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A Comparison of US, Europe, Japan and India Biosimilar Regulation

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Abstract

Biosimilars have emerged as a crucial alternative to reference biologics, offering cost-effective treatment options while maintaining comparable efficacy and safety. Regulatory pathways for biosimilars differ across key global markets, including the United State (US), European Union (EU), India and Japan, reflecting distinct approaches to approval, evaluation, and market entry.

The EU a pioneer in biosimilar regulations, established a well- defined approval framework under the European Medicines Agency (EMA), setting global standards. The US Food and Drug Administration (FDA)follows the Biologics Price Competition and Innovation Act (BPCIA), which provides a structured but rigorous pathway for biosmilar approval. India, an emerging biosmilar hub, has developed guidelines that emphasize comparability studies, balancing affordability with regulatory stringency. Japan, under the Pharmaceutical and Medical Devices Agency (PMDA), follow a case-by-case approach, ensuring biosmilars meet high safety and efficacy standards.

This review article compares and contrasts biosimilar regulations across these regions, analyzing approval processes, interchangeability policies, clinical study requirements, and market dynamics. Understanding these regulatory landscapes is essential for global harmonization efforts, facilitating biosimilar access while ensuring patient safety.

Keywords: Biosimilar, USFDA, Biogenerics, Regulation, Litigation, CDSCO, EU, Japan, Biologics, Reference product

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1. Introduction

Biosimilars are biologic medications that contain an active ingredient produced by a living organism or synthesized from one using regulated gene expression techniques or recombinant DNA. In terms of quality, safety, and efficacy, a biosimilar is a biological medication that is comparable to an already-registered reference biotherapeutic product, but not the same. It is designed to work in the same way for the same illnesses as the original biopharmaceutical medications. These medications may also be referred to as follow-on protein products, biosimilar products, or subsequent-entry biologics.

Biosimilars often have a high molecular complexity and can be highly sensitive to modifications in the starting material, production processes, and control mechanisms. (1)

Biosimilars have emerged as a result of the expiration of patent protection and regulatory data protection for several biotechnological medications. The procedure used to create the original, cutting-edge biotechnology medication is attempted to be replicated by biosimilars. While the term "biosimilars" is used in the European Union, "follow-on biologics" is a far more common term in the United States. The distinction between biosimilars and (bio)generics must be made. Biosimilars are attempts to replicate already-approved biological medications or protein medications. The end result is not the same, though, because they are produced using a separate cell line and a distinct production and purification procedure. (2)

The creation and manufacturing of generic equivalents for small-molecule medicines is very simple. Biosimilars, on the other hand, are not generic versions of the originator products. The European Medicines Agency (EMEA) embraced this viewpoint, which serves as the foundation for its biosimilar approval procedures. This is due to the fact that a biosimilar's active components differ from those of the original product. Biopharmaceuticals are significantly more complex than small-molecule medicines since they are complex proteins that need diverse manufacturing techniques. The properties of the finished product are closely linked to the manufacturing methods of biopharmaceuticals, in contrast to traditional medications. (3)

Manufacturers of biosimilars will therefore be unable to accurately duplicate any protein product. Furthermore, variations among biopharmaceutical products may go unnoticed since analytical methods are not yet available to detect or predict all of the biological and clinical characteristics of proteins. Regulations must require strict pharmacovigilance and take into consideration the distinctions between biosimilars and their reference products. Biosimilars, on the other hand, are 100–1000 times bigger than biologics. They contain hundreds of amino acids (with an average molecular weight of 150 per amino acid), which are biochemically connected by peptide bonds to form polypeptides in a certain order. Furthermore, a molecule's complexity and the number of atoms that make up its structure increase with its size.

