

Ethical Governance of Biosimilars in India and the United States: A Comparative Review of Patient Safety, Accessibility, and Regulatory Accountability

Mohit Kumar¹, Neelam Painuly², Abhishek Agrawal³, Dr. Ashutosh Pathak⁴, Pratibha Malik⁵

¹Assistant Professor, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad-244001, U.P., India; mohitgoyal21111@gmail.com; 0009-0001-8236-7396.

²Associate Professor, School of Pharmacy & Research, Dev Bhoomi Uttarakhand University, Naugaon, Dehradun, India; Email ID : neelu.painuly@gmail.com

³Associate Professor, IITM COLLEGE OF PHARMACY, Murthal, Sonapat; Email ID : abhishek060688@gmail.com

⁴Assistant Professor, Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad UP, India; 0009000091589356

⁵Assistant Professor, Department of law and legal studies, Teerthanker Mahaveer College of law and legal studies, Teerthanker Mahaveer University, Moradabad UP, India Pin- 244001; Email ID : Pratibhamalik.06121996@gmail.com

Corresponding Author:

Mohit Kumar

Assistant Professor, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad-244001, U.P., India; Email ID : mohitgoyal21111@gmail.com; 0009-0001-8236-7396.

ABSTRACT

Background: Biological medicines have transformed the management of several serious and chronic diseases, but their complex manufacturing processes and high development costs may create substantial barriers to treatment. Biosimilars offer an opportunity to increase therapeutic options and improve the affordability of biological therapies. Their adoption, however, raises ethical questions concerning patient safety, clinical evidence, informed consent, substitution, equitable access, commercial influence, and regulatory accountability.

Objective: This review critically examines the ethical governance of biosimilars in India and the United States, focusing on patient safety, accessibility, regulatory responsibility, interchangeability, pharmacovigilance, and the professional obligations of pharmacists and other healthcare stakeholders.

Methods: A comparative narrative review framework was adopted. Regulatory and scientific materials from the World Health Organization, the Central Drugs Standard Control Organization and Department of Biotechnology of India, and the United States Food and Drug Administration were considered alongside established literature on biosimilar development, immunogenicity, interchangeability, healthcare justice, and pharmaceutical ethics. The analysis uses the principles of beneficence, non-maleficence, autonomy, justice, transparency, and accountability to evaluate the ethical implications of biosimilar governance. This is a critical narrative review rather than a systematic review or meta-analysis.

Results and discussion: Biosimilar approval is based on a comprehensive comparability exercise demonstrating high similarity to an authorized reference biological product and the absence of clinically meaningful differences in relevant characteristics. Scientific similarity does not, by itself, resolve all ethical questions surrounding treatment switching, patient communication, medicine traceability, or equitable access. India and the United States have established regulatory pathways for biosimilars, but differences in regulatory terminology, substitution arrangements, healthcare financing, market structure, and institutional capacity create distinct ethical challenges. In the United States, the legal distinction between a biosimilar and an interchangeable biosimilar has important implications for pharmacy-level substitution. In India, the regulatory framework for similar biologics provides a pathway for authorization, while implementation of substitution, prescribing, pharmacovigilance, and patient communication requires careful consideration of clinical context and applicable rules. In both settings, affordability should not be pursued at the expense of safety, treatment continuity, or patient autonomy.

Conclusion: Ethical biosimilar governance requires an integrated approach combining scientific rigor, transparent regulation, responsible manufacturing, robust pharmacovigilance, informed clinical decision-making, and equitable access. Strengthening pharmacist participation, product traceability, patient education, conflict-of-interest safeguards, and public reporting of safety information may improve trust and responsible biosimilar adoption in India and the United States. Regulatory and health-policy reforms should remain sensitive to the different healthcare environments of the two countries...

Keywords: Biosimilars; biopharmaceuticals; pharmaceutical ethics; patient safety; healthcare justice; accessibility; interchangeability; substitution; pharmacovigilance; India; United States; regulatory accountability

1. INTRODUCTION

1.1 Background and evolution of biological medicines

Biological medicines are therapeutic products derived from living organisms or biological systems and include recombinant proteins, monoclonal antibodies, hormones, cytokines, and other complex molecules. They have substantially influenced the treatment of cancer, autoimmune diseases, endocrine disorders, inflammatory diseases, and several rare conditions. Unlike many conventional small-molecule medicines, biological products are generally structurally complex and are produced through highly sensitive biological manufacturing processes. Their quality characteristics may be influenced by cell lines, culture conditions, purification procedures, formulation, storage, and manufacturing controls. Consequently, biological medicines require specialized scientific and regulatory approaches that differ from those traditionally used for conventional small-molecule generic medicines [1–3].

The development of biological therapies has generated major therapeutic benefits, but the high costs associated with research, development, manufacturing, and healthcare delivery can create barriers to patient access. The expiry of patents and relevant exclusivity periods for reference biological products has created opportunities for the development of biosimilars. These products can provide additional biological treatment options and may contribute to competition, healthcare savings, and improved access when appropriately integrated into healthcare systems [4–6].

The emergence of biosimilars has therefore created a dual policy objective: preserving the quality, safety, and effectiveness of biological therapy while promoting a more sustainable and equitable healthcare system. Although biosimilars are often compared with generic medicines, they are not identical copies in the same sense as many conventional small-molecule generics. Their approval relies on a structured demonstration of similarity to a reference product, including analytical and functional characterization and, where appropriate, nonclinical and clinical evidence [1–3]. The WHO specifically describes biosimilar licensing as relying, in part, on evidence generated for an already licensed reference product after sufficient similarity has been demonstrated.

From a pharmaceutical-ethics perspective, this distinction is important. A reduction in treatment cost may contribute to improved access to effective care, but cost reduction alone cannot justify inadequate product quality, insufficient monitoring, misleading communication, or inappropriate substitution practices. The ethical assessment of biosimilars therefore extends beyond price and includes the responsibilities associated with development, authorization, procurement, prescribing, dispensing, patient communication, switching, substitution, and post-marketing monitoring [5–8].

1.2 Concept of biosimilarity

A biosimilar is a biological product that is highly similar to an already authorized reference biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically

meaningful differences in safety, purity, and potency or effectiveness according to the applicable regulatory framework [1,2,9]. The demonstration of biosimilarity is based on a comprehensive comparability exercise rather than on an assumption that the two products are molecularly identical.

The biosimilar development process generally begins with extensive analytical characterization. This may include evaluation of primary structure, higher-order structure, post-translational modifications, purity, aggregation, charge variants, biological activity, and other critical quality attributes. Analytical evidence is followed by additional studies determined by the product, residual uncertainty, mechanism of action, and applicable regulatory requirements. The purpose is to establish whether meaningful differences remain between the biosimilar and reference product and whether those differences could affect clinical performance [1–3].

