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BIOLOGICS AND BIOSIMILARS: REGULATORY AND THERAPEUTIC PERSPECTIVES

[*1]Dilkash Mehboob, [1]Bablu, [1]Suraj Kumar, [1]Dr. Nakul Gupta, [2]Anamika Kulshrestha

[1]Director, IIMT College Of Pharmacy, Greater Noida.

[2]Associate Professor, IIMT College Of Pharmacy, Greater Noida.

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***Corresponding Author: Dilkash Mehboob**
Director, IIMT College Of Pharmacy, Greater Noida

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ABSTRACT

Biologics have transformed modern medicine by offering targeted therapies for complex diseases such as cancer, autoimmune disorders, and genetic conditions. However, their high cost has limited accessibility. Biosimilars, which are highly similar versions of approved biologics, provide a cost-effective alternative while maintaining comparable safety and efficacy. This article explores the regulatory framework governing biologics and biosimilars, along with their therapeutic significance and challenges.

Regulatory frameworks for biosimilars emphasize a stepwise, evidence-based comparability approach prioritizing robust analytical characterization, supplemented by non-clinical and clinical data as warranted. In the United States, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 established the 351(k) abbreviated licensure pathway, requiring demonstration of "highly similar" attributes to a reference product. The FDA has approved over 80 biosimilars to date, with recent draft guidance (2025) streamlining development by reducing the routine need for comparative efficacy studies when supported by strong analytical and pharmacokinetic/pharmacodynamic evidence, alongside efforts to refine interchangeability designations to facilitate substitution. Europe, through the EMA, has led globally since 2006 with numerous approvals and high market uptake, recently reflecting similar trends toward waiving certain Phase III trials under robust similarity data.

Therapeutically, approved biosimilars exhibit equivalent efficacy, safety profiles (including immunogenicity), and switching outcomes compared to originators, as evidenced by extensive real-world data, particularly from Europe and emerging US experience. They deliver substantial cost savings—often 20–40% lower pricing—while increasing treatment access for chronic conditions.

This review synthesizes current regulatory perspectives, highlighting evolving global harmonization, recent streamlining initiatives, and therapeutic equivalence supported by scientific and clinical evidence. Biosimilars represent a mature paradigm shift balancing biologic innovation with affordability, poised to further reshape healthcare delivery in oncology, rheumatology, gastroenterology, and beyond as patent expirations accelerate competition.

1. INTRODUCTION

Biologics are complex medicines derived from living organisms, including proteins, monoclonal antibodies, and vaccines. Unlike conventional small-molecule drugs, biologics are produced using biotechnology and are highly sensitive to manufacturing conditions.

With the expiration of patents for many biologics, biosimilars have emerged as an important category in the pharmaceutical industry. Regulatory agencies such as the World Health Organization and the U.S. Food and Drug Administration have established guidelines to ensure their quality, safety, and efficacy.

Key characteristics of biologics include structural complexity, post-translational modifications (e.g., glycosylation, phosphorylation), and inherent batch-to-batch variability due to living production systems. These factors make exact replication impossible, distinguishing them from chemically synthesized small-molecule drugs.

Biosimilars are biological products that are highly similar to an FDA-, EMA-, or other regulatory-approved reference (originator) biologic. They must demonstrate no clinically meaningful differences in safety, purity, potency, or efficacy through a rigorous **totality-of-evidence** approach. Minor differences in clinically inactive components are permitted.

Unlike generics (which require only bioequivalence), biosimilars undergo extensive analytical, non-clinical, and tailored clinical comparability exercises. Their primary goals are to increase competition, enhance patient access, and generate substantial healthcare cost savings—often 20–60% lower than reference products—without compromising therapeutic outcomes.

Global uptake of biosimilars has accelerated, driven by patent expirations on major biologics (e.g., adalimumab, trastuzumab, rituximab) and supportive policies.

BIOSIMILARS

The term “biosimilar” is a regulatory definition that refers to a biologic product that is developed to be highly similar to, and treat the same conditions as, an existing licensed or

approved biologic product. A biosimilar, as defined by the WHO, is a "biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product," in which similarity is defined as the "absence of a relevant difference in the parameter of interest". Biosimilars are highly similar versions of marketed biologic medicines and are supported by appropriate analytical and immunogenicity testing and non-clinical and clinical trials to demonstrate that they are sufficiently "similar" in quality, efficacy, and safety to their reference (originator) biologics. Unlike conventional medicines, also called "small molecules," biologic drugs are large, structurally complex molecules. Because they are biologics, biosimilars should not be viewed as generic medicines, and unlike small-molecule generics, they cannot be manufactured to be identical to the originator biologic. Manufacturing of biosimilars is generally more complex than manufacturing generics. In addition, the regulatory process for biosimilar approval is very different from the approval process for small-molecule generic medicines, and it is precisely the regulatory process that defines these categories. Although both biosimilars and generics require pharmacokinetic bioequivalence studies, biosimilars must demonstrate high similarity to the originator product, whereas small-molecule generics must show proof of quality (i.e., identical chemical structure).