The immunogenicity of biopharmaceuticals and low molecular weight medications is another significant distinction. Regardless of whether they are fully human homologs or (partially) non-human, almost all therapeutic proteins cause antibodies. By neutralizing endogenous components, they may reduce efficacy or cause serious side effects. Therefore, complicated and frequently costly biologics present significant business hurdles. A few fundamental characteristics that can affect the final product's quality are temperature, pH, agitation, and container type. (4)

1.1 Definition

US: A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency

EU: Biological products which demonstrated its equivalence to an already approved reference product with regards to quality, safety and efficacy

JAPAN: Biological products which demonstrated its equivalence to an already approved reference product with regards to quality, safety and efficacy

INDIA: Biosimilars are defined as officially approved new version of innovator biotherapeutic products for which the patent has expired.

2. Regulatory Framework in United States

The US President signed a bill regulating biosimilars into law on March 23, 2010. Biological goods that are demonstrated to be biosimilar to previously licensed reference products may be licensed under the Biologics Price Competition and Innovation Act of 2009 (BPCIA). As outlined in 42 USC 262(k), BPCI offers a method for the application of follow-on biological products. To guarantee uniformity in its regulatory strategy for follow-on biologics, the FDA has formed three committees for this purpose. The Biosimilar Implementation Committee (BIC), the Center for Biologics Evaluation and Research (CBER), and the CBER Biosimilar Review Committee are the three committees. The cross-center policy concerns pertaining to the BPCI Act's implementation will be the main focus of the CBER. (5)

Three draft guidance documents, titled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," and "Biosimilars," were released by the FDA on February 9, 2012, to help the industry develop follow-on biologic products.

2.1 Requirement for approval of a biosimilar product:

FDA evaluates each proposed biosimilar individually and advises manufacturers on the scope and extent of testing needed to show biosimilarity. (6)

Figure 1. Development of Biosimilar

3. Regulatory Framework in Europe

The European Union (EU) has taken the lead in creating a biosimilar product regulation framework. Formal

evaluation of the scientific problems raised by biosimilar goods was initiated by the European Medicines Agency (EMA) in January 2001. A new category of applications for "similar biological medicinal products" was created in 2003 by the European Commission, which also modified the EU secondary legislation's standards for marketing authorization applications for pharmaceuticals. The European Medicines Agency (EMA) released a general guideline on comparable biological medicines in 2005. (7)

EMA produced a concept paper in 2011 regarding the reform of the guideline on comparable biological medical products. The European Medicines Agency (EMA) requires that a biosimilar product have the same active ingredient, pharmaceutical form, strength, and route of administration as the reference product. The EMA also requires thorough and justified comparability studies between the biosimilar and the reference products at the quality, nonclinical, and clinical levels. These requirements are detailed in the EMA guidelines. (8)

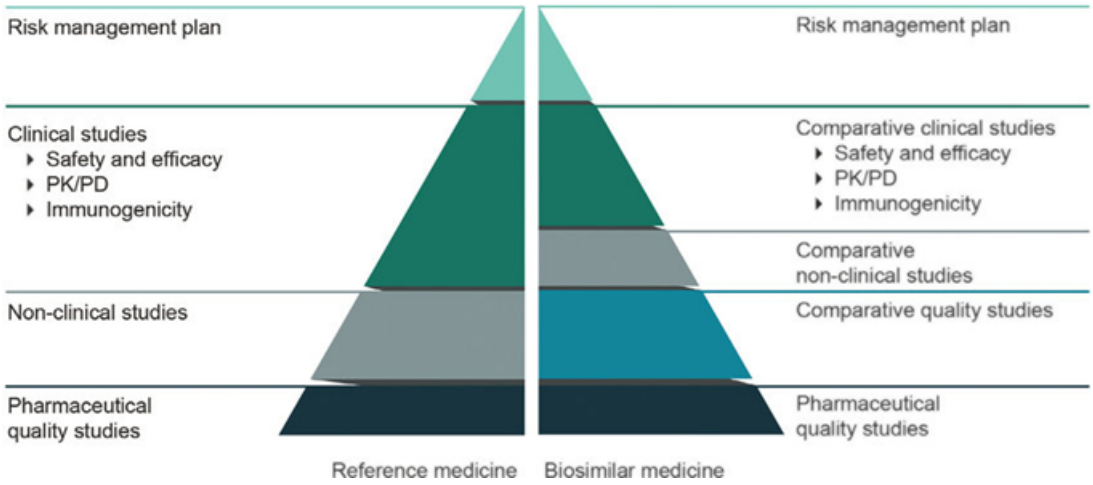

Figure 2. Comparison of Data requirement for approval of Biosimilar versus and Reference medicine as per EU