This scientific framework also has an ethical dimension. Requiring unnecessary clinical studies may increase development costs and delay access, whereas insufficient evidence may expose patients to avoidable uncertainty. Ethical regulation should therefore seek proportionality: evidence requirements should be scientifically justified, sufficiently rigorous, and appropriately tailored to the remaining uncertainty. The WHO's revised framework provides science-based principles for biosimilar evaluation and allows national regulatory authorities to establish appropriate licensing frameworks [1].

1.3 Why biosimilars raise pharmaceutical ethics questions

Pharmaceutical ethics addresses the responsibilities of individuals and institutions involved in discovering, developing, manufacturing, regulating, distributing, prescribing, dispensing, and using medicines. Biosimilars create ethical challenges at several levels [7,10].

1. Patient safety

Biological products can induce immune responses, and immunogenicity may potentially influence safety, pharmacokinetics, therapeutic response, or treatment discontinuation. Appropriate analytical characterization, immunogenicity assessment, manufacturing controls, and pharmacovigilance are therefore important components of biosimilar governance [3,11].

2. Patient autonomy

Patients may require understandable information concerning their treatment, the rationale for initiating or switching therapy, expected benefits, potential risks, and available alternatives. Meaningful communication is particularly relevant when treatment changes are influenced by formulary, reimbursement, or procurement considerations [7,12].

3. Professional responsibility

Prescribers and pharmacists have professional responsibilities to consider scientific evidence, regulatory status, patient circumstances, treatment continuity, and affordability when biosimilar therapy or switching is considered. The authority to substitute a biological product, however, depends on the relevant national and subnational legal framework [9,13].

4. Distributive justice

Biosimilars may contribute to lower healthcare expenditure and potentially expand access to biological therapies. From an ethical perspective, these potential economic benefits are relevant to distributive justice because limited healthcare resources can influence access to high-cost biological medicines [5,6,14].

5. Regulatory accountability

Regulatory authorities are responsible for establishing scientifically defensible requirements for quality, safety, efficacy, biosimilarity, manufacturing, and post-marketing monitoring. Transparency and consistency in regulatory decision-making are important for maintaining confidence among healthcare professionals and patients [1–3].

6. Commercial ethics

Manufacturers and other commercial stakeholders have responsibilities concerning accurate and non-misleading communication regarding biosimilars and reference biological products. Commercial interests should not compromise the accuracy or completeness of information provided to healthcare professionals or patients [15].

7. Continuity of care, traceability, and pharmacovigilance

Effective pharmacovigilance requires reliable identification and traceability of biological products used by individual patients. Product-specific information facilitates the detection, investigation, and attribution of adverse events and safety signals [16].

These issues become particularly significant when comparing India and the United States. Both countries have established regulatory approaches for biosimilars, but their regulatory structures, healthcare financing arrangements, reimbursement mechanisms, purchasing systems, pharmacy practices, and approaches to substitution and interchangeability differ [2,9,13,17]. Ethical governance should therefore be evaluated within each country's institutional and socioeconomic context rather than through a single universal policy model.

1.4 Rationale for comparing India and the United States

India is an important producer and supplier of biological medicines and has established a regulatory pathway for similar biologics through the Central Drugs Standard Control Organization (CDSCO) and Department of Biotechnology (DBT). The *Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India* establish requirements concerning quality, preclinical and clinical evaluation, manufacturing, and post-marketing surveillance [2]. CDSCO continues to list the 2016 Biosimilar Guideline among its biological-product guidance documents.

India's large population, differences in healthcare affordability and infrastructure, and substantial pharmaceutical manufacturing capacity make access to biological medicines an important public-health consideration. Biosimilars may contribute to expanded access, although the practical impact depends on factors including pricing, procurement, prescribing practices,

physician confidence, patient acceptance, and pharmacovigilance [5,6,17].

The United States has a statutory biosimilar pathway under section 351(k) of the Public Health Service Act, established through the Biologics Price Competition and Innovation Act (BPCI Act) of 2009. The FDA evaluates biosimilar applications using a comparative scientific framework and distinguishes biosimilar products from products that additionally meet the statutory requirements for interchangeability [9,13].

The distinction between biosimilarity and interchangeability is particularly important for an ethical analysis because it can affect approaches to treatment switching and pharmacy-level substitution. FDA's 2019 final guidance describes considerations for demonstrating interchangeability, while the FDA issued an updated draft interchangeability guidance in 2024 based on accumulated regulatory and scientific experience. The 2024 document should therefore be identified as draft guidance rather than as a binding final requirement [13,18].

The US market also involves multiple stakeholders, including manufacturers, healthcare providers, insurers, pharmacy benefit managers, hospitals, specialty pharmacies, pharmacists, and patients. Consequently, affordability and access cannot be evaluated solely through regulatory approval; reimbursement, procurement, formulary decisions, substitution rules, and patient-level treatment decisions can also influence practical access [5,6,17].

A comparative ethical analysis can therefore identify common principles and country-specific challenges. It can also clarify how regulatory decisions influence the responsibilities of pharmacists and prescribers, patient participation in treatment decisions, pharmacovigilance, substitution and switching, competition, affordability, and equitable distribution of biological therapies [1,2,9,13].

1.5 Aim and objectives

Aim

To critically review the ethical governance of biosimilars in India and the United States, with particular emphasis on patient safety, accessibility, patient autonomy, professional responsibility, pharmacovigilance, and regulatory accountability [1,2,7,13].

Specific objectives

To explain the scientific and regulatory foundations of biosimilar medicines, including biosimilarity, analytical comparability, clinical evidence, immunogenicity, and the totality-of-evidence approach [1–3,9].

To examine the ethical principles applicable to biosimilar development and clinical use, including patient safety, autonomy, beneficence, non-maleficence, professional responsibility, and distributive justice [7,10,14].

To compare the biosimilar regulatory approaches of India and the United States, with particular attention to approval pathways, evidence requirements, interchangeability, substitution, and post-marketing surveillance [2,9,13,17].

To analyze ethical challenges related to interchangeability, substitution, informed communication, treatment switching, traceability, and pharmacovigilance [11–13,16,18].

To evaluate the relationship between biosimilar competition, affordability, healthcare-resource allocation, and equitable access to biological therapies [5,6,14].

To assess the responsibilities of pharmacists, prescribers, manufacturers, patients, payers, and regulatory authorities in promoting safe, transparent, evidence-based, and ethically responsible biosimilar use [7,13,15,16].

To propose ethically informed recommendations for responsible biosimilar governance in India and the United States, while recognizing the different regulatory, healthcare-financing, and institutional contexts of the two countries [1,2,9,13].

