World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Review Article

BIOSIMILARS AND BIOBETTERS IN INDIA: REGULATORY FRAMEWORK, SCIENTIFIC CHALLENGES, AND IMPLEMENTATION STRATEGIES – A COMPREHENSIVE REVIEW

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Received: 20-07-2025 / Revised Accepted: 21-07-2025 / Published: 23-07-2025

ABSTRACT:
Background: In response to India's increasing need for cutting-edge treatments, biosimilars provide an affordable substitute for pricy original biologics. A regulatory framework for biosimilar approval has been established by the Central Drugs Standard Control Organisation (CDSCO), with a focus on post-marketing safety monitoring, clinical comparability, and analytical similarity. The purpose of this review is to critically examine the scientific, regulatory, and implementation environment surrounding biosimilars and biobetters in India, with a focus on present issues and potential future paths. Methods: With an emphasis on stakeholder perceptions, pharmacovigilance, and regulatory compliance, a narrative synthesis of Indian biosimilar guidelines, scientific development pathways, and practical implementation barriers was carried out. Findings: With a strong regulatory environment and expanding domestic production capacity, India has become a global centre for biosimilars. Nonetheless, there are still issues with post-marketing surveillance, immunogenicity evaluation, and clinical trial design. Although they need specific regulatory pathways, biobetters, as next-generation biologics, represent an emerging innovation space. Enhancing biosimilar adoption and guaranteeing patient safety requires capacity-building, regulatory harmonisation, and stakeholder education. In conclusion, maximising the potential of biosimilars and biobetters in India requires improving pharmacovigilance systems, encouraging local innovation, and fortifying regulatory infrastructure. In line with national health priorities, strategic policy interventions can further enhance therapeutic affordability and accessibility.
Keywords: Analytical similarity, Biosimilars, Biobetters, CDSCO, India, Pharmacovigilance, Regulatory framework.

INTRODUCTION

Biological products have revolutionized the treatment of many chronic and life-threatening diseases, including a variety of cancers, autoimmune diseases, and metabolic disorders in the human body [1]. However, one issue that has limited patients' access to these therapies in almost all situations is that the prices of originator biologics are prohibitively high, especially in low- and middle-income countries (LMICs) [2]. That is why biosimilars came into existence. Biosimilars are highly similar to an already-licensed reference biologic in terms of safety, purity, and potency; they show no clinically meaningful differences from the reference biologic with regard to efficacy or immunogenicity[3].

Biosimilars are not generic products because they are not biologics or equivalent in the sense of complexity. In addition, they are made from living systems, which means their requirements of development include rigorous, stepwise comparability demonstration through analytical, nonclinical, and clinical means [4]. Along with this, the biobetters, otherwise called as biosuperiors, are the next-generation biologics with improvements over existing

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How to Cite this Article: Bhimana Sasidhar, Biosimilars And Biobetters In India: Regulatory Framework, Scientific Challenges, And Implementation Strategies – A Comprehensive Review, World J Pharm Sci 2025; 13(03): 57-75; https://doi.org/10.54037/WJPS.2022.100905

molecules based on their efficacy, safety, stability, or dosing convenience. Whereas biosimilars aim to replicate, the biobetters aim to innovate [5].

The market for biosimilars is growing worldwide with respect to two factors: blockbuster biologics going off-patent and the rising costs of healthcare along with the increasing need for sustainability in treatment options [6]. Recent predictions stated that the global biosimilars market would reach more than USD 75 billion by 2030, primarily because of emerging economies benefiting from favorable demographics and burgeoning burdens of chronic diseases. Thus, India emerged as a hub for leading biosimilar development under the Central Drugs Standard Control Organization's (CDSCO) major role in defining regulatory pathways[7]. However, countries like Yemen house biosimilar regulation that is still underdeveloped depending mostly on the WHO guidelines and the more mature markets' regulatory decisions.

Thus, this review intends to give a broad scrutiny of regulations, scientific, and implementation issues surrounding biosimilars and biobetters with specificity to India and Yemen. Hence, the objectives are to achieve:

(1) Comparing regulatory frameworks and approval processes in both countries.

(2) Determining the scientific and technical challenges faced in developing biosimilars.

(3) Indicating future directions in improving access and innovation in biologics therapies, particularly in resource-constrained places.

In developing countries, the scope of this multidisciplinary examination will include discussion of harmonization of the biosimilar regulations and enhancement of pharmacovigilance systems to encourage continued innovation in the public arena against the background of harmonization and improvement [8].

2. Background

2.1 Origin and Evolution of Biologics

Biologics medicines are applicable to treat chronic and life-threatening diseases, including cancer, autoimmune diseases, and metabolic disorders. Biologics are large, complex molecules (often proteins) produced using advanced techniques such as recombinant DNA technology and cell culture systems, thus distinguishing them from conventional small-molecule drugs [9]. The introduction of biopharmaceuticals over the last quarter of the 20th century, therefore, signified a paradigm shift in pharmacotherapy itself, characterized by very specific and targeted mechanisms of action. Some of the older examples, such as recombinant insulin and erythropoietin, set the stage for the more recent development of monoclonal antibodies and therapeutic proteins of the lion's share of present-day biotherapeutic interventions [10].

2.2 Emergence of Biosimilars

The end of the patent periods on all blockbuster biologics marketed as monoclonal antibodies therapeutic proteins ushered much into the arena of biosimilar opportunities. It is quite evident that biosimilars are biologic products that are highly comparable or similar to a reference biologic in regard to its quality, safety, and efficacy without any clinically meaningful difference. Unlike general medications, these biosimilars cannot be exactly replicates as a result of the variabilities in these biological systems and the complicated processes of manufacture[11].

First Approvals and Major Milestones: The European Medicines Agency (EMA) endorsed the first biosimilar, Omnitrope® (somatropin), in 2006, with some approvals following in such highly regulated markets as the United States and Japan[12]. One of the earliest was India, which approved its first biosimilar in the year 2000: a hepatitis B vaccine. Since then, the global pipeline has swelled rapidly, with many other biosimilars-for cancer, rheumatology, and endocrinology-distributed in the market today [13].