4. Regulatory Framework in Japan

The regulation of biosimilar or follow-on biologic products has also presented a new issue to the Japanese Ministry of Health, Labor, and Welfare (MHLW). Japanese guidelines for the quality, safety, and effectiveness of biosimilar products were issued in 2009, and they were based on the EMA's similarity concept. (9)

The recommendation covers recombinant plasma proteins, recombinant vaccines, PEGylated recombinant proteins, and highly purified and defined non-recombinant proteins. In contrast to the EU, the guideline does not include polyglycans such low-molecular weight heparin. Synthetic peptides are another product type that is not included. Two follow-on biologics, "Somatropin" and "Epoetin alfa BS," have recently received approval in Japan in accordance with this guideline. (10)

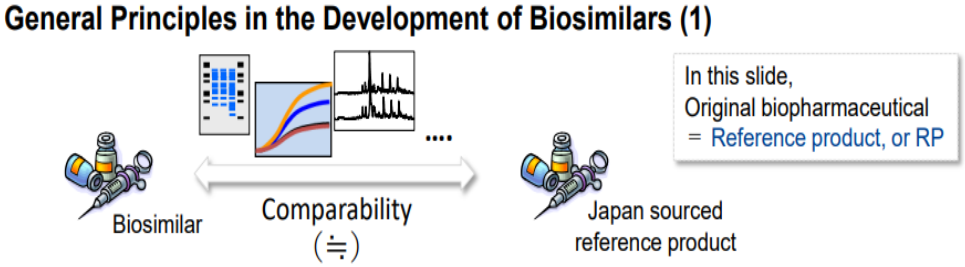

Figure 3. Development of Biosimilar in Japan

5. Regulatory Framework in India

When it comes to biosimilars, the Central Drugs Standard Control Organization (CDSCO) is the highest regulatory authority under the Government of India (GoI). The approval process for comparable products (SBPs), often known as biosimilars, involves two additional competent agencies.

5.1 Review Committee on Genetic Manipulation Biologics (RCGM):

The Ministry of Science and Technology's Department of Biotechnology (DBT) oversees the Review Committee on Genetic Manipulation Biologics (RCGM). According to the DBT standards, RCGM controls import, export, research, preclinical authorization, clinical trial (CT) no objection certificates, and other associated operations involving genetically modified organisms (GMOs).

5.2 Genetic Engineering Approval Committee (GEAC)

The Department of Environment (DoE) oversees the Genetic Engineering Approval Committee (GEAC), a statutory body that reviews and approves large-scale applications of genetically modified organisms and their products in field applications, industrial production, research and development, and environmental release. The proposed CDSCO guideline covers pre-market

regulatory requirements, such as comparability exercises for quality, non-clinical and clinical investigations, and post-market regulatory requirements for biosimilars, as well as standards pertaining to the manufacturing process and quality elements. (11)

