International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Current Status: Regulatory Oversight of Biosimilars in India, United States of America and Europe

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Abstract: ***Background: A similar biologic product, also known as a biosimilar or follow - on biologic, is very similar to the reference product in terms of quality, safety, and efficacy. These pharmaceuticals are used both as primary treatments and as stand - ins for primary treatments for numerous chronic conditions. Each country has created its own rules for development and approval, and some nations are embracing WHO recommendations. The relevant bodies engaged in the approval procedure in India include the Institutional Bio - Safety Committee (IBSC), Review Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), and CDSCO. The legal basis of Directive 2001/83/EC's Article 10 (4) in the EU specifies the criteria for Marketing Authorization Applications (MAAs) based on the proof of the similarity between the two biological medical products. Biotech products may be licenced under the US Biologics Price Competition and Innovation Act of 2009 (BPCIA). This article provides a table - formatted review of the regulatory frameworks in India, the USA, and the EU. Objectives: The objective of this topic is to compare the regulatory oversight of biosimilars in India, USA, and Europe. This comparison intends to highlight significant parallels and discrepancies between each region's approval procedures and post - marketing surveillance policies and regulations for biosimilars. Conclusion: In comparison to India and the USA, Europe leads in the development of biosimilars, with distinctions in definitions, guidelines, reference product selection, and data requirements. Although there are similarities, regulatory standards must be unified for global clearance of biosimilars.***

Keywords: Biosimilar, CDSCO, US FDA, EMA, Litigation, Regulation, Comparability

1. Introduction

A biological medicine is one whose main component is a living organism or a living organism by product. E. g., A living entity, such as a bacterium or yeast, that has received the gene allowing it to generate insulin, produces insulin. A biological medicine that has already received approval (the "biological reference medicine") is comparable to a biosimilar drug. A biosimilar drug's active component is comparable to that of the biological reference drug. In general, the same dosage of both biosimilar and biological reference medications is used to treat the same illness. The decision of whether to treat a patient with a reference or a biosimilar medicine should be made in accordance with the opinion of a qualified healthcare practitioner given that biosimilar and biological reference are similar but not identical. According to the criteria provided above, the following three factors determine what a biosimilar product is:

It must meet the following requirements:

a) It must be a biologic product;
b) The reference product must be an already - licensed biologic product; and
c) It must demonstrate a high degree of similarity in terms of safety, quality, and efficacy.

Additionally, it is widely accepted that the comparability should be verified applying a series of all - inclusive procedures at the clinical, non - clinical, and quality levels. Products cannot be referred to as biosimilars if they are not approved through this regulatory procedure for comparability [1 - 3].

2. Overview of Regulatory Framework for Biosimilars in India

The Similar Biologics Guideline was published in 2012 by the Department of Biotechnology and the Central Drugs Standard Control Organisation (CDSCO). In the Indian context, four committees—the Institutional Bio - safety Committee (IBSC), evaluation Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), and the CDSCO—play a significant role in the evaluation and approval process for biosimilars. The IBSC both monitors on - site biosafety and evaluates applications that might be forwarded to the RCGM. The RCGM approves preclinical data assessment, permits the exchange of genetically altered cell banks for research and development, and authorises the conduct of research and development. All applications involving living or genetically modified organisms in the finished therapeutic product are reviewed and approved by the GEAC. The primary regulatory authority responsible for approving clinical studies is the CDSCO. It consists of Subject Expert Committees (SECs) that examine the clinical trial data and give the CDSCO professional recommendations. Following careful research and analysis, the CDSCO grants marketing permission [1, 4 - 14].

3. Overview of Regulatory Framework for Biosimilars in USA

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) established the legislative framework for the licencing of biosimilars in the United States. The BPCI Act altered the Public Health Service Act (PHS Act) to create a speedier approval procedure for biological products