Role of Patent Expiration: The "patent cliff" for biologics, such as trastuzumab, rituximab, and adalimumab, has driven the birth of many biosimilars. Patent expiries have opened up markets to low-cost alternatives, increasing accessibility and relieving some economic burden on health care systems [14].

2.3 Introduction to Biobetters

Biobetters represent the next stage of innovation beyond biosimilars. These drugs are designed to improve upon certain characteristics such as potency, safety, stability, or dosing frequency in contrast to biosimilars that aim to replicate already available major biologics[15]. Improvements in these characteristics would translate into enhanced patient adherence, better therapeutic outcome, and perhaps reduced immunogenicity. For example, pegylated forms of biologics and Fc-engineered monoclonal antibodies are types of biobetters [16].

They Differ From Biosimilars: The fundamental difference originates from the developmental approach. While the biosimilar routes require strict demonstration of similarity to a reference product through comparability exercises, biobetters involve considerable structural changes and may require complete clinical development comparable to that of a new biologic. Whereas biosimilars compete mainly on price, biobetters create value based on innovation and often secure intellectual property protection to sustain their premium pricing[17].

3. Regulatory Landscape

3.1 Overview of Global Regulatory Approaches

Developing and approving biosimilars worldwide requires adherence to rigorous regulatory frameworks to assure safety, effectiveness, and quality [18]. The European Medicines Agency (EMA) set the stage for biosimilar development, creating the first guidelines in 2005 and setting a gold standard for exercises on comparability. A stepwise approach is required that consists of analytical similarity, preclinical pharmacology, and confirmatory clinical studies while also stressing immunogenicity and post-marketing pharmacovigilance [19]. Similar to the above, the U.S. Food and Drug Administration also enacted the Biologics Price Competition and Innovation Act of 2009, providing an abbreviated licensure pathway established for product submission under section 351(k) of the Public Health Service Act [20]. Therefore, proving biosimilarity and interchangeability under FDA framework has been guided by analytical characterization, animal studies (if needed), clinical pharmacokinetics/pharmacodynamics, and adding at least one clinical study to support immunogenicity and efficacy[21].

WHO has issued overreaching guidance to member states, including a science-based focus on comparability, risk-based clinical requirements, and pharmacovigilance[22]. Therefore, the guidance from WHO becomes a reference to countries that lack complete regulatory frameworks. It would be a step towards harmonization across regions[23].

3.2 Indian Regulatory Framework (CDSCO)

India has emerged as a major hub for biosimilar development, driven by its large biologics market and skilled biopharmaceutical industry[24]. The regulatory pathway is defined by the Central Drugs Standard Control Organization (CDSCO) in collaboration with the Department of Biotechnology (DBT), under the document titled "Guidelines on Similar Biologics" (revised 2016) [25]. The approval process involves:

Table 1. Key Regulatory Guidelines for Biosimilars in India

Summary of CDSCO biosimilar guidelines (2016, revised), including comparability requirements and post-marketing surveillance	
Guideline Issuing Authority	Central Drugs Standard Control Organization (CDSCO) in collaboration with the Department of Biotechnology (DBT)
Guideline Title	*Guidelines on Similar Biologics*(Revised 2016)
Objective	To provide a structured regulatory framework for the development and approval of biosimilars in India, ensuring therapeutic equivalence, safety, and efficacy
Scope	Applies to all biosimilar products derived from biotechnology processes, including monoclonal antibodies, recombinant proteins, and therapeutic enzymes
Key Principles	- Stepwise development approach - Demonstration of analytical and clinical comparability with the reference biologic - Risk-based reduction of clinical data if analytical similarity is robust
Reference Product Requirements	- Must be a licensed biologic in India or in a stringent regulatory jurisdiction (e.g., US, EU, Japan) - Should have a well-established safety and efficacy profile
Analytical Similarity	- Comprehensive physicochemical and functional characterization - Use of state-of-the-art analytical tools (e.g., mass spectrometry, chromatography, bioassays) - Assessment of primary and higher-order structure, post-translational modifications, impurity profiles
Preclinical Evaluation	- Comparative pharmacokinetic (PK), pharmacodynamic (PD), and toxicity studies in relevant animal models - May be waived if strong analytical similarity is demonstrated
Clinical Development Requirements	Phase I: PK/PD study in healthy volunteers or patient population Phase III

Pre-Approval Requirements: Submission of comparability data against a licensed reference biologic approved in India or a recognized jurisdiction[26].

Analytical Studies: Extensive structural and functional characterization to establish similarity.

Preclinical Evaluation: Comparative animal studies to assess toxicity, pharmacokinetics, and pharmacodynamics.

Clinical Trials: Phase I PK/PD studies and at least one confirmatory Phase III trial in a relevant patient population to demonstrate efficacy, safety, and immunogenicity.

Post-marketing surveillance and periodic safety updates are mandatory to ensure long-term safety and effectiveness. India also encourages risk-based reduction of clinical data if robust analytical similarity is demonstrated, aligning with international best practices [27].