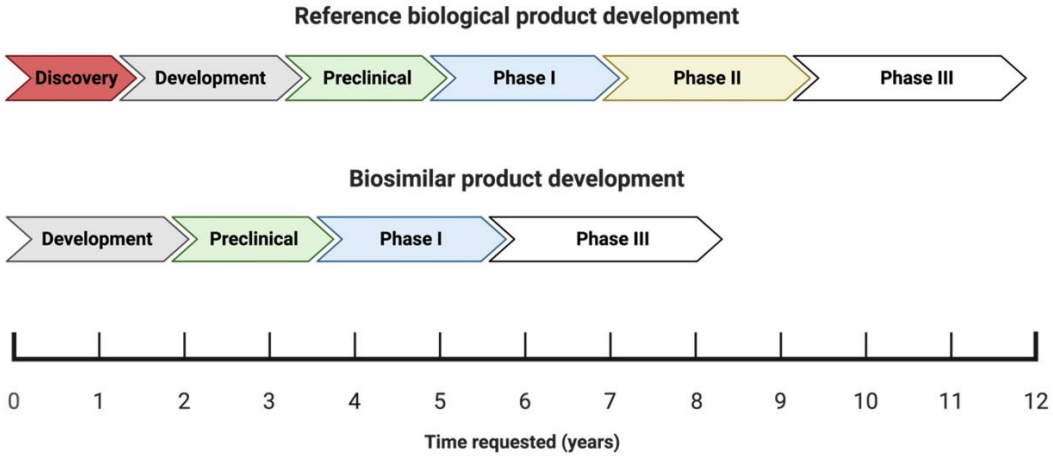

Figure 4. Schematic illustration of the development phases and the timeline (in years) of reference biologics versus biosimilars

Table 1. Comparation Parameters of US, Europe, Japan and India

Parameters	US	Europe	Japan	India
Regulatory Authority	U.S. Food and Drug Administration (FDA	European Medicines Agency (EMA)	Pharmaceuticals and Medical Devices Agency (PMDA)	Central Drugs Standard Control Organization (CDSCO)
Term	Follow-on biologics	Biosimilars	Follow-on Biologics	Similar Biologics products
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 with regards to quality, safety and efficacy	A biosimilar product is a biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived innovator product.	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 (BPCI)	Committee for medicinal products for human use (CHMP) of the EMA	Ministry for Health Labor and Welfare (MHLW)	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 Japan	Authorized in India
Data Exclusivity	12 Years, A section (k) application may not be filed until 4years after reference product approval	11 Years, comprising 10 years for new biologics (8-year data exclusivity and 2-year market exclusivity) and a 1-year extension for a new indication	Not Specified	Not Specified

Approval Pathway	351(k) Biologics License Application (BLA) pathway	Centralized procedure through EMA (for all member states	New Drug Application (NDA) with biosimilar specific data	Biologic License Application (BLA)
Pre-litigation procedure	Present	Absent	Absent	Absent
Jurisdiction	Pre-clinical and clinical investigation is exempt from infringement under 35 U.S.C 271(e)(1)	Conducting necessary trials or studies for biosimilar approval is not infringement under Article 10(6) of Directive 2004/27/EC.	Not Defined	Not Defined
Interchangeability	Present	Absent	Absent	Absent
Data requirement	Analytic data that show similar to the reference, animal studies, identity of mechanism of action	Purity, Physiochemical properties, Biological activity, Clinical studies, Preclinical, and Immunogenicity studies	Clinical studies, Preclinical, and Immunogenicity studies	Biological activity, Clinical studies, Preclinical and Immunogenicity studies
Reference Product	Must be FDA-approved for at least 12 years	Must be authorized in the EU for at least 10 years	Must be approved in Japan or another recognized market	Must be approved in India or another recognized market
Guidance	Published guidance under 262(k)(8)	Published guidance under GHMP/437/04., EMEA/CHMP/BWP/49348/2005, and EMEA/CHMP/BMWP/4035	Published guidance under MHLW	Published guidance under CDSCO
Stability Requirement	Long Term and Accelerated	Accelerated and under stress condition	Not Necessary	Long Term and Accelerated

6. Conclusion

Biosimilars play a crucial role in improving patient access to biologic therapies while reducing healthcare costs. The regulatory pathways for biosimilar approval vary across regions, with the European Union (EU) being a pioneer in establishing a comprehensive framework. The United States (US) has developed a structured yet evolving approach under the Biologics price Competition and Innovation Act (BPCIA), while India and Japan have their own distinct regulatory requirements tailored to their respective healthcare systems.

Despite differences in guidelines, all regulatory agencies emphasize rigorous comparability studies, quality assurance and post-market surveillance to ensure biosimilar safety and efficacy. Harmonization of global biosimilar regulations could further streamline approvals and enhance accessibility worldwide. As the biosimilar market continues to expand, regulatory frameworks will likely evolve to accommodate scientific advancements and emerging therapeutic needs.

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Conflict of Interest

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

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