2.1 Review design

This article is designed as a comparative narrative review integrating regulatory analysis, scientific evidence, and pharmaceutical-ethics reasoning. It is not presented as a systematic review, meta-analysis, or original clinical study. Its purpose is to synthesize relevant evidence and critically examine ethical issues associated with biosimilars in India and the United States.

The review framework is organized around the following domains:

Scientific similarity and regulatory evidence.

Patient safety and immunogenicity.

Interchangeability and treatment switching.

Patient autonomy and informed communication.

Accessibility, affordability, and distributive justice.

Pharmacovigilance and product traceability.

Responsibilities of healthcare professionals and manufacturers.

Regulatory transparency and accountability.

2.2 Evidence sources

The principal sources for the review include:

World Health Organization (WHO) guidelines on the evaluation of biosimilars [19].

CDSO–DBT *Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India* [20].

US Food and Drug Administration (FDA) guidance and educational materials concerning biosimilar and interchangeable biosimilar products [21–22].

Peer-reviewed literature on biosimilar development, analytical comparability, clinical switching, immunogenicity, pharmacovigilance, and healthcare policy [25–30].

Bioethical literature addressing autonomy, beneficence, non-maleficence, justice, transparency, accountability, and related principles [39].

The Indian and US regulatory documents are treated as primary sources for describing their respective regulatory frameworks. Scientific and ethical literature is used to evaluate the implications of those frameworks. The regulatory status of individual guidance documents is considered as of the time of manuscript preparation because regulatory requirements may be revised over time [19–22].

2.3 Ethical principles used for analysis

TABLE 1. The analysis applies the following principles:

Ethical principle	Application to biosimilars
Beneficence	Promoting effective treatment, therapeutic benefit, and improved access.
Non-maleficence	Preventing avoidable harm through appropriate evidence, manufacturing controls, safety monitoring, and clinical decision-making.
Autonomy	Respecting patient participation, informed choices, and meaningful communication.
Justice	Promoting fair access and avoiding unjustified disparities in biological treatment.
Transparency	Communicating evidence, risks, uncertainties, product identity, regulatory status, and relevant financial interests.
Accountability	Ensuring that manufacturers, regulators, clinicians, pharmacists, payers, and institutions are answerable for decisions affecting patients.
Proportionality	Matching evidence and regulatory requirements to scientific uncertainty and potential risk.

The four-principle framework of biomedical ethics provides a useful foundation for this analysis, particularly through the principles of autonomy, beneficence, non-maleficence, and justice [39]. However, biosimilar governance also requires attention to public health, institutional responsibilities, commercial influence,

transparency, accountability, and global health equity.

2.4 Scope and limitations

The review focuses on therapeutic biosimilars and related biopharmaceutical governance. It does not attempt to provide an exhaustive assessment of every biological

product category, every state-level US substitution law, or every Indian state procurement policy. Regulatory requirements may change, and applicable local legal provisions should be checked before the manuscript is submitted or used for policy interpretation.

The review also recognizes that evidence concerning the safety and effectiveness of switching may vary according to the molecule, indication, patient population, product characteristics, duration of follow-up, and study design. Evidence from switching studies should therefore be interpreted in a product-specific and clinically contextual manner [24-25].

3. Scientific and Regulatory Foundations of Biosimilars

3.1 Biosimilars versus reference biological products

A reference biological product is an authorized biological medicine against which a proposed biosimilar is compared. The reference product has an established body of evidence supporting its quality, safety, and effectiveness. A biosimilar may rely, to an extent determined by the applicable regulatory framework, on relevant evidence generated for the reference product after demonstrating sufficient similarity [19-21].

The scientific rationale is that extensive similarity in structure, function, and quality attributes can reduce the need to repeat every component of the reference product's development programme. This approach can reduce unnecessary duplication of research and allow development resources to be directed toward resolving clinically relevant residual uncertainty [19,21,23].

However, biosimilarity does not mean that manufacturing processes, excipients, delivery devices, or every analytical attribute must be identical. Biological medicines are inherently complex products, and some degree of molecular and manufacturing variability may occur even between batches of the same biological product [19,23].

The ethical justification for an abbreviated development pathway is consequently conditional. It is acceptable only when the scientific evidence is sufficiently robust and when the regulatory system can identify and manage residual uncertainty. A shorter development pathway should not become a mechanism for lowering quality standards or transferring unreasonable risk to patients [19-21,23].

3.2 Comparability and critical quality attributes

The assessment of biosimilarity is based on a comprehensive comparison of the proposed product with the reference product. Critical quality attributes may include:

Molecular identity and primary structure.

Higher-order structure.

Glycosylation and other post-translational modifications.

Purity and impurities.

Aggregation and degradation products.

Charge heterogeneity.

Biological activity and potency.

Stability and formulation-related characteristics.

Product-related and process-related impurities.

The precise analytical package depends on the product and the applicable regulatory framework. The objective is to identify differences that could potentially affect safety, effectiveness, or immunogenicity [19-21,23].

The analytical assessment is particularly important from an ethical standpoint because it can identify relevant differences before patients are exposed to the product. Strong analytical characterization can therefore support the principle of non-maleficence by reducing uncertainty at an early stage of development [19,23].

3.3 Clinical evidence and residual uncertainty

Clinical studies for biosimilars are not necessarily designed to independently establish the entire benefit-risk profile from the beginning, as would normally be required for an entirely novel biological product. Instead, clinical evidence forms part of a totality-of-evidence approach in which analytical and functional similarity are established first, and clinical studies address remaining uncertainty [19,21,23].

Depending on the product and regulatory requirements, studies may include pharmacokinetic and pharmacodynamic comparisons, clinical efficacy and safety evaluations, and immunogenicity assessments. Regulatory authorities determine the evidence necessary to establish that there are no clinically meaningful differences between the biosimilar and reference product [19-21].

Ethically, clinical evidence must be adequate to protect trial participants and future patients. At the same time, regulators should avoid requiring studies that are unlikely to provide scientifically useful information. The appropriate balance is therefore a proportionate evidence strategy that protects participants while avoiding unnecessary duplication of research [19,21,23].

3.4 Immunogenicity and patient safety

Immunogenicity refers to the capacity of a biological product to induce an immune response. Such responses may be clinically insignificant, or they may affect pharmacokinetics, treatment effectiveness, tolerability, or safety. Factors influencing immunogenicity can include molecular characteristics, impurities, aggregation, formulation, route of administration, manufacturing processes, and patient-related factors [19,27].

Because biosimilars are produced through biological systems, changes in manufacturing processes or product characteristics require scientific assessment. Regulatory oversight must therefore include appropriate controls for manufacturing consistency, quality changes, and immunogenicity monitoring [19,20,27].