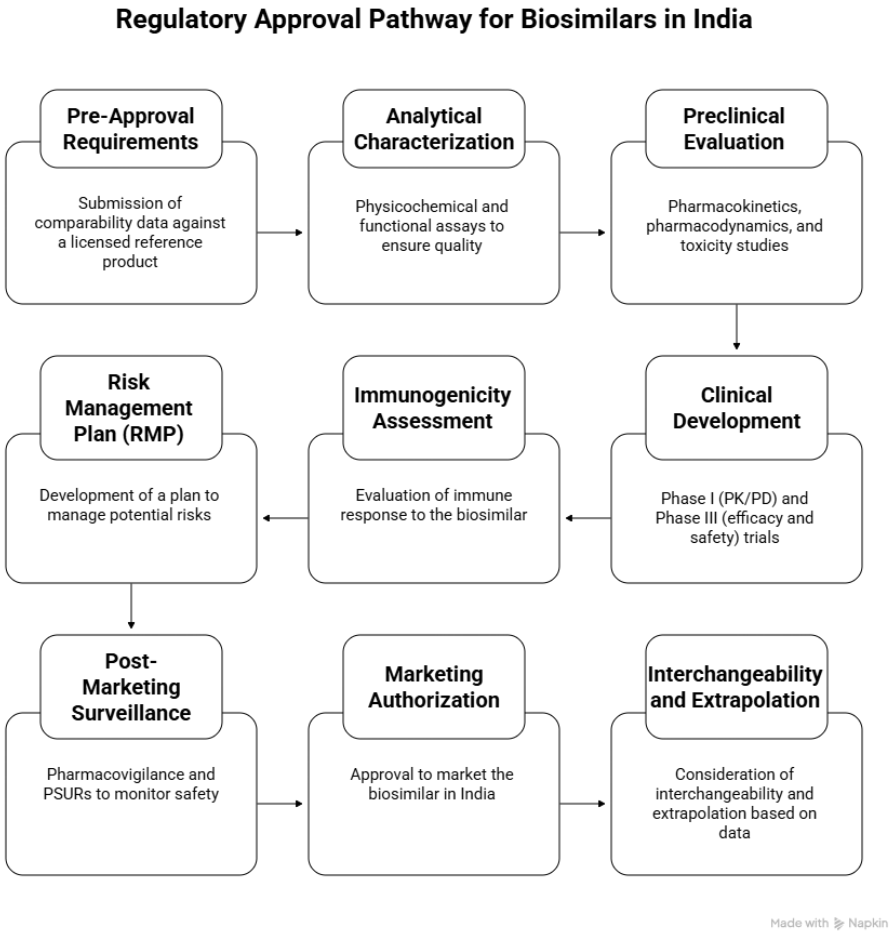


Figure 1. Regulatory Approval Pathway for Biosimilars in India Flowchart showing the stepwise process from analytical characterization to post-marketing surveillance under CDSCO guidelines.
"The regulatory approval of biosimilars in India follows a structured, stepwise process as outlined in the CDSCO Guidelines on Similar Biologics (2016 revised). This process includes analytical characterization, preclinical evaluation, clinical development, and mandatory post-marketing surveillance. A schematic representation of the biosimilar approval pathway is presented in Figure 1."

3.3 Biosimilar Regulation in Yemen and Other Emerging Markets

In contrast to India, countries such as Yemen have underdeveloped regulatory frameworks for biosimilars [28]. The approval process often relies on WHO guidelines and the recognition of reference product approvals from stringent regulatory authorities such as EMA or FDA. While this reliance facilitates access, it raises challenges related to:

Regulatory Gaps: Lack of national technical expertise and structured approval pathways.
Pharmacovigilance Limitations: Inadequate post-marketing surveillance infrastructure.
Quality Assurance: Dependence on imported products without robust local oversight.

Other emerging markets face similar hurdles, emphasizing the need for capacity building, regulatory harmonization, and regional cooperation to strengthen biosimilar governance[30].

4. Scientific and Technical Considerations

The unique scientific and technical challenges arise in the development of biosimilars and biobetters due to the very complex biological nature of these products and the requirement to be very closely similarity to the reference biologics[31]. The important stages in the biosimilars development pipeline are laid out in this article with the key analytical, preclinical, clinical, and manufacturing bases required for regulatory approval and therapeutic equivalence[32].

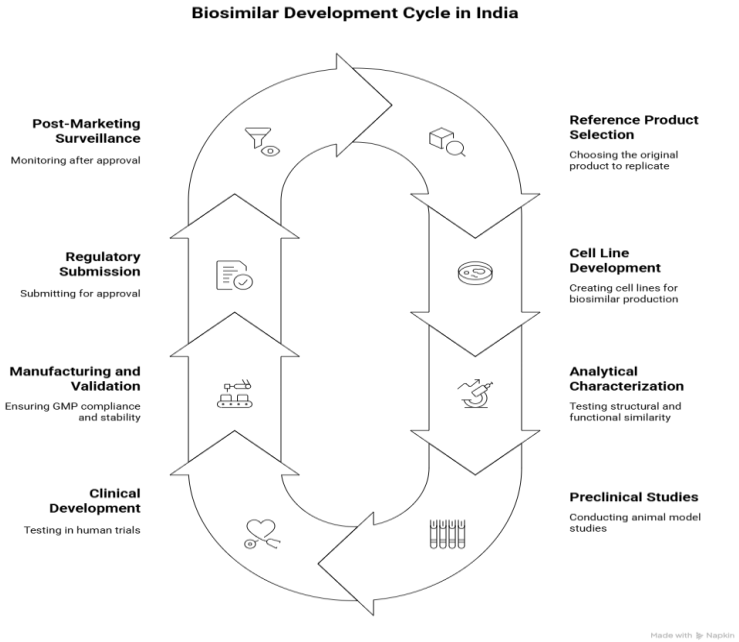


Figure 2. Biosimilar Development Pipeline in India Visual representation of the biosimilar lifecycle, including analytical, preclinical, clinical, and manufacturing phases.

"The development of biosimilars in India follows a structured pipeline involving multiple scientific and technical stages. These include reference product selection, analytical characterization, preclinical and clinical evaluation, manufacturing validation, and regulatory submission. A visual representation of this pipeline, highlighting key developmental phases and potential bottlenecks, is presented in Figure 2."

Table 2. Scientific and Technical Challenges in Biosimilar Development

Categorization of challenges across analytical, preclinical, clinical, and manufacturing domains specific to Indian biosimilar developers.		
Analytical Characterization	High complexity of biological molecules	Biologics are large, structurally complex molecules with post-translational modifications (e.g., glycosylation), making complete analytical characterization challenging.
	Limited access to reference standards	Indian developers often face difficulties in obtaining the originator product for comparative analysis, which is essential to demonstrate analytical similarity.
	Need for advanced analytical tools	State-of-the-art techniques such as mass spectrometry, bioassays, and high-resolution chromatography are required but may not be widely accessible or affordable in India.
Preclinical Evaluation	Limited predictive value of animal models	Preclinical models may not reliably predict human immunogenicity or efficacy, reducing their utility in waiving clinical trials.
	Regulatory expectations for pharmacokinetic (PK)/pharmacodynamic (PD) studies	Indian biosimilar developers must align with global standards for preclinical PD/PK studies, which can be resource-intensive.
Clinical Development	Conducting confirmatory clinical trials	Phase III trials in sensitive patient populations are required, posing challenges in recruitment, trial design, and regulatory compliance.