[15]. All FDA - approved organic products, including reference products and biosimilar products, have undergone extensive inspection, giving patients confidence in their efficacy, safety and quality. A proposed biosimilar product is compared to a reference product, the only biological product that has already gained FDA clearance [16]. It is approved by the submission of an "independent" application that must contain all the information needed to demonstrate the safety and effectiveness of the reference product. Clinical evidence for the disease indications sought by the manufacturer is typically included in the data and information needed to prove the safety and effectiveness of a reference product [17]. In terms of safety, purity and potency (safety and efficacy), a biosimilar is essentially comparable to an existing reference medicine that has received FDA approval. It also has no clinically significant differences. A biosimilar development programme aims to demonstrate the bio - similarity between the proposed biosimilar product and the reference product rather than independently proving the safety and efficacy of the proposed product [18]. The Law on Innovation and Competition on Biological Prices has been amended to include Section 351 (k) of the Public Health Services Act (PHS), which establishes an approval procedure for biosimilars, provides exclusion periods and establishes interchangeability norms [19]. According to Section 351 (k) of the PHSA, an organisation that wishes to market a biosimilar product in the US must first submit an application to the FDA that includes data from analytical studies, animal studies (toxicity tests), and studies or clinical studies (tests on human subjects) [20]. The agency has the right to determine whether a certain study is required for a biosimilar application or not. The secretary may also opt out of any requirement if they deem it insignificant, according to the legislation. The biosimilars law also establishes a 12 - year exclusivity period for the reference product (the original organic product) during which it cannot be approved as a biosimilar and a four - year exclusive period for the reference product during which no biosimilar can submit an application. As per section 351 (k) of the Biologics Price Competition and Innovation Act, the applicant may request interchangeability status either at the time the application is filed for approval or at a later time [21]. In the event that a biosimilar is "interchangeable," a chemist may use a prescription for the reference product in place of the biosimilar without a doctor's approval. The BPCIA distinguishes between the approval standards for figuring out exchange capacity and figuring out bio - similarity, with the latter requiring stricter guidelines to qualify as interchangeable. When the following conditions are satisfied, the BPCIA permits the FDA to designate a product as interchangeable:

- The proposed biosimilar can be anticipated to achieve the same clinical outcome as the reference product in a specific patient; the proposed product is biosimilar in comparison to the reference product.
- Using the reference product repeatedly without modification is just as safe and effective for patients as switching between the proposed biosimilar product and the reference product [2, 4 - 10].

4. Overview of Regulatory Framework for Biosimilars in Europe

The European Medicines Agency (EMA), also known as Similar Biologics Medicinal Products, was the first organization to create a regulatory process for approving biosimilars in October 2005 [22]. The legal framework in the EU offers a centralized marketing authorization mechanism, as well as decentralized, mutual recognition, and national marketing authorization procedures [23]. These marketing authorization processes are a representation of the various stages of evolution in the EU regulatory framework. The centralized process is used to license nearly all novel pharmaceuticals [24]. According to EU law, all currently marketed biosimilars are biotechnologically produced proteins that must go through the centralized procedure supervised by the EMA. As a result of the centralized procedure, a single marketing permission is granted, and it is valid across the EU. Biosimilars are approved based on a comparability exercise with the "Reference Biologic" product specific data requirements, which are more in - depth than those for generic drugs in terms of clinical data, preclinical data and analytical data [25]. This is done with a thorough physicochemical and biological characterization towards pharmacokinetics, pharmacodynamics, and clinical evaluation. When comparing the prerequisites for innovator biological products and generic (low molecular weight) biological products to those for biosimilars authorization, the differences will be that while the data for generic biological products refer to quality, stability, and purity as well as a novel biological medicine, there is an additional post - marketing monitoring and comparability module for biosimilar products, and the clinical and pre - clinical data are condensed [26]. Data on immunogenicity, stability, potency, and entire preclinical and clinical investigations are also accessible in addition to these three elements. Studies on risk management and post - approval pharmacovigilance are required due to the fact that many dangerous side effects take years to become apparent. On a case - by - case basis, EMA permits extrapolation of authorization to additional indications [3, 4 - 10].

5. Regulations and guidelines comparison between India, United Stated of America and Europe

The current study focuses on the laws and policies surrounding biosimilars in India, the USA and Europe. Biosimilars are safe and effective treatment options for many disorders, including arthritis, kidney issues, cancer, chronic bowel and skin conditions (including psoriasis, irritable bowel syndrome, Crohn's disease, and colitis) [27]. Biosimilars might increase access to life - saving medications at a lower price. Biosimilar manufacturers frequently encounter processing and packaging challenges because to the variety of large molecules and the need to provide the nation's regulatory body with acceptable evidence of clinical safety [28]. To detect recently implemented modifications in rules or newly issued regulations compliance with the regulatory bodies, a complete analysis of regulations and guidelines for biosimilar products in India, the USA and Europe was

conducted. It is important to understand how India, the USA and Europe differ from each other in terms of their biosimilar legislation, regulations, and data needs. Certain parallels and differences were found when biosimilars' parameters were compared [1 - 3]. Regulations and guidelines comparison between India, United Stated of America and Europe are presented in various key points which are given in **Table 1**.

