for biosimilarity.

G. Quantity

Using appropriate assay, quantity should be determined correctly and must be expressed in the same units as the reference medicinal product. The similar strength is established between reference and similar biologic product.

H. Specifications

The choice of tests and specifications mentioned for both drug substance and drug product is product specific for biotechnology derived products. The product shelf life, storage condition, accepted range of different parameters should be justified with full stability data for the similar biologic. Real-condition stability studies and comparative real-time between the reference and biosimilar medicinal product are not mandatory.

Pharmacovigilance

It is very difficult to discover rare adverse effects during clinical studies. As a result, after post authorization of biosimilar product, clinical safety of the product is regularly monitored on constant basis with continued benefit-risk assessment. In the market authorization application, the sponsor should provide risk management plan and description of the Pharmacovigilance system in harmony with the EU regulations.

120	CHMP adopts overall conclusion and review of scientific data. Clock stop for GMP/GCP/GLP inspection procedure
121	Submission of response, SmPC and labelling, packaging leaflets.
150	Pharmacovigilance Risk assessment committee circulates RMP report
157	Circulation of joint response assessment report by CHMP called 150-day Assessment report and applicant receive this report for information purpose only.
170	Comments from CHMP, EMA and other members. Response to Module 3 Quality questions reviewed by BWP.
180	CHMP decision on the critical issues or any oral application is needed by applicant. In case of oral explanation by applicant clock stop for oral preparation by applicant.
181	Restart of clock and circulation of Final report.
183	Pharmacovigilance Risk assessment committee circulates RMP assessment report.
197	Adoption of RMP overview and advice by Pharmacovigilance Risk assessment committee.
210	Adoption of CHMP assessment report and opinion.
additional 5 days after assessment report	Applicant provide SmPC, labelling, packaging leaflet to EMA in different EU languages for review.
Additional 22 days after assessment report	Comments received from different member states within 19 days after adoption of assessment report.

Table 4 Comparability parameters for biosimilars across US, Europe and India

Parameters	US	EU	INDIA
Term	Follow-on Biologics	Biosimilars	Similar biologics
Definition	A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency	Biological products which demonstrated its equivalence to an already approved reference product about quality, safety, and efficacy	Biosimilars are defined as officially approved new version of innovator biotherapeutic products for which the patent has expired
Laws and Regulation	Biologics Price Competition and Innovation Act (BPCIA)	Committee for Medicinal Products for Human Use (CHMP) of the EMA	Review Committee on Genetic Manipulation (RCGM) and Genetic Engineering Approval Committee (GEAC) of Central Drugs Standard Control Organization (CDSCO)
Reference Product	Authorized in US	Authorized in EU	Authorized in India
Interchangeability	Present	Absent	Absent
Similarity data	Structural study, functional study, Animal study, Clinical study	Analytical study, physiochemical study, biological activity, Immunological properties, purity, impurity and specification	Analytical studies, product characterization, specification, stability and quality comparability study

5. Biosimilar Regulations for different regions

EMA

Since 2005, in Europe the biosimilar regulations are controlled by CHMP (Committee for Medicinal Products for Human Use) under the EMA (European Medicines Agency). Europe had a regulatory approval pathway in place for Biosimilars before any other developed

country. EMA understood early, the economic impact of Biosimilars on the health system.

In 2006, “Omnitrope” was the first Sandoz’s somatotropin biosimilar drug approved in Europe in April 2016. Out of 53 applications, forty-eight have been approved in Europe. Three applications have been withdrawn by the marketing authorization holders after post market approval phase.

Table 5 European Medicines Agency List of Approved Biosimilar Drugs (data collected on 14 December 2018)(29)

Sr. no.	Year of Approval	No. of Approved Applications	Product Name
1	2018	17	Fulphila*, Halimatoz, Hefiya, Hulio, Hyrimoz, Herzuma, Kanjinti, Mvasi, Ogivri*, Pelgraz*, Pelmeg, Semglee, Trazimera, Truxima, Udenyca, Zessly, Ziextenzo
2	2017	15	Amgevita, Blitzima, Cyltezo, Erelzi, Imraldi, Insulin lisproSanofi, Lusduna, Movymia, Ontruzant, Ritemvia, Rituzena, Rixathon, Riximyo, Solymbic, Terrosa
3	2016	4	Benepali, Flixabi, Inhixa, Thorinane
4	2015	0	
5	2014	3	Abasaglar, Accofil, Bemfola
6	2013	4	Grastofil, Inflectra, Ovaleap, Remsima
7	2012	0	
8	2011	0	
9	2010	1	Nivestim
10	2009	2	FilgrastimHexal, Zarzio
11	2008	2	Ratiograstim, Tevagrastim
12	2007	5	Abseamed, Binocrit, EpoetinalfaHexal, Retacrit, Silapo
13	2006	1	Omnitrope

* Drugs under approval pipeline, CHMP has positive opinion on the listed drugs.