	Immunogenicity assessment	Comprehensive evaluation of anti-drug antibodies (ADAs) is mandatory and requires standardized assays and long-term monitoring.
	Interchangeability and extrapolation limitations	Indian regulators are cautious about extrapolation of indications and interchangeability, requiring additional clinical data.
Manufacturing	Complexity of bioprocessing	Production in living systems (e.g., mammalian cells) introduces variability; maintaining batch-to-batch consistency is critical.
	Cost of process validation and comparability studies	Ensuring manufacturing consistency post-scale-up or process change requires extensive validation, increasing development costs.
	Limited availability of GMP-certified facilities	While India has a strong biopharma industry, not all manufacturers have access to facilities compliant with international GMP standards.
	Stability and formulation challenges	Ensuring product stability under diverse climatic conditions in India requires robust formulation and stress-testing protocols.
Regulatory and Quality Systems	Alignment with international standards	Indian developers must align with ICH, EMA, and FDA expectations to enable global market access, necessitating investment in quality systems.
	Risk-based reduction of clinical data not fully utilized	Although allowed by CDSCO, many developers still c

4.1 Analytical Characterization

Analytical comparability is the cornerstone in the development of biosimilars. The enormous array of physicochemical and functional assays exists to demonstrate structural and biological similarity to the reference product. Key elements include profiling of primary structure and higher-order structure (e.g., peptide mapping, NMR, and CD spectroscopy), post-translational modifications (e.g., glycosylation profiling), aggregation state, and product-related impurities [33]. Functional characterization usually encompasses in vitro bioassays assessing mechanisms of action such as binding affinity, receptor activation, and effector function. Advanced analytical tools including mass spectrometry, chromatography, and cell-based assays must be harnessed to provide robust comparability [34].

4.2 Preclinical Evaluation

Analytical similarity is just the first step; then follows the assessment of pharmacological activity and toxicity by means of preclinical studies [35]. These studies will use animal models to provide pharmacokinetics (PK), pharmacodynamics (PD), and safety profiles comparison of the biosimilar to that of the reference. They should also provide evidence regarding possible off-target effects or unexpected immune responses [36]. Finally, it would not be out of order to state there are regulations to minimize or waive all preclinical requirements if there is strong analytical comparability already established and in keeping with the stepwise approach principles established by regulation, for animal models are doubtful in humans when it comes to immunogenicity and efficacy predictions [37].

4.3 Clinical Development

Basically, clinical investigations into biosimilar development aim to establish human PK/PD, effectiveness, safety, and immunogenicity similarities [38]. PK and PD studies would be conducted either in healthy volunteers or in patient populations depending on the particularity of the molecule. Following this, confirmatory efficacy trials are often comparative in nature but conducted with a well-outlined endpoint in a sensitive population [39].

Clearly, immunogenicity assessment forms a cornerstone in clinical evaluation. This involves the incidence and effects of anti-drug antibodies (ADAs) in terms of the efficacy or safety of a particular drug [40]. By definition,

biosimilars should not have a clinically meaningful difference in immunogenicity compared to the reference biologic.

Together with this, regulatory authorities may also consider interchangeability and extrapolation. Interchangeability is what allows transition from one biosimilar to the other without loss of efficacy or increase of risk. Extrapolation allows a biosimilar approved for one indication to be allowed for other indications of the reference product given that its action mechanism and clinical evidence justify it [41].

4.4 Manufacturing Complexities

These biosimilars are intrinsically complex to make due to their production in living cells such as those of animal or human origin, which introduce variability that needs to be very strictly controlled [42]. The selected cell lines, together with upstream and downstream processing and purification methods, all play a very significant role in assuring the quality and consistency of the final product.

The formulation needs to guarantee the stability, solubility, and bioavailability of the product. Stability studies can evaluate degradation pathways, for example, aggregation, deamidation, and oxidation, under stress conditions. Furthermore, the biosimilar production should also be scalable without compromising quality, for which optimized validation and control strategies have to be established [43].

Changes in the manufacturing process during development or after approval require comparability studies according to ICH Q5E guidelines. Increasingly, the continuous registration of the process and application of QbD principles are being implemented to ensure reproducibility and compliance with regulatory standards [44].

5. Legal and Market Challenges

The development and marketing of biomedicine are tied closely to deep legal and market consideration. Notwithstanding all the advancements in the regulations meant to shape the global arena for biosimilars, IP barriers, pricing strategies, and perceptions by various stakeholders continue to define and characterize the global biosimilar landscape [45].

5.1 Patent and Intellectual Property Issues

The patent system is designed to stimulate innovation; however, it frequently erects insurmountable barriers to biosimilars entering the marketplace. The primary patents covering reference biologics provide exclusivity to the marketplace, while secondary patents on formulations, delivery systems, or manufacturing processes entrench monopolies for longer than the original patent term [46]. This practice is sometimes referred to as "evergreening," and makes free-to-operate assessments for biosimilar manufacturers all the more difficult, delaying patient access to affordable alternatives. Patent validity and infringement disputes are among some of the persistent challenges faced, thus making it imperative that patent landscaping, as well as legal strategies for litigation planning, be done on a rigorous level for biosimilar developers [47].

5.2 Market Access and Cost Implications

Market access for biosimilars is largely contingent on pricing and reimbursement policies employed. While biosimilars do promise some cost savings, the development costs are still quite substantial- owing to rigorous regulatory requirements; therefore, price reductions will always remain modest compared to generics [48]. The cost-effectiveness of a drug constitutes the strongest impetus for its adoption in resource-poor settings like some parts of Africa, South Asia, or the Middle East. Governments use different models, such as tendering systems, reference pricing, and differential pricing, to improve affordability [49]. Lack of centralized procurement in fragmented healthcare markets and limited insurance coverage add to these factors and hinder uptake at large, placing the burden of out-of-pocket expenses on the patients[50].