Available clinical and regulatory evidence generally supports comparable immunogenicity profiles for approved biosimilars and their reference products, although assessment methods, molecules, indications, and patient populations vary. Consequently, immunogenicity should remain an important component of both pre-

approval evaluation and post-marketing surveillance [27-28].

The ethical principle of non-maleficence requires manufacturers and regulators to identify and manage potential risks. The principle of beneficence requires that the resulting therapy provide meaningful clinical value. Patients should receive clear, balanced information about the evidence supporting a biosimilar without being led to believe that biological products are completely risk-free [27-28].

3.5 Biosimilarity, interchangeability, and substitution

These three concepts should be distinguished carefully.

Biosimilarity is a scientific and regulatory determination that a biological product is highly similar to a reference product and has no clinically meaningful differences in the relevant safety and effectiveness characteristics [19-21].

Interchangeability is a regulatory or legal designation whose meaning depends on the jurisdiction. In the United States, an interchangeable biosimilar must satisfy additional statutory and regulatory requirements under the applicable FDA framework. It is therefore not synonymous with ordinary biosimilarity [21-22].

The FDA explains that an interchangeable biosimilar is a biosimilar that meets additional requirements and, subject to applicable state pharmacy law, may be substituted for the reference product at the pharmacy without intervention by the prescribing healthcare professional [21-22].

Substitution refers to the practical act of replacing one medicine with another. Whether substitution is permitted, who may authorize it, and whether the patient or prescriber must be notified are matters of applicable law, policy, and clinical practice [21-22].

In India, the regulatory concept of a similar biologic should not automatically be equated with the US statutory designation of interchangeability. The Indian framework should therefore be described using its own regulatory terminology and applicable prescribing, dispensing, and institutional requirements [20,28].

Confusing these terms may undermine patient understanding and professional accountability. Ethical communication should explain the evidence and legal or regulatory status of the product accurately, without overstating either the risks or the benefits of substitution [21,22,28].

4. Ethical Foundations of Biosimilar Governance

4.1 Beneficence: Promoting patient welfare

Beneficence requires healthcare decisions to promote patient welfare and produce meaningful therapeutic benefit [29]. In biosimilar governance, this principle supports the development of safe, effective, and potentially more affordable biological medicines. Biosimilars may increase the number of available treatment options and may promote competition and access to biological therapies [19,28,30].

The ethical value of biosimilar competition, however,

depends on whether its benefits reach patients. A reduction in a manufacturer's selling price does not automatically translate into lower patient expenditure. Final costs may be influenced by insurance arrangements, procurement contracts, distribution margins, hospital policies, reimbursement rules, formulary arrangements, and pharmacy purchasing practices [30-31].

Consequently, an ethical evaluation of biosimilar affordability should examine the entire medicine-supply chain rather than focusing exclusively on the manufacturer's price. Evidence from comparative market analyses demonstrates that biosimilar uptake and treatment costs can differ substantially between health systems because of differences in regulatory, reimbursement, and market structures [30].

Beneficence also requires that clinical decisions remain patient-centered. A clinician should not recommend a biosimilar solely because it is less expensive if the proposed product is unsuitable for the patient's clinical circumstances, administration requirements, or treatment continuity. Conversely, a patient should not be denied an appropriate biosimilar solely because of unsupported assumptions that the product is inherently inferior to the reference medicine [19,24,28].

4.2 Non-maleficence: Preventing avoidable harm

The principle of non-maleficence requires healthcare stakeholders to avoid causing preventable harm [29]. For biosimilars, this principle applies throughout the product lifecycle:

Research participants must be protected through appropriate ethical review and informed consent.

Manufacturers must implement validated processes and robust quality controls.

Regulatory authorities must evaluate evidence objectively.

Healthcare professionals must prescribe and dispense responsibly.

Patients must receive appropriate instructions and monitoring.

Pharmacovigilance systems must identify and investigate safety signals.

Biological products can be affected by manufacturing variability, storage conditions, handling, delivery systems, and immunogenicity-related factors. Therefore, a responsible regulatory system must ensure that quality and safety are assessed before approval and monitored after market entry [19-20,26,36].

Non-maleficence does not imply that every possible uncertainty must be eliminated before a biosimilar can be authorized. Absolute certainty is rarely possible in medicine. Rather, the ethical requirement is that uncertainty be scientifically assessed, communicated proportionately, and managed through appropriate risk-minimization and pharmacovigilance measures [19,26,36].

4.3 Autonomy: Respecting patient participation

Patient autonomy requires that individuals be treated as capable participants in decisions concerning their health [29]. In biosimilar therapy, autonomy may become particularly relevant when a patient is asked to change from a reference biological product to a biosimilar or, where clinically and legally applicable, from one biosimilar to another.

Respect for autonomy does not necessarily mean that every patient must independently authorize every routine substitution. Practical requirements depend on applicable law, clinical circumstances, the nature of the decision, and the patient's capacity. Nevertheless, patients should receive understandable information when a change is clinically significant or when they reasonably wish to know which biological product they are receiving [21,22,24,25].

Ethically appropriate communication should explain:

What a biosimilar is.

How it was compared with the reference product.

Why the proposed product is being selected.

What is known about its safety and effectiveness.

Whether the change involves a different biological product, delivery device, formulation, or administration procedure.

How adverse events and treatment response will be monitored.

Whom the patient should contact if concerns arise.

Information should be neither promotional nor unnecessarily alarming. A patient should not be told that a biosimilar is “exactly identical” to the reference product when that statement is scientifically inaccurate. Similarly, the patient should not be led to believe that a biosimilar is inherently unsafe merely because it is not molecularly identical to the reference product [1,5,10].

Evidence from switching studies should also be communicated with appropriate qualification. Systematic reviews have generally not identified major differences in efficacy, safety, or immunogenicity following studied switches between reference biological products and their biosimilars, although limitations remain regarding rare adverse events, multiple switching, individual products, and long-term follow-up [24,25].

4.4 Justice: Equitable access to biological therapies

Justice concerns the fair distribution of healthcare benefits, risks, and resources [11]. The high cost of biological medicines may create unequal access among patients, particularly those with limited income, inadequate insurance, or insufficient healthcare infrastructure. Biosimilars may contribute to improved access by increasing treatment options and competition [19,29,30].

However, justice requires more than the existence of lower-cost products. A biosimilar may remain inaccessible because of:

High out-of-pocket expenditure.

Inadequate reimbursement.

Limited availability in rural or underserved areas.

Weak cold-chain infrastructure.

Shortages or inconsistent supply.

Lack of trained healthcare professionals.

Limited patient awareness.

Unequal access to diagnostic and monitoring services.

In India, socioeconomic and geographical differences can influence access to specialist care and biological medicines. The Indian literature has identified affordability and access as important considerations in the use of similar biologics, while also emphasizing the need for appropriate regulatory and quality safeguards [28,31].