- Biograstim, Filgrastim ratiopharm, Somatropin withdrawn by the applicant.
Biopartners, Valtropin these drugs are

Table 6 EMA list of Biosimilars under evaluation for Market Authorization (Data collected on 25 Jan 2019)(30)

Common name	Therapeutic area	Number of applications	EMA-approved originators	Originator company
Adalimumab	Immunosuppressant	3	Humira	AbbVie
Etanercept	Immunosuppressant	1	Enbrel	Amgen/Pfizer
Pegfilgrastim	Immunostimulant	1	Neulasta	Amgen
Rituximab	Antineoplastic medicine (anticancer)	2	MabThera/Rituxan	Roche

US

Before 2009, the US did not have a regulatory framework until the enactment of BPCIA (Biologics Price Competition and Innovation act)2009. However biosimilar draw some attention of policymakers over the last few years due to educational efforts made by stakeholders and other manufacturers. There are slow uptakes of biosimilar in US. is just a reflection of branded approach both by the physician and patient. Lack of awareness and less training programmes are one

of the reasons for slow growth of biosimilar market in the US.

“Zarxio” Sandoz’s filgrastim biosimilar received the first approval in US in 2015 almost a decade after the first biosimilar approval in Europe. Zarixio (US) and Zarzio (Europe) is the Biosimilar drug product to the reference drug product Neupogen originally licensed in 1991 marketed by Amgen. Here is the list of approved biosimilar product by the US FDA (31).

Table 7 USFDA, CDER list of Approved Biosimilar Drugs (data collected on October 22, 2018) (32).

Sr. no.	Year of Approval	No. of Approved Applications	Drug product
1	2019	3	Eticovo, Trazimera, Ontruzant
2	2018	7	Herzuma, Truxima, Udenyca, Hyrimoz, Nivestym, Fulphila, Retacrit
3	2017	5	Ixifi, Ogivri, Mvasi, Cyltezo, Renflexis
4	2016	3	Amjevita, Erelzi, Inflectra
5	2015	1	Zarxio

Table 8 Biologics that already expired or expired soon in the US, that have Biosimilars in the regulatory channel.

Drug Product	Primary US Patent Expiry
Filgrastim	2013
Epoetin alfa	2013
Pegfilgrastim	2015
Adalimumab	2016
Rituximab	2018
Infliximab	2018
Bevacizumab	2019
Trastuzumab	2019
Ranibizumab	2020
Darbepoetin Alfa	2024
Etanercept	2028

India

India has greatest acceptance for Biosimilars than the other drug regulated countries. Indian biopharmaceutical industry is leading the way of biosimilar sector and affecting the economics of health sector in a positive way. The first biosimilar product approved and marketed in India was “Hepatitis B” vaccine in 2000. In recent years, more than 50 biopharmaceutical products have been approved for marketing, with more than half of them being “Biosimilars”. There are about 25 Indian

companies currently working on developing biosimilar products that paved the way to unfold global opportunity (33).

Biosimilar sale around the world

According to IGBA (2018) survey, out of total biosimilar sale around the world, Europe shared about 87 percent as compared to 2 percent in the US., while the biologic sale in the US is 59 percent as compared to 22 percent in Europe as shown in figure-6.

Table 9 ‘Similar biologics’ approved and marketed in India (data collected on 15 February 2018)

Sr. no.	Year of Approval	No. of Approved Applications	Product Name
1	2017	2	Acellbia, Krabeva
2	2016	3	Adfrar, Bevacirel, Cizumab
3	2015	4	Intacept, Maball, Razumab, RituxiRel
4	2014	4	Actorise, Darbatitor, Exemptia, Infimab,
5	2013	10	AbcixiRel, CanMab, Etacept, Filgrastim, Folisurge, MabTas, Molgramostim, Peg-filgrastim, Peg-interferon alfa 2b, Rituximab
6	2012	3	Rasburicase, Teriparatide, Teriparatide
7	2011	7	Choriorel, Eporec, Insulin, Peg-grafeel, Relibeta, Repoitin, Zavinex
8	2010	7	Cresp, Emgrast, FostiRel, Pegex, Platelet derived growth factor, Terifrac, Zyrop
9	2009	3	Basalog, Glaritus, Mirel
10	2008	3	Reliferon, Religrast, Relipoietin
11	2007	3	Intalfa, Neupeg, Reditux
12	2006	0	
13	2005	2	EpoFit/Erykine, Shanpoietin,
14	2004	2	Neukine, Shankinase,
15	2003	1	Wosulin
16	2002	1	Shanferon
17	2001	1	Wepox
18	2000	1	Biovac-B