5.3 Stakeholder Perceptions and Adoption

Ultimate acceptance of biosimilars will be determined by physician-, pharmacist-, and patient-level confidence in their safety and efficacy [51]. Myths surrounding immunogenicity and therapeutic equivalence continue to be propagated, especially in markets with weak pharmacovigilance infrastructure. Therefore, educational initiatives and honest communication building upon comparability data, interchangeability policies, and post-marketing safety outcomes are vital to allaying ill notions held by stakeholders. Other determinants might influence the behaviour of physicians in their prescribing such as brand loyalties, originator company promotions, and clarity of regulations on substitution policies. Patient acceptance is hinged on perceived therapeutic worth and affordability, thereby necessitating awareness campaigns and stakeholder engagement [52].

Table 3. Barriers to Biosimilar Adoption in India

Summary of legal, economic, and stakeholder-related challenges affecting biosimilar uptake in the Indian healthcare system		
Legal and Regulatory Barriers	Complex intellectual property (IP) landscape	Secondary patents on formulations, delivery systems, and manufacturing processes delay market entry of biosimilars through a practice known as "ever greening."
	Lack of clear interchangeability guidelines	CDSCO does not automatically grant interchangeability status; additional data is required for substitution, limiting physician confidence in switching.
	Inconsistent enforcement of biosimilar regulations	Variability in regulatory enforcement across states and lack of uniformity in post-marketing surveillance hinder market confidence.
Economic Barriers	High development costs despite cost-saving potential	Biosimilar development requires significant investment in analytical, clinical, and manufacturing processes, limiting price reductions compared to generics.
	Limited price differentiation	Biosimilars are not always significantly cheaper than originator biologics due to patent settlements, brand loyalty, and marketing strategies of originator companies.
	Fragmented healthcare financing	Lack of centralized procurement and reimbursement mechanisms in public and private sectors leads to uneven access and affordability.
Stakeholder and Perception Barriers	Physician skepticism and brand loyalty	Many physicians prefer originator biologics due to familiarity, despite evidence of biosimilar comparability and safety.
	Limited awareness among prescribers and patients	Lack of education on biosimilars, immunogenicity, extrapolation, and interchangeability leads to misconceptions and underutilization.
	Marketing influence of originator companies	Originator firms often engage in aggressive marketing, restrictive hospital contracts, and direct-to-consumer advertising that deters biosimilar uptake.
	Pharmacists and payers not fully integrated into biosimilar adoption	Pharmacists and insurance providers play a limited role in biosimilar substitution and reimbursement decisions in India.
Infrastructure and Systemic Barriers	Weak pharmacovigilance systems	Underreporting of adverse drug reactions and limited post-marketing surveillance reduce confidence in biosimilar safety.
	Limited real-world evidence (RWE)	Lack of comprehensive patient registries and outcome tracking limits evidence generation for biosimilar performance in real-world settings.
	Supply chain and formulation challenges	Issues with cold chain logistics, storage, and stability in diverse c

6. Pharmacovigilance and Post-Marketing Surveillance

6.1 Importance of Real-World Evidence

Pharmacovigilance is central to assessing the safety and efficacy of biosimilars postmarketing. While clinical trials generate an evidence base subjected to controlled conditions, real-world data (RWD) and real-world evidence (RWE) allow us to assess drug performance in diverse patient populations, each with distinct comorbidities and long-term usage scenarios [53]. The complexity of biosimilars as large molecules produced in living systems indicates that even slight differences might create distinctions in their immunogenicity profiles. For this reason, adverse event reporting systems, patient registries, and observational studies must be monitored constantly to detect very rare or delayed adverse effects that might not have presented during pre-qualification clinical studies [54].

6.2 Regulatory Requirements: India vs. Other Markets

Many countries have established a regulation system of strict and effective post-marketing surveillance around the world to ensure the safety of the public [55].

India: The Central Drugs Standard Control Organization (CDSCO) stipulates Risk Management Plan (RMP) and Periodic Safety Update Reports (PSURs) according to its guidelines for biosimilars in 2016. Furthermore, the Pharmacovigilance Programme of India (PvPI) takes charge of collecting and analyzing adverse drug reaction (ADR) reports. Marketing authorization holders must continually contribute safety summaries and should join in signal detection activities [56].

European Union (EMA): Manufacturers of biosimilars must adhere to Good Pharmacovigilance Practices (GVP) and must also establish a product-specific RMP that includes post-authorization safety studies (PASS) whenever necessary [57].

United States (FDA): Pharmacovigilance plans should comply with ICH E2E guidelines, with an emphasis on active surveillance and integration of real-world data. The applicants are also mandated to make sure that there are distinguishable non-proprietary names and lot numbers so as to ensure robust traceability under the Biologics Price Competition and Innovation Act (BPCIA) [58].

Comparatively, while India may be making significant strides in progress, resource manifold and underreporting of ADRs remain major drawbacks in emergent markets such as Yemen, where the countries' pharmacovigilance systems mostly follow WHO guidelines and international data [59].

6.3 Role of Risk Management Plans

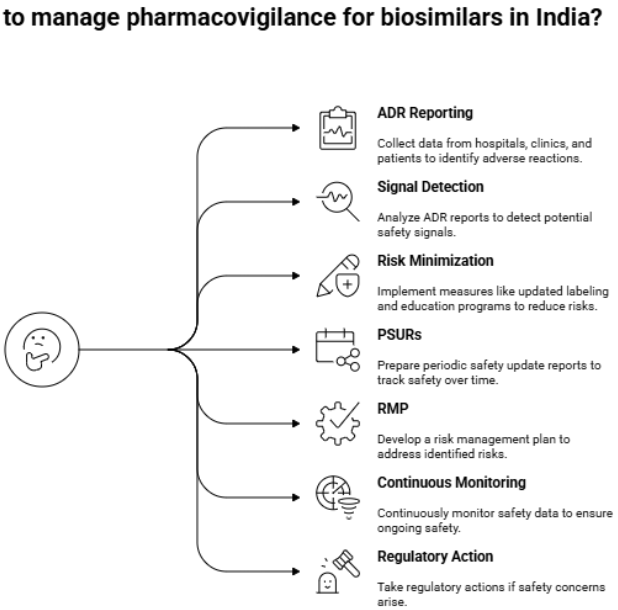
The risk management plan is the aspect under which a life cycle of a biosimilar is developed to identify, characterize, and mitigate the risks in advance. RMPs generally include:

Safety Specification: The documentation of known and unknown risks as well as uncertainties arising from limited clinical exposure.