Non-comparable biotherapeutic products (intended copies)

Prior to the implementation of science-based regulatory pathways for the approval of biosimilars, copies of originator biologic products were introduced in some countries. The basis for approval of these copies has not been clear as they lack comparative studies to an appropriate reference product. Most, if not all of these products, can be considered as non-comparable biotherapeutic products, or intended copies (sometimes referred to as biomimics. Intended copies of biologics can be defined as copies of already licensed biologic products that have not met the requirements of the WHO, EMA, or FDA to establish biosimilarity. In other words, intended copies are products for which the manufacturer intended to make a copy but did not follow a comparative development pathway with the reference medicine. Their similarity exercises may be incomplete, analytical evidence may be insufficient, or they may either lack clinical trials or were studied only in limited or methodologically inadequate clinical trials. Often, intended copy products are developed independently and are not directly compared against a licensed biologic product, and they may or may not be compared clinically. Thus, the data available to assess intended copies do not provide adequate comparable efficacy and safety to the licensed product. These products may have clinically

significant differences in formulation, dosages, efficacy, or safety from what is required for a biosimilar. There is no clear evidence that intended copies have efficacy and safety similar to the originator biologic or a biosimilar owing to the absence of rigorous clinical testing.

It is important that rheumatologists distinguish between intended copies and biosimilars. In some countries without biosimilar regulations or with non-stringent regulatory environments, intended copies are being approved as generic drugs, which allows pharmaceutical manufacturers to make and sell copies of the reference drug without establishing proper biosimilarity between these products and the reference products. Furthermore, in some countries with less stringent regulation, copies of biologics have been marketed without clinical trials or based on studies that were limited in scope, size, or scientific rigor. For example, intended copies of etanercept are marketed in several countries, including China, India, Colombia, and Mexico. Additionally, an intended copy of rituximab is manufactured in India and marketed in India and several Latin American countries despite the apparent lack of a comparative clinical trial with the originator biologic in patients with RMDs. Because data are lacking to establish that these products are highly similar to the originator biologic, they cannot be considered to be biosimilars . Compounding this problem is the challenge of finding detailed study methods and results for these copies in the public domain (e.g., clinical trial registries, published congress abstracts, and indexed publications) that would permit independent evaluation of products. This is in sharp contrast to the monoclonal antibody CT-P13 (Remsima™/Inflectra™), approved by EMA and under review by the FDA as a biosimilar to reference infliximab (Remicade®). In analytical studies, CT-P13 demonstrated an identical amino acid sequence as the originator infliximab, production on the same type of cell line, comparable pharmacodynamics, including binding activity to human tumor necrosis factor alpha (TNFα), and cytotoxic activities against a cell line expressing transmembrane human TNFα . This detailed in vitro characterization was followed by clinical evaluations that demonstrated comparable efficacy, safety, and immunogenicity to originator, infliximab. Although in Europe these findings were not part of the product label, the study methods and results were made available through European public assessment reports (EPAR) and peer-reviewed publications.