In the United States, insurance coverage, formulary design, benefit structures, reimbursement arrangements, and patient cost-sharing can influence whether patients actually benefit from biosimilar competition [30]. An ethically sound policy should therefore evaluate access at the patient level rather than relying solely on national market statistics.

4.5 Transparency and accountability

Transparency requires accurate communication of evidence, regulatory status, risks, uncertainties, product identity, and relevant financial interests. Accountability requires that institutions and individuals accept responsibility for decisions that affect patients [31].

In biosimilar governance, transparency may include:

Publicly accessible regulatory information.

Clear product identification and labelling.

Disclosure of the evidence supporting regulatory authorization.

Appropriate reporting of safety concerns.

Transparent procurement and reimbursement arrangements.

Disclosure and management of conflicts of interest.

Accessible patient education.

Pharmacovigilance is particularly dependent on accurate product identification. Because multiple biological products may share the same therapeutic target or non-proprietary name, adverse-event reporting systems need sufficient information to identify the specific product and, where possible, the manufacturer and batch. Accurate traceability supports signal detection and helps distinguish product-specific safety concerns [32-33].

Accountability should be distributed across the healthcare system. Manufacturers are responsible for product quality, manufacturing controls, and accurate scientific communication; regulators are responsible for scientifically defensible oversight; clinicians and pharmacists are responsible for appropriate patient care and product identification; institutions are responsible for safe medicine-use systems; and payers are responsible for policies that do not create unjustified barriers to medically appropriate treatment [19-23,32-33].

Accordingly, ethical biosimilar governance should integrate scientific rigor with transparency, traceability, patient participation, equitable access, and clearly defined responsibilities across the product lifecycle.

5. Comparative Regulatory Governance in India and the United States

5.1 Overview of the Indian regulatory framework

India's biosimilar regulatory pathway has historically been associated with the Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT). The *Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India* established a regulatory framework for products claiming similarity to an authorized reference biological product and were revised in 2016 to incorporate a more structured, science-based comparability approach [44-45].

The Indian framework addresses the development and authorization of similar biologics through quality, preclinical, clinical, manufacturing, and post-marketing considerations. It recognizes the importance of a comparability exercise to establish similarity to the reference product and guides the evidence expected for marketing authorization [44-45].

The 2016 framework was subsequently revised. The current Indian *Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India* were issued in 2025 and expressly replace the 2016 guideline. The updated document reflects developments in scientific knowledge and regulatory experience and should therefore be consulted when describing the current Indian regulatory position [45].

CDSCO functions as India's national drug regulatory authority, while DBT has played an important role in the development and oversight of biotechnology-related regulatory frameworks. The allocation of responsibilities between the agencies and other applicable authorities should be interpreted according to the prevailing Indian legal and regulatory framework.

From an ethical perspective, India's regulatory framework provides an institutional basis for balancing public-health access with scientific quality and patient protection [44-45]. However, the ethical effectiveness of a regulatory

framework depends not only on written requirements but also on implementation, inspection capacity, manufacturing consistency, post-marketing monitoring, and enforcement of applicable standards [34,42,45].

5.2 Overview of the US regulatory framework

In the United States, the Biologics Price Competition and Innovation Act (BPCI Act) of 2009 established an abbreviated licensure pathway for biosimilar and interchangeable biological products under section 351(k) of the Public Health Service Act [13]. The US Food and Drug Administration (FDA) evaluates biosimilar applications using a science- and evidence-based framework that considers analytical, nonclinical, clinical, and other relevant evidence [37,38].

The FDA defines a biosimilar as a biological product that is highly similar to a reference product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences in safety, purity, and potency between the products [38,47].

The FDA also recognizes a separate category of interchangeable biosimilar products that satisfy additional statutory requirements relating to interchangeability [38,47]. The FDA explains that an interchangeable product may, subject to applicable state pharmacy law, be substituted for the reference product at the pharmacy without intervention by the prescribing healthcare professional [38,47].

An interchangeable designation therefore has specific regulatory and legal significance. It does not mean that a non-interchangeable biosimilar is unsafe or ineffective. FDA-approved biosimilars and interchangeable biosimilars must meet the applicable FDA standards for biosimilarity, and interchangeability should not be interpreted as a general ranking of clinical superiority [38,47].

The US framework illustrates an important ethical principle: legal distinctions affecting substitution must be communicated accurately. Patients, prescribers, pharmacists, insurers, and healthcare institutions should understand the difference between the scientific finding of biosimilarity and the legal authority to substitute a product [38,47].

5.3 Comparative regulatory analysis (Table 2.)

Regulatory dimension	India	United States
Principal regulatory institutions	CDSCO and DBT, together with other applicable authorities [11,12]	FDA under the Public Health Service Act and BPCI Act [37,46]
Terminology	“Similar biologics” has historically been used in the Indian framework; the 2025 guideline continues the Indian regulatory framework for similar biologics [44-45]	“Biosimilar” and “interchangeable biosimilar” are distinct FDA terms [38,47]
Scientific foundation	Comparability with an authorized reference biological product [44-45]	Comprehensive demonstration of biosimilarity to an FDA-licensed reference product [37,38]

Evidence requirements	Quality, preclinical, clinical, manufacturing, and post-marketing requirements according to the applicable framework [44-45]	Stepwise, totality-of-evidence assessment; requirements depend on the product and statutory pathway [37-38]
Interchangeability	Must be interpreted according to applicable Indian legal and professional requirements; biosimilarity alone should not be assumed to authorize automatic substitution [44-45]	FDA may grant an interchangeable designation when applicable statutory requirements are met [38,47]
Pharmacovigilance	Post-marketing monitoring and applicable reporting responsibilities [44-45]	FDA safety monitoring and applicable adverse-event reporting systems [42,48]
Ethical policy priority	Balancing affordable access, manufacturing capability, quality, and patient protection [10-12]	Balancing competition, patient access, scientific evidence, and legal substitution requirements [4,13-15]

The table is a high-level comparison rather than a complete statement of either country's law. Indian terminology and requirements should be verified against the current CDSCO framework, while US substitution rules must be interpreted with reference to applicable state law and institutional policy [38,45-46].

The FDA and CDSCO frameworks establish scientific and regulatory foundations, but implementation remains essential to ethical governance [34, 42-43].

5.4 Regulatory convergence and divergence

Both countries share a fundamental scientific principle: biosimilar authorization should be based on evidence demonstrating high similarity to an appropriate reference biological product. Both systems recognize the importance of product quality, clinical safety, effectiveness, and post-marketing oversight [34,37,44-45].