Pharmacovigilance Plan: Studies of safety post-marketing, registry participation as well as active surveillance mechanisms.

Risk Minimization Measures: These changes would allow labeling changes and physician education programs and also have information leaflets for patients which ensure informed usage.

Immunogenicity is yet another essential aspect of risk during biosimilars' application and therefore risk management plans. adopt enhanced monitoring strategies during switches or interchangeability events considering the increased risk. Continuous RMP updates from real world data are critical toward ensuring patient safety and regulatory compliance [60].



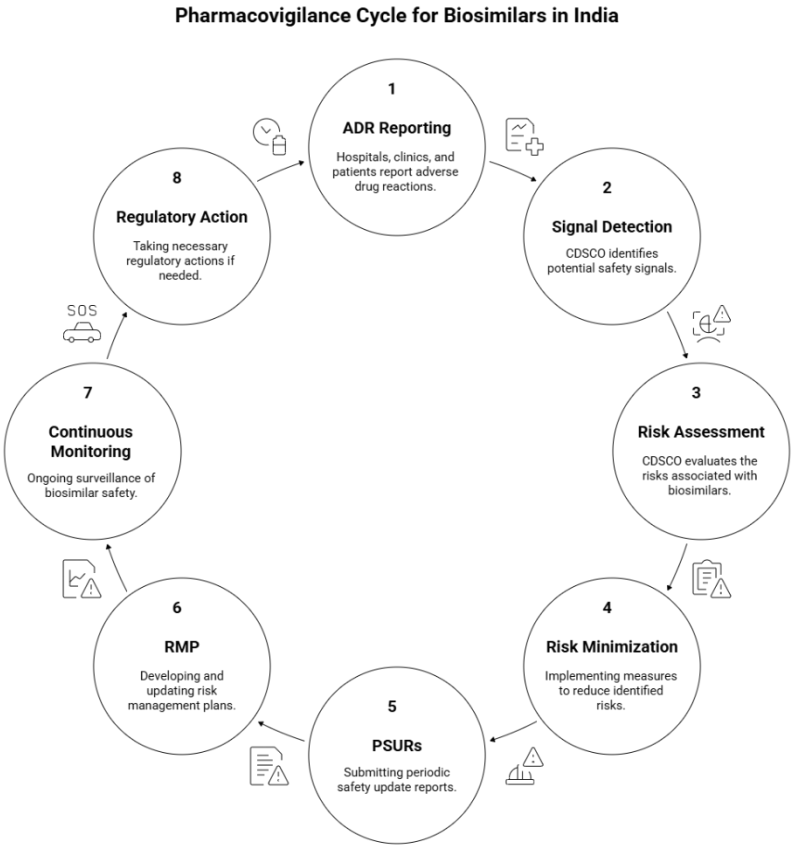


Figure 3. Pharmacovigilance Framework for Biosimilars in India Diagram illustrating the PvPI structure, adverse drug reaction reporting, and risk management plan requirements.

"The Pharmacovigilance Programme of India (PvPI) plays a central role in ensuring the post-marketing safety of biosimilars. It involves structured adverse drug reaction (ADR) reporting, signal detection, and risk minimization strategies. A schematic overview of the pharmacovigilance framework for biosimilars in India is presented in Figure 3."

7. Biobetters: The Next Step in Biologic Innovation

Table 4. Comparative Features of Biosimilars and Biobetters

Side-by-side comparison of regulatory status, development approach, clinical requirements, and market positioning in the Indian context		
Definition	Biological product highly similar to a licensed reference product with no clinically meaningful differences in safety, purity, or potency.	Next-generation biological product with intentional molecular modifications to improve efficacy, safety, pharmacokinetics, or dosing convenience.
Regulatory Status in India	Regulated under the"Guidelines on Similar Biologics (2016, revised)"by CDSCO.	Treated asnew biological entities; evaluated under theNew Drug Approvalpathway. No dedicated regulatory framework exists for biobetters.
Development Approach	Stepwise demonstration ofanalytical, preclinical, and clinical comparabilityto the reference product.	Requiresde novo development, including full preclinical and clinical evaluation. No requirement for strict similarity to the reference product.
Reference Product	Mandatory requirement for alicensed reference biologic(India or a stringent	No requirement for direct similarity to a reference product; focuses onnovelty

Requirement	regulatory jurisdiction).	and therapeutic improvement.
Analytical Requirements	Extensive physicochemical and functional characterization to demonstrateanalytical similarity.	Structural modifications are intentional and may not align with the reference product; analytical focus is oncharacterizing the new molecule.
Preclinical Requirements	May bewaived or reducedif strong analytical similarity is demonstrated.	Full preclinical evaluation required to assesssafety and mechanism of actionof the modified molecule.
Clinical Trial Requirements	- Phase I: PK/PD study - Phase III: At least one confirmatory trial in a sensitive patient population - Immunogenicity assessment mandatory	Full clinical development pathway required: - Phase I–III trials - Comprehensive immunogenicity and efficacy evaluation
Interchangeability and Extrapolation	Interchangeability may be considered if additional data supports it. Extrapolation of indications is allowed based on mechanism of action and clinical data.	No automatic extrapolation; each indication must be independently studied and approved.
Regulatory Submission Pathway	Submitted underSchedule YandGuidelines on Similar Biologics.	Submitted undernew drug application (NDA)process; follows the path ofinnovator biologics.
Post-Marketing Surveillance	Mandatory Risk Management Plan (RMP), including pharmacovigilance and Periodic Safety Update Reports (PSURs).	Similar pharmacovigilance requirements apply; may requireadditional monitoringdue to novel modifications.
Market Positioning	Positioned ascost-effective alternativesto originator biologics. Competes primarily onprice and affordability.	Positioned asinnovative improvementsover existing biologics. May commandpremium pricingbased on enhanced therapeutic value.
Intellectual Property (IP) Considerations	Faces IP barriers from originator patents but may avoid infringement if not identical.	May securenew patentsfor molecular modifications, offering better IP protection and market exclusivity.
Examples in Indian Market	- CT-P13 (Biosimilar infliximab) - SB4 (Biosimilar etanercept)	- Pegfilgrastim - Insulin analogs (e.g., insulin glargine analogs with improved pharmacokinetics)
Regulatory Challenges	Ensuringstringent comparabilityacross all domains; managingimmunogenicity concerns.	