Scientific and Manufacturing Foundations

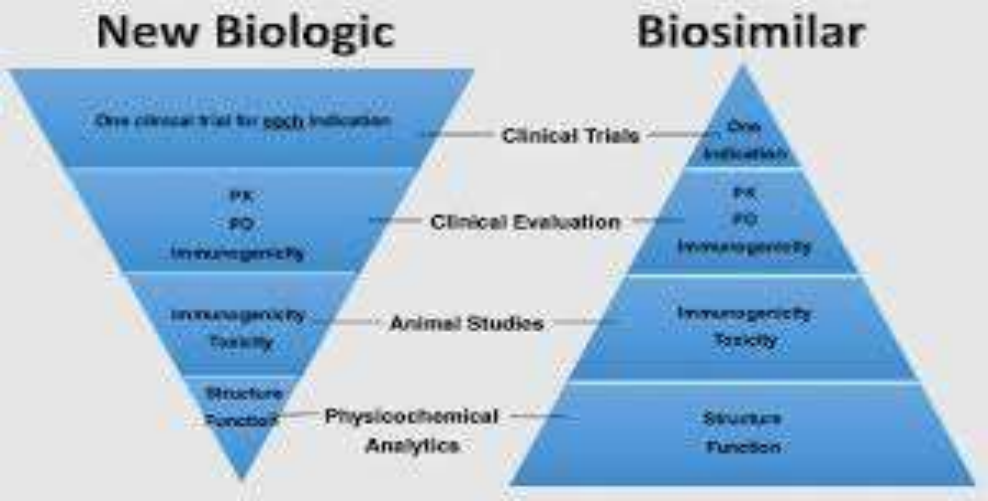
Biologics and biosimilars are manufactured via complex upstream (cell line development, fermentation) and downstream (purification, formulation) processes. Critical quality attributes (CQAs) include primary/secondary/tertiary structure, glycosylation patterns, charge

variants, aggregates, and impurities, all of which can influence pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and clinical performance.

Stepwise comparability exercise (the cornerstone of biosimilar development):

- **Analytical comparability** — Extensive orthogonal testing (mass spectrometry, NMR, capillary electrophoresis, bioassays, etc.) to demonstrate high similarity in structure and function. Modern analytics are now highly sensitive and often more discriminatory than clinical trials.
- **Non-clinical studies** — In vitro functional assays; animal studies are increasingly waived under the 3Rs principle (Replace, Reduce, Refine) when justified.
- **Clinical studies** — Human PK/PD similarity (often the pivotal study); comparative efficacy/safety trials only when residual uncertainty remains; thorough immunogenicity assessment (anti-drug antibodies, neutralizing antibodies).

Recent regulatory shifts emphasize that **comparative analytical assessment (CAA)** combined with PK/PD and immunogenicity data is frequently sufficient, as comparative efficacy studies (CES) have low sensitivity for detecting differences in well-characterized molecules.



2. Understanding Biologics

2.1 Definition and Characteristics

Biologics are therapeutic products derived from living cells and include:

Monoclonal antibodies

Recombinant proteins

Vaccines

Gene therapies

They are characterized by:

High molecular complexity

Sensitivity to environmental conditions

Need for specialized storage and handling

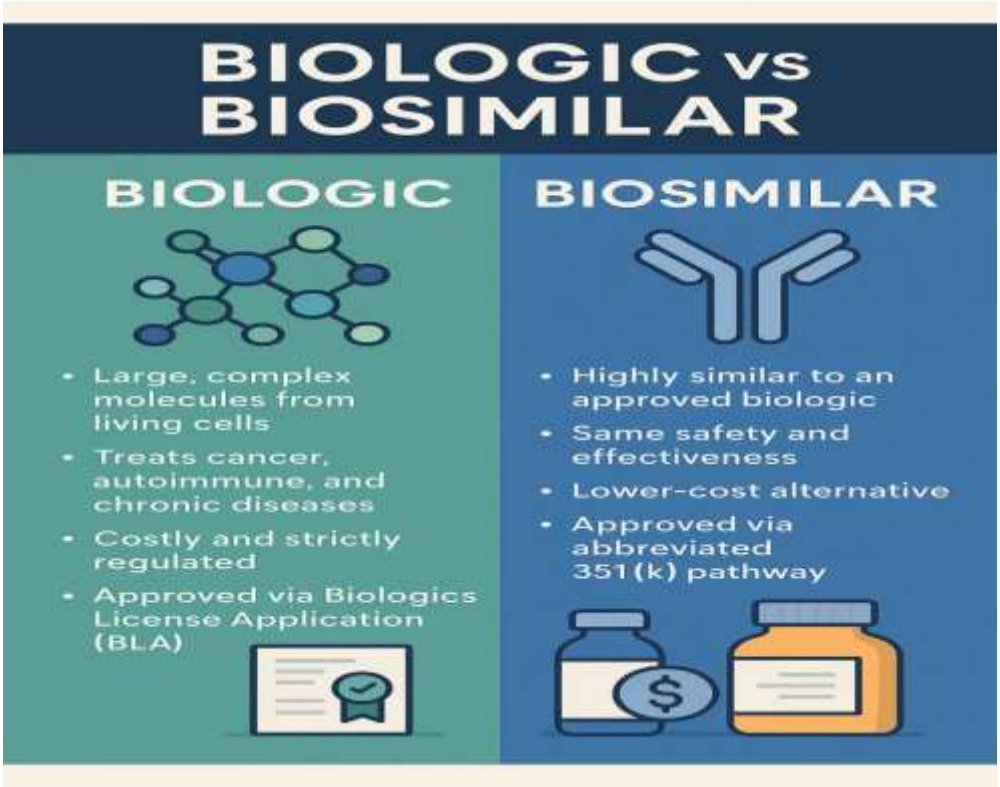
2.2 Examples of Biologics

Some widely used biologics include:

Adalimumab

Trastuzumab

Insulin



3. Biosimilars: Concept and Development

3.1 What are Biosimilars?

Biosimilars are biologic medical products that are highly similar to an already approved reference product. They show no clinically meaningful differences in safety, purity, and potency.

Biosimilars are medications that are *similar to* medicines called biologics. Biologics come from living things, like animal and plant cells, bacteria and yeast. This can make them harder and more costly to produce than synthetic drugs.

Like biologics, biosimilars are made of living things. But they usually cost less. This allows some people to get treatment they wouldn't otherwise be able to access. It may help to think of biologics as name-brand drugs. Think of biosimilars as generic (less expensive) drugs.

But while a generic drug contains the same active ingredients as its brand-name counterpart, biosimilars and biologics aren't an exact match. This means that biosimilar manufacturers have to meet strict Food and Drug Administration (FDA) guidelines for approval.

3.2 Key Differences Between Biologics and Biosimilars

Biologics:-

Biologic medicines contain substances that have been created by using living cells or organisms. Examples of biologic medicines include gene therapies, transplant tissue, recombinant proteins, stem cell therapies, and monoclonal antibodies. They are often used to treat many severe and life-threatening diseases.

Biologics differ from traditional drugs in terms of material sources, structural complexities, manufacturing process, and regulatory requirements.1 As a result, biologics can sometimes have a higher price, which can create barriers to access for some patients.

Biosimilars were created to help increase access to biological therapies and thus help improve patient outcomes.

Manufacturing chemical drugs is a controlled, predictable chemical process, allowing identical copies (generic versions) to be replicated exactly. The manufacturing process for biologics is complex, involving several stages of cell selection, cell culture, purification, formulation, production and validation of the final product.

Every biologic manufacturer uses a unique cell line and a proprietary process. No two production batches of biologics are identical. Originator biologics also have intrinsic natural variability because batches can differ and the manufacturing process can itself change.

During manufacturing, primary amino acid sequences can become modified through glycosylation, changing the shape of a protein because of alterations in the way it folds. These modifications are not controlled by the recombinant DNA inserted into the host cell but are affected by the cell line and the environment in which the cell line is grown.

BIOSIMILARS

Biosimilars are biological medicines that are highly similar to already approved biological medicines, says the European Medical Agency (EMA). Biosimilars are approved according to the same standards of pharmaceutical quality, safety, and efficacy that apply to all biological medicines.

Because biosimilars are made in living organisms there may be some minor differences from the reference medicine. These minor differences are not clinically meaningful – in other words, no differences are expected in safety and efficacy, says the EMA.

The approval process for biosimilars is more streamlined than it is for biologics, as the data submitted only needs to demonstrate its clinical and efficacy equivalence to the reference biologic. Because of this abbreviated approval process, biosimilars may be less expensive than the reference biologic.

The Association for Accessible Medicines confirms that biosimilar competition has lowered costs for both reference products and their biosimilars. Biosimilars alone generated $9.4 billion in savings throughout 2022 and $23.6 billion since 2015. But, much more importantly, in IQVIA's Global Use of Medicines Report for 2023, biosimilars are projected to generate $290 billion in savings around the world through 2027.

4. Regulatory Framework

United States (FDA)

The Biologics Price Competition and Innovation Act (BPCIA, 2010) created the 351(k) abbreviated licensure pathway. A biosimilar must be "highly similar" to the reference product with "no clinically meaningful differences" in safety, purity, and potency, demonstrated via the "totality of evidence."

- **Interchangeability**: An additional designation requiring evidence (often switching studies) that alternating or switching between the biosimilar and reference does not increase risks compared to continuous use of the reference. In 2025, FDA streamlined this, reducing routine switching studies reliance on advanced analytics.
- As of late 2025, the FDA has approved over 70–80 biosimilars, with 19 approvals in 2024 alone. Recent guidance de-emphasizes routine CES for many products.

  The FDA maintains the Purple Book listing licensed biologics with exclusivity and biosimilarity information.