Important differences may arise in terminology, legal substitution arrangements, institutional practice, procurement, and the organization of healthcare delivery. In the United States, the FDA's interchangeable designation has a specific statutory significance. In India, the practical implications of biosimilar substitution must be assessed under the applicable regulatory, legal, and professional framework rather than inferred from the US designation [38,45-46].

Ethically, regulatory divergence is not necessarily a defect. Different healthcare systems may use different institutional arrangements to pursue similar objectives of safety, effectiveness, access, and accountability [43-44].

However, divergence can create confusion when manufacturers, clinicians, or patients interpret one country's terminology as if it had identical legal significance in the other country [5,12,14].

6. Patient Safety and Ethical Risk Management

6.1 Quality assurance and manufacturing consistency

The quality of a biological medicine is closely related to its manufacturing process. Changes in cell culture, purification, formulation, storage, or production conditions may influence relevant quality attributes.

Consequently, biosimilar manufacturers must maintain appropriate process controls, validation, analytical testing, and quality-management systems [34,36,44-45].

Critical quality attributes used in biosimilar analytical comparability assessments may include structural characteristics, higher-order structure, post-translational modifications, purity, impurities, aggregation, charge variants, and biological or functional activity [35-36].

Analytical comparability is a central component of biosimilar development because extensive analytical similarity can reduce residual uncertainty that must subsequently be addressed through nonclinical and clinical evidence [34-36].

The ethical obligation of manufacturers extends beyond obtaining marketing authorization. Manufacturers should ensure that production remains consistent, deviations are investigated, post-approval changes are appropriately assessed, and relevant quality or safety information is communicated to regulatory authorities [42, 44-45].

Quality assurance also has a public-health dimension. A defective batch may affect multiple patients across different healthcare institutions. Strong manufacturing oversight, effective inspection, quality systems, and appropriate recall procedures are therefore important instruments of non-maleficence and accountability [42,45].

6.2 Immunogenicity and clinical monitoring

Immunogenicity remains a relevant safety consideration for biological products. The development of an immune response may be influenced by the biological molecule, product impurities, aggregates, manufacturing changes, formulation, administration route, and patient characteristics [42].

A scientifically sound biosimilar assessment should consider immunogenicity within the totality-of-evidence framework. Analytical and functional characterization, clinical studies where required, and appropriate post-marketing surveillance collectively contribute to the assessment of immunogenicity [34,37,41].

After authorization, continued monitoring may be needed to identify uncommon or delayed safety concerns, particularly where patient exposure is extensive, or treatment is prolonged [41-41].

Ethical monitoring should be proportionate to the product's known and potential risks. It should not create unjustified fear among patients, but it should also avoid minimizing uncertainties. Patients should receive information about clinically relevant adverse effects and the mechanisms available for reporting suspected reactions [41-42].

6.3 Product traceability

Traceability is essential for effective pharmacovigilance. Biological products may be marketed under different brand names, may be manufactured at different facilities, and may undergo manufacturing or formulation changes. A clear record of the exact product administered or dispensed can assist investigators in determining whether a safety signal is associated with a specific product or manufacturing lot [42,48].

Ethically responsible traceability requires:

Accurate recording of the product name.

Recording of the manufacturer and relevant product identifiers.

Batch or lot documentation when appropriate.

Clear prescribing and dispensing records.

Communication between healthcare professionals.

Reliable adverse-event reporting [42,48].

A failure to identify the product involved in a suspected adverse event may delay investigation and weaken the ability to detect product-specific safety signals. Traceability is therefore not merely an administrative task; it is a component of patient safety and institutional accountability [9,15].

6.4 Risk communication

Risk communication should be evidence-based, comprehensible, and proportionate [5,8]. Patients may have concerns about changing from a familiar reference product to a biosimilar. These concerns may arise from misunderstanding the term "similar," previous experiences with medicines, media information, or inadequate counselling [39,43].

Healthcare professionals should avoid both extremes:

Over-reassurance: claiming that biosimilars are completely identical or entirely free from risk [34,38].

Unnecessary alarm: suggesting that biosimilars are inherently inferior or unsafe merely because they are not molecularly identical copies [34,38-39].

The appropriate approach is to explain the regulatory evidence, the clinical rationale, the monitoring plan, and the patient's options under the applicable legal and clinical framework [38-39,47].

7. Interchangeability, Substitution, and Patient Autonomy

7.1 Ethical distinction between interchangeability and substitution

Interchangeability and substitution are closely related but should not be treated as interchangeable terms. Biosimilarity is primarily a scientific and regulatory determination. Interchangeability may have a jurisdiction-specific legal meaning, whereas substitution describes the practical replacement of one medicine by another [38,45,47].

In the United States, the FDA distinguishes an approved biosimilar from an interchangeable biosimilar. The latter must satisfy additional statutory requirements related to interchangeability [38,47]. Pharmacy-level substitution is then subject to applicable state law and other practice requirements [38,47].

In India, the ethical and legal implications of substitution should be assessed using the applicable regulatory and professional framework. A biosimilar authorization should not automatically be interpreted as unrestricted pharmacy-level substitution without examining the relevant law, clinical circumstances, and institutional policies [45].

7.2 Ethical considerations in switching treatment

Switching a patient from a reference biological product to a biosimilar may be clinically appropriate. However, the ethical evaluation should consider the patient's disease, treatment history, clinical stability, previous adverse reactions, administration method, and ability to receive appropriate follow-up [39,40].

A clinically justified switch may promote beneficence by reducing costs or improving availability. Nevertheless, a switch that is imposed without adequate explanation may undermine patient trust and autonomy [39,40].

Evidence from systematic reviews of switching studies has generally not identified major differences in efficacy, safety, or immunogenicity following studied switches between reference biological products and biosimilars. However, limitations remain concerning rare adverse events, repeated switching, specific molecules, and long-term follow-up [39,40].

The ethical approach should therefore be individualized. A patient who is clinically stable should not automatically be excluded from a biosimilar switch, but the decision should be supported by appropriate evidence and monitoring. Similarly, a patient's concern should not automatically be interpreted as evidence that the biosimilar is unsuitable.

7.3 Informed consent and shared decision-making

The degree of information and consent required depends on the clinical and legal circumstances. Shared decision-making is particularly important when a treatment change has meaningful consequences for the patient or when reasonable treatment alternatives exist [43,49].

A suitable counselling discussion may include:

The identity of the reference product and proposed biosimilar [38,47].

The scientific basis for biosimilarity [34,37-38].

The expected therapeutic role of the proposed medicine [37-38].

The reason for the proposed change [6,10].

Available information about switching and relevant safety considerations [39-40].

The monitoring and follow-up plan [41-42].

The process for reporting adverse events [42,48].

The patient's opportunity to ask questions [40,49].