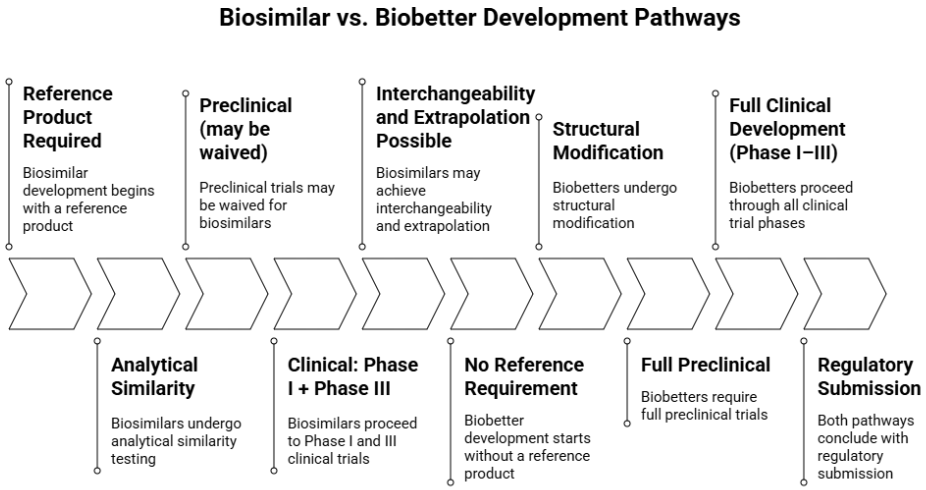


Figure 4. Biosimilar vs. Biobetter Development Pathway (Comparative Flowchart) Side-by-side comparison of biosimilar and biobetter development pathways, showing differences in regulatory requirements, clinical development, and approval processes in India and globally.

"The regulatory and developmental pathways for biosimilars and biobetters differ significantly due to their distinct objectives — biosimilars aim to demonstrate similarity, while biobetters aim to innovate. A comparative flowchart illustrating these differences in development and approval requirements is presented in Figure 4."

7.1 Definition and Advantages Over Biosimilars

Biobetters, or biosuperiors, define themselves under these classes of biologics, engineered therefore to develop therapeutics with better therapeutic efficacy, safety, or pharmacokinetics apart from the usual reference product stability and patient convenience.

The biobetters' key advantages are:

More than one of the parameters are optimized-for example, the improved safety or efficacy expected through improved binding to the target or reduced immunogenicity.

Improved pharmacokinetic properties, for less frequent dosing adherence by the patient.

More stable formulations for simplified storage and distribution.

Such characteristics define biobetters to be seen as the next generation of solutions surmounting the constraints of first-generation biologic therapies while maintaining the therapeutic backbone of the original molecule. Any other benefit or usefulness a biobetter, say, might be conferred, will accrue from the attributes.

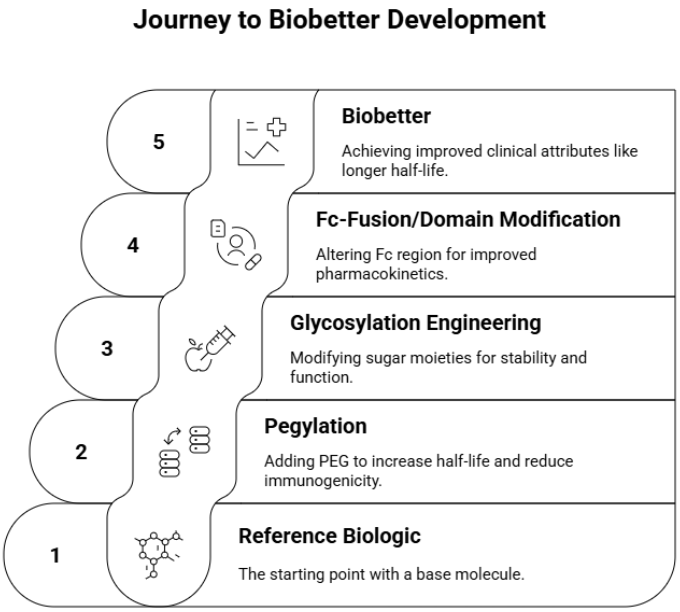


Figure 5. Molecular Modifications in Indian Biobetter Development
Diagram showing structural changes (e.g., pegylation, glycosylation, fusion proteins) in next-generation biologics developed in India.
"Biobetters are distinguished from biosimilars by their intentional molecular modifications, which aim to improve clinical performance over the reference product. These modifications include pegylation, glycosylation engineering, and Fc-fusion technologies, among others. A schematic representation of these molecular alterations and their therapeutic implications is shown in Figure 5."

7.2 Regulatory Considerations

Biobetters are differentiated from biosimilars in terms of regulatory approaches since they do not have any potential for superimposition with their reference product. Hence, biobetters are treated as novel biological entities and would require preclinical and clinical development programs in their entirety, which include comprehensive assessments of pharmacokinetics, pharmacodynamics, and safety [61].

FDA in the United States: Biobetters are considered original biologics under the Biologics License Application pathway.

European Medicines Agency: It recognizes biobetters as new active substances that require similar extensive applications as innovative biologics.

Currently there is no separate biobosser's pathway in India. Developers usually go through the process of new drug approval with emphasis on comparative clinical studies as relevant. Lacking harmonization across countries, rules on biobutters place a further need for convergence on international regulation before emerging market approvals; thus they are not met.

7.3 Case Studies and Examples

Biobetter has already reinvented patient management in a number of different areas. Some of these include:

Insulin Degludec (Tresiba®): Engineered as a long-acting, pan-branched insulin analog with pharmacodynamic stability enhanced beyond the level of insulin glargine, thereby permitting flexible dosing schedules.