European Union (EMA)

EMA pioneered biosimilar regulation (first approval in 2006: Omnitrope). Guidelines (e.g., CHMP/437/04) require head-to-head comparability in quality, safety, and efficacy. EMA does not centrally designate interchangeability; decisions are left to member states. Recent reflection papers support reduced clinical data burdens where analytical/PK similarity is robust.

EMA has approved more biosimilars over a longer period, with extensive real-world evidence supporting safety.

World Health Organization (WHO) and Global Harmonization

WHO guidelines (2009, updated) assist countries in establishing frameworks, promoting "similar biotherapeutic products." Efforts by ICH aim for greater alignment, but differences persist in clinical requirements, foreign comparator use, and interchangeability policies.

India (CDSCO): India has a mature biosimilars market with guidelines for "similar biologics." It benefits from lower development costs and a skilled workforce but faces challenges in global harmonization and raw material imports. Indian firms are increasingly exporting to regulated markets.

Key differences: FDA often requires U.S.-specific or bridging data; EMA is more flexible with foreign comparators in some cases. Convergence is increasing, particularly on analytical primacy.

5. Therapeutic Perspectives

Multiple meta-analyses and real-world studies show no clinically meaningful differences in efficacy or safety between biosimilars and reference products. Switching studies (single or multiple) demonstrate comparable outcomes in safety (deaths, serious adverse events, discontinuations), immunogenicity (ADA/NAb rates), and effectiveness.

Examples of widely used biosimilars:

- **Trastuzumab** (Herceptin reference): For HER2+ breast cancer; several biosimilars approved.
- **Adalimumab** (Humira): TNF inhibitor for autoimmune diseases; numerous U.S./EU biosimilars launched post-patent expiry, with some designated interchangeable.
- **Infliximab** (Remicade): For IBD, RA; biosimilars like Inflectra, Renflexis.
- **Rituximab** (Rituxan): For lymphoma, RA.
- Others: Filgrastim, pegfilgrastim, bevacizumab, insulin glargine.

Interchangeability enhances pharmacy-level substitution (subject to state laws in the U.S.), but many biosimilars are used successfully without this designation through physician prescribing. Real-world evidence from Europe (nearly 20 years) and U.S. studies supports safe switching in most cases, with no increased immunogenicity or loss of efficacy.

Therapeutic advantages of biosimilars include expanded access for patients who previously could not afford biologics, reduced healthcare system burden, and potential for earlier or broader use in treatment algorithms.

6. Challenges and Opportunities

Challenges:

- **Regulatory**: Divergent requirements across jurisdictions increase costs and complexity; need for global harmonization.
- **Clinical/Scientific**: Demonstrating similarity for highly complex molecules (e.g., mAbs with multiple indications—extrapolation requires justification).
- **Market/Perception**: Physician and patient hesitancy, originator marketing, patent litigation (BPCIA "patent dance"), and reimbursement policies.
- **Manufacturing**: Ensuring consistent quality and supply chain robustness.
- **India-specific**: High reliance on imports for critical materials, evolving regulatory alignment for exports.

Opportunities:

- Cost savings: Billions projected globally; in the U.S., significant reductions in spending on biologics.
- Innovation: Funds reinvested into next-generation "biobetters" or new biologics.
- Access in LMICs: WHO-supported pathways and Indian production capacity.
- 2025–2026 regulatory streamlining (FDA/EMA) is expected to accelerate approvals and lower barriers.

The biosimilar market continues rapid growth as more high-value biologics lose exclusivity.

Manufacturing and Analytical Complexity:

Expression System Variations: Using different cell lines than the innovator can alter post-translational modifications (e.g., glycosylation), impacting product safety and efficacy.

Process Unavailability: Manufacturers cannot access the original, proprietary production process, making precise replication impossible.

Stability and Purity: Achieving consistent, high-purity batches and overcoming physical/chemical instability.

Regulatory and Clinical Hurdles:

Extensive Clinical Trials: Requirement for comparative clinical studies (pharmacokinetics/pharmacodynamics) to show no clinically meaningful differences.

Global Variability: Divergent regulatory guidelines (e.g., FDA vs. EMA vs. BRICS-TM) complicate global development strategies.

Immunogenicity Assessment: Proving that the biosimilar does not cause a higher immune response than the reference product.

Opportunities (2026 onward):

Further cost reductions (up to 50% per program) from waived studies.

Accelerated approvals amid major patent cliffs (> $200 billion biologic sales at risk by 2030).

Expansion into newer modalities (e.g., bispecifics, antibody-drug conjugates).