Table 1: Regulations and guidelines comparison between India, United Stated of America and Europe

Parameters	India	USA	Europe
Pre - litigation procedure	Absent	Present	Absent
Terms Used for Biosimilar	Similar biologics [29].	Biosimilars [30].	Biosimilars medicines [30].
Definition	According to comparability, a similar biologic product is one that meets standards for effectiveness, safety, quality and equivalent to an authorised reference biological product [31].	The biologics that came after the first innovator biologics are duplicates of those. Their exact structure cannot be duplicated, which could result in variations in efficacy and safety. Therefore, laws governing biologics are intricate [32].	A biosimilar is a biological medicine that is strikingly similar to another biological medicine that has already received authorization from the European Union and is known as the "reference medicine" [33].
Authorities involved	1. Central Drugs Standard Control Organization (CDSCO) 2. Institutional Bio - Safety Committee (IBSC) 3. Review Committee on Genetic Manipulation (RCGM) 4. Genetic Engineering Appraisal Committee (GEAC) [34].	1. US FDA 2. CBER 3. CDER [35]	1. EMA 2. Committee for Medicinal Products for Human Use (CHMP) [36].
Data Requirement	Studies on biological activity, clinical research, preclinical research and immunogenicity [37 - 43].	Analytical evidence that is comparable to the source, animal studies, clinical research and the identification of the mechanism of action [4, 10, 42, 43].	Clinical investigations, preclinical research, biological activity, purity, physiochemical characteristics and studies on immunogenicity [3 - 10, 42 - 45].
Guidance	Published guidance under CDSCO [1, 4 - 10].	Published guidance under 351 (k) [4 - 10, 42, 43, 46]	Published guidance under CHMP/437/04., EMEA/CHMP/BWP/49348/2005. and EMEA/CHMP/BMWP/403 [3 - 10, 42 - 45].
Naming	If a brand name is not known, the active substance name should come after the INN of the biologics [10].	A hyphen separates the core name from the INN of the reference product, which is then followed by a distinguishing four - letter suffix that has no meaning (such as trastuzumab - dkst or adalimumab - atto) [10].	INN is the same for comparable biosimilars; nevertheless, trade name and batch number are distinguished at all levels, particularly in the case of ADRs [10].
Data exclusivity	India provides for no market exclusivity period beyond patent rights [1, 4 - 10].	A section (262k) application may not be filed until 4 years following the approval of the reference product. Twelve years after the approval of the reference product may pass before a biosimilar is approved [4 - 10].	11 Years, including a 1 - year extension for a new indication and 10 years for new biologics (8 years of data exclusivity and 2 years of market exclusivity) [4 - 10].
Laws and Regulation	The Drugs and Cosmetics Act of 1940, the Drugs and Cosmetics Rule of 1945, the New Drugs and Clinical Trials Rule of 1949 and the 1989 Rule for the manufacture, import, export, use and storage of hazardous microorganisms/ genetically modified organisms or cells (Rule 1989) notified under the environment protection act of 1986, Guidelines on similar biologics "2012" by CDSCO and DBT, Recombinant DNS safety Guidelines 2017, CDSCO Guidance for industry 2008. Guidance for GDP for biological product, Guidance on Pharmacovigilance for Biological and biosimilar product [1, 4 - 10, 47, 48].	The Patient Protection and Affordable Care Act of 2010, The Biologics Price Competition and Innovation Act of 2009 - a component of PPACA, Guidance for Industry: scientific considerations in demonstrating bio - similarity to a reference product, Guidance for industry: quality considerations in demonstrating bio - similarity to a reference protein product, Guidance for industry: biosimilars – questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009, Guidance on Considerations in Demonstrating Interchangeability with a Reference Product (2019), Guidance for Industry: Labelling for Biosimilar Products (July 2018) [2, 4 - 10, 49, 50].	Directive 2001/83/EC, as amended, Guideline on similar biological medicinal products. Issued October 2005 (CHMP/437/04 Rev 1), Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/ 2012), Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non - clinical and clinical issues (EMEA/CHMP/BMWP/4283 2/2005 Rev1), Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/1432 7/2006 Rev 1), Other product - specific guidelines are available from the EMA website at; www.ema. eu [3, 4 - 10, 47, 51].