Pegfilgrastim (Neulasta®): A pegylated version of filgrastim with an extended half-life that decreases injection frequency for neutropenia therapy.

Darbepoetin alfa (Aranesp®): Engineered erythropoiesis-stimulating agents particularly with more sialic acid residues resulting in prolonged activity and reduced injection burden.

Such examples exemplify the strategic usefulness of biobetters in the bridging niche of innovation and affordability, especially in chronic disease management.

Table 5. Case Studies of Indian Biobetters

Examples of biobetters developed in India, including therapeutic class, molecular modifications, and clinical advantages						
1	Pegfilgrastim biosimilar (e.g., Peg-ELOX™, Ogivri™)	Hematopoietic growth factor	Filgrastim	PEGylation of the protein to extend serum half-life	Reduced frequency of administration (weekly vs. daily), improved patient compliance, lower risk of febrile neutropenia	Biocon Ltd., Mylan N.V.
2	Insulin Glargine Analog (e.g., Basalog™, Glargin™)	Insulin analog (diabetes)	Insulin Glargine	Amino acid substitution and acylation	Improved pharmacokinetic profile with more stable glucose control, reduced hypoglycemic episodes	Wockhardt Ltd., Zydus Cadila
3	Trastuzumab Derivative (e.g., TZMAB™)	Monoclonal antibody (oncology)	Trastuzumab	Fc-region modification to enhance antibody-dependent cellular cytotoxicity (ADCC)	Increased potency, improved tumor response rates	Biocon Ltd., Dr. Reddy's Laboratories
4	Erythropoietin (EPO) analog (e.g., Retropin™)	Erythropoiesis-stimulating agent	Epoetin alfa	Hyperglycosylated form with extended half-life	Less frequent dosing (every 2–4 weeks), improved hemoglobin maintenance in chronic kidney disease patients	Emcure Pharmaceuticals
5	Rituximab Derivative (e.g., Reditux™)	Monoclonal antibody (oncology/autoimmune)	Rituximab	Minor structural modifications in Fc region and glycosylation	Enhanced target binding and improved ADCC; cost-effective alternative for lymphoma and rheumatoid arthritis	Cipla, Intas Pharmaceuticals

6	Recombinant Human Growth Hormone (rhGH) analog	Growth hormone	Somatropin	PEGylated long-acting formulation	Weekly administration instead of daily injections, improved adherence in pediatric patients	Biocon Ltd., Panacea Biotec
7	Adalimumab Biosimilar with enhanced formulation	TNF-alpha inhibitor (autoimmune)	Adalimumab			

8. Future Prospects and Recommendations

8.1 Policy Harmonization Needs

The global regulatory framework for biosimilar and biobetter legislators remains heterogeneous; secondly, it entails different requirements and a longer period of approval, especially in emerging markets. Regulatory harmonization that draws on WHO guidelines and aligns with EMA (European Medicines Agency) and US FDA best practices is a precondition for accelerating public acceptance of biosimilars. Such international cooperation can occur under such platforms as the International Council for Harmonisation (ICH) as convergence, avoidance of duplicative evaluations, and mutual recognition agreements among regulatory authorities. Aside from speeding up access for patients, this also reduces costs for manufacturers [62].

8.2 Strategies to Improve Regulatory Capacity in Emerging Markets

Countries such as Yemen and others in low-resource environments usually hinge on foreign approvals, owing to a lack of local expertise and infrastructure. Strengthening regulatory capacity will require:

Training programs for assessors and inspectors on comparability exercises, immunogenicity evaluation, and pharmacovigilance.

Support for laboratory infrastructure for analytical and quality testing of biologics.

Regional collaborations in regulatory functions, like reliance models and shared assessment mechanisms, to build on existing expertise and not duplicate effort.

Risk-based, tiered review systems would additionally optimize for regulatory efficiency without compromising patient safety [63].

8.3 Encouraging Local Innovation and Manufacturing

Biosimilars and biobetters manufactured locally could drastically cut the import dependency, increase affordability, and guarantee uninterrupted supply in LMICs. There is a need for policymakers to implement incentive-based frameworks to attract investments for biologics manufacturing, such as tax holidays, subsidies, and technology transfer agreements. Commercialization of R&D for next-generation biologics could be expedited through the creation of strong academic-industry partnerships and biotechnology clusters in the LMICs. Build-up initiatives in GMP and continuous manufacturing technologies will be key for quality sustainability and scalable development.

8.4 Long-Term Vision

Biosimilars and biobetters will have a future in a global strategy that includes regulatory convergence with local capacity building and innovative approaches to development. Digitalization through artificial intelligence to draw comparability in analysis and collecting real-world evidence would enhance post-marketing safety monitoring and quicker development cycles of these agencies and manufacturers. Thus, an affordable, accessible, and innovative policy ecosystem would ensure long-term commitment in the changes that biosimilars and biobetters would bring to the global health landscape, particularly to poorly served populations [64].

9. CONCLUSION

The development and uptake of biosimilars and biobetters indeed have the hallmarks of a paradigm shift in contemporary therapy intended to meet the global demand for affordable but high-quality biologic medicines. This review highlights that biosimilars promise a more sustainable solution to the increasing healthcare costs, whereas biobetters engender innovative avenues beyond copycat biology. But their successful implementation would still be dependent on overcoming scientific, regulatory, and market hurdles, especially resource-limited settings.

Multidisciplinary collaboration among regulatory authorities, pharmaceutical manufacturers, clinicians, and policymakers is required for streamlining approval processes, strengthening robust pharmacovigilance, and instilling confidence in all stakeholders. Harmonized regulatory frameworks, supported with evidence-based guideline development and capacity enhancement initiatives, will further strengthen the accessibility and confidence in such products.

Looking forward, biosimilars and biobetters are set to transform global health care by expanding the therapeutic access, optimizing patient outcomes, and further innovating biological drug development. Strategic investments in regulatory harmonization, manufacturing capabilities, and post-market surveillance will be indispensable in harnessing the full potential and achieving equitable health care worldwide.

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