India’s strengthened role as a global supplier with harmonized guidelines.

Integration of advanced analytics, AI-driven characterization, and real-world evidence in regulatory decisions.

he biosimilar market offers significant opportunities driven by expiring patents on major biological drugs, potentially reducing treatment costs by up to 50%. Major opportunities exist in monoclonal antibodies (mAbs), oncology, and autoimmune treatments, with high growth projected in the U.S. and emerging markets. Increased competition allows for improved patient access, while high technical barriers create a lucrative market with profit margins potentially reaching

Market Growth and Patent Expirations: A significant "patent cliff" for major biologics (e.g., Humira, Keytruda) provides opportunities for manufacturers to gain market share.

Cost Savings and Access: Biosimilars offer 20-30% lower costs than originator biologics, reducing the burden on healthcare systems and increasing patient access to treatments, especially in oncology and chronic diseases.

Emerging Markets and Manufacturing: India is emerging as a key hub for biosimilar manufacturing, with expectations of a strong domestic market growth and global participation, according to insights shared on Remedy Publications.

Strategic Outsourcing and Development: Companies focusing on cost-effective manufacturing, such as upstream and downstream specialists, are in demand, as shown in job listings on Naukri.com.

Specialized Markets: Opportunities exist for "biosimilar orphans" (rare disease drugs) where smaller patient populations may still provide significant market potential.

7. Future Perspectives

The biosimilar market is rapidly expanding, with increasing acceptance among healthcare providers. Advances in biotechnology and regulatory harmonization are expected to enhance global access to life-saving therapies.

The future of biosimilars is poised for rapid growth, driven by an estimated \(\$180\) billion in potential savings from expiring biologic patents between 2023 and 2027. Key trends include expanded adoption in oncology and chronic disease management, increased market share in emerging economies like India, and the introduction of more complex biosimilars as regulatory frameworks harmonize.

- **Massive Market Expansion:** As key biologics face patent expiration, biosimilars are expected to take up to \(50\%\) of the global pharmaceutical market share in the coming years.
- **Cost Savings & Accessibility:** Biosimilars provide 15%–45% cost savings compared to originators, increasing patient access and reducing the financial burden on healthcare systems.
- **Oncology Growth:** A surge in oncology biosimilars is expected, with competition for blockbuster drugs like Keytruda (2028+) projected to reduce treatment costs.
- **India's Role:** India is becoming a global manufacturing hub for similar biologics, with the domestic market expected to grow, providing, according to analysis in this PubMed Central article, a US$240-billion global opportunity.
- **Technological Advancement:** Future developments will focus on reducing manufacturing complexities and addressing immunogenicity to further improve safety.

Challenges remaining for future growth include the need for increased stakeholder education, streamlined regulatory pathways, and fostering trust among healthcare providers.

8. CONCLUSION

Biologics and biosimilars play a crucial role in modern therapeutics. While biologics have revolutionized treatment, biosimilars ensure affordability and accessibility. Strong regulatory frameworks and continuous monitoring are essential to maintain their safety and effectiveness.

With accumulating real-world data confirming equivalence and safe switching, the focus should shift toward education, supportive policies, and global harmonization. For India and other emerging markets, updated guidelines position them to contribute significantly to worldwide supply. Ultimately, widespread biosimilar adoption will alleviate healthcare burdens, improve equity, and sustain investment in next-generation biologics and biobetters.

Biosimilars are not identical to biologics but lie within the variability range of the originator biologic.

Government regulators around the world approve biosimilars based on evidence that biosimilars are not inferior to the originator biologic product in terms of safety and effectiveness.

Systematic reviews of switching from biologics to biosimilars found no meaningful differences in safety and effectiveness between them.

Biosimilars are less expensive than originator biologics.

Biologics represent a cornerstone of modern targeted therapy, while biosimilars provide a sustainable model for expanding access through rigorous science-based regulation. Regulatory agencies like FDA and EMA have refined frameworks—shifting toward analytical and PK-centric approaches—while accumulating evidence confirms therapeutic equivalence and switching safety.

Continued harmonization, education of stakeholders, and supportive policies will maximize benefits. For regions like India, leveraging manufacturing strengths alongside regulatory modernization positions it as a key global player. Ultimately, biosimilars uphold the highest standards of quality while delivering meaningful therapeutic and economic value to patients worldwide.

This review draws on established regulatory guidelines and peer-reviewed evidence up to 2025–2026. Ongoing post-marketing surveillance and real-world data will further strengthen confidence in these products.

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