Stability Requirement	Long Term and Accelerated [4 - 10].	Long Term and Accelerated [4 - 10].	Accelerated and under stress condition [4 - 10].
Jurisdiction	Not Defined [1, 5].	According to 35 U. S. C.271 (e), pre - clinical and clinical research are excluded from infringement [5].	According to Article 10 (6) of Directive 2004/27/EC, conducting the requisite tests or studies for biosimilar authorisation does not constitute a violation [5].
Bio - similarity assessment threshold	• Comparable similarity to an already approved reference biologic. • Sequential approach to biosimilar development – followed • Similarity assessment includes: - - Extensive analytical and quality characterization studies. - Abridged preclinical (animal toxicity) and clinical (Phase I and Phase III) data package. - Foregoing phase III trials if phase I trials established high PK - PD profile. - Foregoing confirmatory safety and efficacy studies based on comparable quality and competent PK - PD data [4 - 10, 42].	• High similarity to the reference product • Minor differences in the clinically inactive components – acceptable • Similarity evaluation includes: - Extensive analytical characterization and very less clinical testing. - Phase 2 trials – not required. - At least 2 randomized CTs are critical –one to compare PK of the RP and PB and the other to demonstrate clinical equivalence. - Assessment of residual uncertainty at each step of data generation – required • Totality - of - the - evidence approach – followed • When assessing manufacturing changes, FDA is empowered under BPCIA to waive preclinical and clinical studies • Post - approval changes in manufacturing process warrant preclinical and clinical re - evaluation [4 - 10, 42 - 44, 46].	• High similarity to another already approved biological medicine in the EU. • Strict controls during manufacturing & production processes. • Minor clinically insignificant differences with the reference medicine –acceptable • Minor variability be kept within strict limits • Step - wise scientifically tailored comparative approach to support demonstration of bio - similarity – followed • Determinants for high similarity demonstration includes analytical/structural characterization, biological activity and efficacy, safety and immunogenicity studies. No regulatory requirement to re - demonstrate bio - similarity once marketing approval is granted [4 - 10, 42 - 45].
Pharmacovigilance	For the first 2 years of a mandated, 4 - year period, periodic safety update reports (PSURs) must be provided every 6 months [1, 4 - 10, 52, 53].	Mandatory [4 - 10, 43, 44].	Mandatory - RMP submission is essential [4 - 10, 54, 55].
Extrapolation	Possible if the same MOA/receptors are used for additional indications [1, 4 - 10].	Acceptable if all ailments covered by the Reference product are covered by the PP's target receptors, MOA and medication pharmacokinetics across patient populations [4 - 10, 42 - 44].	Possible if supported by all the scientific evidence gathered from the analytical, non - clinical and clinical comparability investigation [4 - 10, 42 - 45].
Types of studies that need to be conducted	Analytical Studies, pre - clinical studies and Comparative clinical studies [1, 4 - 10, 56].	Analytical Studies, Animal toxicity studies and at least one comparative clinical study that includes immunogenicity [4 - 10, 42 - 44, 56].	Comparative quality studies, Comparative non clinical studies and Comparative clinical studies. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post - change product are not warranted [4, 10, 42 - 45].
Reference product guideline	Reference biologic should be licensed in India or the ICH countries and should be an innovator product [1, 4 - 10, 48, 57].	The reference product should be a US – licensed reference product. For Non - US licensed comparator products - It is possible to use data from clinical studies and animal experiments to compare a proposed biosimilar product to a non - US - licensed product [4 - 10, 42 - 44, 58].	Must be authorised in the European economic area. If a non - EEA authorised comparator is used, bridge data comparing all 3 products, including analytical studies with clinical and non - clinical data, must be provided [4 - 10, 26, 42 - 44].

6. Conclusion

In terms of creating biosimilars, Europe has been far ahead of other nations like India and the USA. The definitions of bio - similarity, the scale of the guidelines, the selection of the reference product, the data necessary for product approval, and certain other parts of the regulatory requirements for the approval of biosimilar products are similar yet slightly different.

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