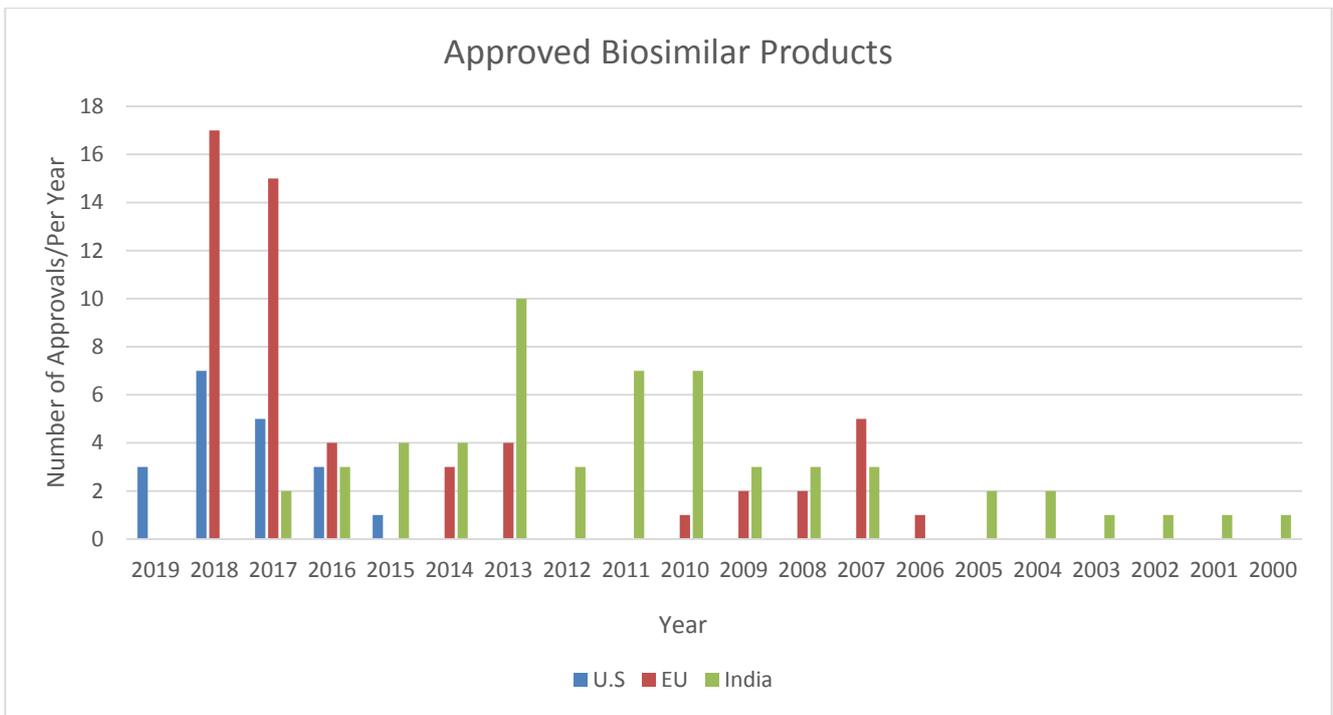
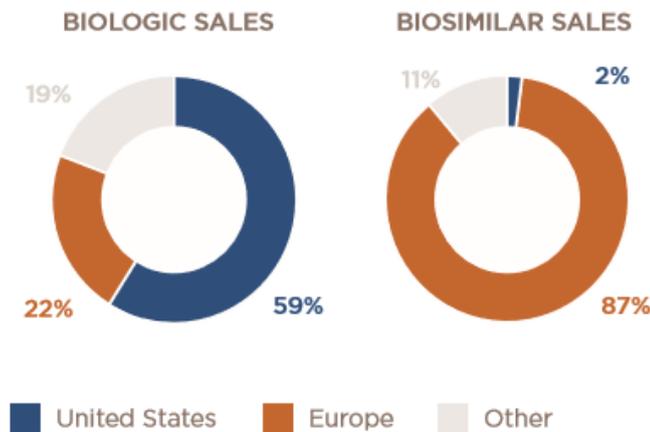


Figure 5. Graphical representation of number of approved biosimilar products in US, EU, INDIA Vs Time (Year)



Source: IGBA.

Figure 6. Sales of biologics and biosimilar in United States and Europe (34)

6. SWOT analysis (35, 36)

Strengths

- Less price and same safety and effectiveness as compared to innovator biologics.
- Less regulatory time required for approval as compared to originator Biologics.
- Less regulatory data required for safety and efficacy than originator products.
- Less expenditure and high profit return than the originator product. High consumer demand for discounted high-quality treatment, due to increased healthcare cost.