Information should be adapted to health literacy and language. In India, multilingual communication may be important in clinical practice. In the United States, language access and health-literacy considerations may similarly affect whether patients understand treatment decisions [43,49].

The ethical objective is not simply to obtain a signature or provide a technical leaflet. It is to support meaningful understanding and participation [43,49].

7.4 Pharmacist responsibility in biosimilar substitution

Pharmacists have an important role in the safe and ethical use of biosimilars. Their responsibilities may include:

Verifying product identity and relevant regulatory status [38,47].

Reviewing the prescription and applicable substitution rules.

Confirming storage and handling requirements.

Counselling patients regarding administration and adverse effects [41-42].

Documenting dispensing information appropriately [42,48].

Supporting communication with prescribers.

Monitoring and reporting suspected adverse events.

Addressing patient concerns without misleading or promotional claims.

Pharmacists must balance professional independence with institutional policies, procurement arrangements, and legal requirements. Commercial incentives should not override patient safety or applicable professional obligations [43,49].

In the United States, the pharmacist's role in substitution may depend on the product's regulatory designation and state law [38,47]. In India, pharmacists must act within the applicable regulatory and professional framework [35]. In both countries, accurate documentation and communication are essential components of safe biological-medicine use [42,48].

8. Accessibility, Affordability, and Healthcare Justice

8.1 Biosimilars and affordability

A principal public-health rationale for biosimilars is that they may promote competition and expand access to biological therapy [34,37,43]. By relying partly on the established evidence for an approved reference product, biosimilar development can avoid duplicating every stage of originator development and may support a more competitive market [34,35].

However, biosimilar competition does not guarantee a

particular degree of price reduction. Actual patient savings depend on relationships among manufacturers, purchasers, insurers, hospitals, pharmacies, distributors, and patients [43,50].

The ethical assessment of affordability should therefore distinguish between:

Manufacturer price.

Institutional procurement price.

Reimbursement price.

Patient out-of-pocket expenditure.

Total cost of treatment and monitoring [43,50].

A policy that produces lower institutional expenditure but increases financial burdens on vulnerable patients may raise concerns under the principle of healthcare justice [43,50].

8.2 Accessibility in India

India has a large population with substantial differences in income, healthcare infrastructure, and access to specialist services. Biosimilars may provide opportunities to expand treatment options when biological medicines are otherwise unaffordable [43,51].

Nevertheless, several barriers may limit access:

Unequal distribution of specialist healthcare.

Limited availability of biological therapies in some regions.

Inadequate cold-chain facilities where required [44-45].

High expenditure on diagnosis and monitoring [43].

Differences in public and private procurement [43,51].

Variable patient awareness.

Financial barriers to long-term treatment.

Ethical biosimilar policy in India should therefore combine regulatory quality with access-oriented procurement, appropriate reimbursement, patient education, and investment in healthcare infrastructure [10,18]. The availability of a biosimilar in the national market should not automatically be equated with equitable access for every patient.

8.3 Accessibility in the United States

In the United States, the affordability of biological medicines is influenced by insurance coverage, benefit design, formulary arrangements, reimbursement, and patient cost-sharing [17].

Biosimilars may promote competition, but the economic benefit experienced by an individual patient may vary substantially according to insurance arrangements and treatment setting [17].

An ethically responsible system should therefore examine whether savings generated by biosimilar use reach patients who need treatment. It should also avoid policies that create incentives for inappropriate switching, delay treatment, or impose disproportionate administrative burdens on vulnerable patients [10,17].

Patient access includes more than the ability to obtain a medicine. It also includes the ability to receive an appropriate product promptly, understand its use, obtain follow-up care, and report adverse events.

8.4 Justice and vulnerable populations

Vulnerable patients may include individuals with low income, chronic illness, limited health literacy, inadequate insurance, geographical barriers, or restricted access to specialist care. These populations may face greater difficulty understanding treatment changes or obtaining continuity of therapy [43,49].

An ethical biosimilar policy should prioritize:

Affordable treatment options.

Clear communication.

Non-discriminatory access.

Reliable supply.

Continuity of care.

Appropriate monitoring.

Protection from misleading promotion.

Fair allocation of scarce healthcare resources [43,49-50].

Justice also requires attention to patients who may not benefit immediately from competition. For example, a patient may face high administration or monitoring costs even if the medicine's purchase price is reduced [50].

9. Stakeholder Responsibilities in Ethical Biosimilar Governance

9.1 Pharmaceutical manufacturers

Manufacturers have responsibilities extending from research and development to post-marketing surveillance. Their ethical obligations include:

Conducting scientifically sound comparability studies [34-36].

Protecting clinical-trial participants [43,49].

Maintaining good manufacturing practices [44-45].

Ensuring product quality and supply reliability.

Providing accurate regulatory submissions.

Avoiding misleading promotional claims [43].

Reporting relevant safety information.

Supporting appropriate product traceability.

Disclosing and managing relevant conflicts of interest.

Contributing to appropriate patient education.

Manufacturers should not exaggerate the superiority of biosimilars over reference products, nor should they undermine confidence in competing products through unsupported claims. Responsible competition should improve patient options without distorting clinical decision-making [43].

9.2 Regulatory authorities

Regulatory authorities are responsible for ensuring that biosimilars meet applicable standards of quality, safety,

and effectiveness [34,36,44-45]. Their ethical duties include:

Scientific independence [34,36].

Consistent application of regulatory standards.

Transparent decision-making.

Appropriate evaluation of manufacturing and clinical evidence.

Post-marketing safety oversight.

Clear communication of regulatory decisions.

Management of conflicts of interest.

Proportionate and enforceable requirements.

CDSCO and DBT in India and the FDA in the United States provide the principal regulatory structures relevant to this comparison. Their exact responsibilities and procedures are determined by their respective legal frameworks [37,44-46].

Regulatory accountability also includes the ability to explain decisions to the public. Patients and healthcare professionals should have access to understandable information about what regulatory approval means and what it does not mean [37,38,47].

9.3 Prescribers

Prescribers should consider available scientific evidence, the patient's clinical condition, the product's regulatory status, and applicable legal requirements when making treatment decisions [38-39].

They should not allow financial incentives, institutional pressure, or unsupported beliefs to replace professional clinical judgment [43,49].

Prescribers also have a responsibility to explain clinically meaningful treatment changes and to coordinate monitoring where necessary [39-40,43]. If a patient experiences a suspected adverse event, the prescriber should support appropriate documentation and reporting [42,48].

9.4 Pharmacists

Pharmacists are central to medicine safety, dispensing, counseling, and pharmacovigilance [42,48]. Their ethical responsibilities include protecting patients from dispensing errors, verifying the identity of biological products, maintaining appropriate storage conditions, and communicating relevant information [42,45,48].