Weakness

- Lack of awareness among physicians and patients.
- Lack of prescribing biosimilar prescriptions by physicians.
- Biosimilars drug products have relatively high price as compared to conventional generic drug products to consumers in emerging market.
- Due to complexity of biosimilars and strict regulatory guidelines for approval, more funding is required.
- Lack of credibility of biosimilars by the regulatory/policy makers.

- Lack of Interchangeability guidelines.

Opportunities

- Emerging markets have favorable environment for biosimilars.
- Fastest growing sector in pharmaceutical industry.
- Due to high funding in research and development, less marketed biosimilar portfolio of different companies is available.
- Continuous growth in non-saturated market.

Threats

- Comprehensive regulatory framework still needs to be defined for future complex biosimilar approvals.
- Pharmaceutical companies require more focused on new investments for future development.
- Regulated market such as US, have limited biosimilar approval, thus affecting the preference of this sector by pharmaceutical companies.
- More number of patent infringement cases

7. Summary

Biosimilars are the generic version of biologic products and an important component in reducing health care costs and hence more access of lifesaving medications to subjects and patients. Treating the patient with the increased need of the biosimilar therapy who are economically left behind, preserve the individual autonomy for the right to get the medication/ treatment (37).

Globally we are facing the pandemic of non-communicable diseases and biologics have emerged as a lifesaving drugs to the chronic illness like diabetes and cancer. This unmet demand can be fulfilled through high quality, safer and more cost effective Biosimilars.

With the growing media attention for the increased pharmaceutical drug costs for biosimilar drug products, pharmaceutical companies are set to invest heavily in biosimilar market. Biosimilar drugs are proving to be the blockbuster drugs for the companies and are earning great revenue from biosimilar sector. However Indian biosimilar market is well established and regulated than the other regulated countries such as US and Europe. To date, Europe is much ahead than US in having more biosimilar drug options. The global sales of top ten biologic drug products are \$71billion in 2017 approximately.

With the development of Biosimilars sector, substantial growth is witnessed. Every year, number of approvals is granted by regulatory agencies for similar biologics. India is successful in establishing itself as a global player for biosimilar products. India has a much potential and huge market for biosimilars despite of

enormous challenges. To maintain the tag of a global leader; Indian biopharmaceutical companies require continuous advancement in their technology and to improve manpower skill. For this, biopharmaceutical companies require favorable environment from the government and regulatory agencies. According to Deloitte survey in India, physicians prefer to prescribe the drug as a first line therapy if is discounted at a 60 to 70 percent. This provides great opportunity to develop biosimilars committed to provide same safety and efficacy as that of biologics (38).

Stakeholders and other manufacturers from developed markets such as US, EU and Japan are also concentrating on biosimilar development. Currently there are 29 biosimilars molecules in development phase in Europe, 19 in US and 7 in Japan. Government is also directing the sponsor for the market authorization of Biosimilar products in case of confusion (39).

Developed markets have more growth opportunities for Biosimilars as they rationalize their health expenditure, encourage more safe, high quality, affordable medicines.

8. Conclusion

For approval of market authorization of biosimilar product in different countries, different regulatory agencies provide abbreviated approval pathway to ease in approval procedure. Demonstration of similarity to reference product is mandatory for market authorization of biosimilar product involving step-wise approach and totality of data which requires the generation of comparative analytical, non-clinical, preclinical and clinical data. The standard generic approach for demonstrating similarity using different comparability exercise such as bioavailability/bioequivalence study with a reference biologic product which applies to most of the biopharmaceutical products is not appropriate with respect to Biosimilars due to their complexity. The scientific data required for the approval of biosimilar drug product is more than that for generic small molecule drug product and less than that for reference biological product (40).

Demonstration of similarity, analytical tests and non-clinical data both in-vitro and in-vivo requirement are same across countries. Whereas in global clinical trials, Local subject participation is must. By the consent of regulatory authority, local Phase I studies may be waived off in some countries like India and Brazil. So, Phase III trial should be global and multi-centric. Though after the marketing approval of biosimilar product, post-marketing surveillance plan is obligatory for safety and immunogenicity adverse events. There are no guidelines for interchangeability of Biosimilars across most of the geographies.

The selected reference biologic product must be registered in the country where the applicant submitted the application for approval. However, selected reference biologic product registered in other country may be used with bridging data after justification by the applicant. Clinical trials can be done at any time before the patent expiry. But the application is made after the expiry of regulatory and data exclusivity (41).

Acknowledgements

I would like to express my gratitude to International Journal of Drug Regulatory Affairs (IJRA) who gave me the opportunity to publish the article.

Financial Disclosure statement: The authors received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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