In systems where substitution is permitted, pharmacists must follow applicable legal requirements and institutional procedures [38,14]. Where substitution is not authorized or is clinically inappropriate, cost considerations alone should not be treated as sufficient justification for replacing a prescribed biological medicine.

9.5 Healthcare institutions and payers

Hospitals, insurers, pharmacy benefit managers, procurement agencies, and other purchasing organizations influence biosimilar use. Their decisions may affect product availability, clinical protocols, reimbursement, and patient expenditure [43,50].

Institutional policies should be designed around evidence, patient safety, and fair access. Procurement policies should incorporate quality assurance, supply continuity, traceability, and transparent evaluation of economic consequences [42,45,50].

Payers should avoid formulary or reimbursement practices that create inappropriate treatment interruptions. Economic policies should be assessed for their effects on vulnerable patients rather than solely on aggregate financial savings [43,50].

9.6 Patients and patient organizations

Patients should be supported as participants in treatment decisions [43,49]. Patient organizations can contribute to education, awareness, safety reporting, and policy discussions. They may also help identify practical barriers that are not visible through regulatory or economic data alone.

Patient involvement should be meaningful and should not be used merely to legitimize predetermined commercial or institutional decisions. Meaningful participation requires accessible information, an opportunity to ask questions, and appropriate consideration of patient concerns [43,49].

10. Pharmacovigilance, Transparency, and Post-Marketing Accountability

10.1 Importance of pharmacovigilance

Pharmacovigilance is the science and practice of detecting, assessing, understanding, and preventing adverse effects or other medicine-related problems. For biological products, effective pharmacovigilance is particularly important because product-specific information may be needed to interpret safety signals. [54-55]

A robust pharmacovigilance system should support:

Timely adverse-event reporting.

Accurate identification of the product involved.

Evaluation of batch-related or manufacturing-related concerns.

Detection of uncommon adverse reactions.

Assessment of treatment-related patterns.

Communication of clinically relevant safety information.

Appropriate regulatory action. [54-55]

Biosimilar governance should integrate pre-approval evidence with post-marketing monitoring. Approval is therefore not the end of the ethical responsibility to protect patients. [54-55]

10.2 Traceability and naming

Accurate product identification is important for distinguishing among biological medicines. Product names, manufacturer information, batch identifiers, and relevant records may assist in determining whether a safety event is associated with a specific product. Robust traceability is particularly relevant for biological medicines because pharmacovigilance systems must be able to identify the specific biological product involved in an adverse event. [54-55]

The ethical challenge is to improve traceability without creating unnecessary confusion or undermining confidence in biosimilars. Naming and labeling systems should facilitate safe prescribing, dispensing, and reporting while communicating the scientific and regulatory status of the medicine accurately. [54,56]

10.3 Transparency of clinical evidence

Transparency requires that relevant evidence supporting biosimilar authorization be communicated in a way that is accessible to healthcare professionals and, where appropriate, patients. The information should accurately represent both the strength and limitations of the evidence. [54,56]

Selective presentation of favourable results may create unrealistic expectations, while selective presentation of uncertainties may generate unjustified fear. Regulators, manufacturers, and professional organizations should therefore promote balanced communication concerning biosimilarity, clinical evidence, residual uncertainty, and post-marketing safety. [57,58]

10.4 Conflict of interest

Conflicts of interest may arise when individuals or institutions involved in prescribing, purchasing, research, regulation, or education have financial or other interests connected to a biosimilar or reference product. [59]

A conflict of interest does not necessarily establish misconduct. However, it should be disclosed, assessed, and managed to protect the integrity of decisions. Transparent procurement, independent scientific review, and clear professional standards can help reduce the risk that commercial interests override patient welfare. [59,70]

10.5 Ethical responsibilities during shortages

Medicine shortages may create pressure to substitute products or alter treatment plans. During shortages of biological medicines, institutions and healthcare professionals should balance continuity of treatment, product availability, clinical appropriateness, and patient safety. [61]

An ethical shortage response should include:

Transparent communication.

Appropriate clinical review.

Accurate documentation.

Avoidance of unjustified preferential access.

Fair allocation of available supplies.

Monitoring for treatment interruptions.

Timely reporting of supply-related risks. [61]

A shortage should not be used to bypass applicable regulatory or professional requirements. Decisions concerning treatment changes should remain clinically appropriate and should respect patient rights and continuity of care. [62-63]

11. Comparative Ethical Analysis: India and the United States

11.1 Comparative analytical matrix

The following matrix synthesizes the principal ethical issues identified in the regulatory and bioethical literature.

It is an interpretive analysis rather than a quantitative comparison of national outcomes.

Ethical domain	India	United States	Comparative ethical implication
Scientific evidence	Similar biologics are assessed through a comparability-based regulatory framework. [63]	FDA uses a structured biosimilarity pathway under section 351(k). [64-65]	Both systems require scientific evidence, but terminology and implementation differ.
Patient safety	Quality assurance, clinical evidence, and post-marketing oversight are incorporated into the applicable framework. [63]	FDA-approved biosimilars undergo regulatory evaluation for safety, effectiveness, and quality. [65]	Safety should remain independent of price or commercial competition.
Interchangeability	Interpretation depends on the applicable Indian regulatory and professional framework. [63]	FDA has a specific interchangeable biosimilar designation. [65]	Regulatory designations should not be transferred across countries without legal analysis.
Pharmacy substitution	Depends on applicable legal and professional requirements. [63]	Depends on interchangeable status and applicable state pharmacy law. [65-66]	Pharmacists require clear rules and appropriate clinical information.
Affordability	Potential benefits are influenced by income inequality, healthcare infrastructure, procurement, and healthcare financing. [67]	Patient benefit is influenced by insurance, reimbursement, formulary, and cost-sharing arrangements. [68]	Market competition does not automatically guarantee equitable patient savings.
Patient autonomy	Requires understandable counselling and clinically appropriate participation in treatment decisions. [62-63]	Similar ethical duties apply, with additional legal considerations concerning substitution. [62,65]	Shared decision-making should be adapted to the local healthcare context.
Pharmacovigilance	Requires reliable product identification, reporting, and monitoring. [63]	Requires product-specific safety monitoring and appropriate adverse-event reporting. [54-65]	Traceability and reporting are essential in both systems.
Regulatory accountability	Requires effective implementation, inspection, transparency, and enforcement. [63]	Requires scientifically based oversight, transparent regulatory decisions, and continuing monitoring. [64-65]	Written rules are insufficient without effective institutional capacity.

Professional ethics	Pharmacists and prescribers must balance access, safety, evidence, and applicable law. [62-63]	Pharmacists and prescribers must also consider legal substitution and payer arrangements. [62,65]	Professional judgment should not be replaced by commercial or administrative pressure.
---------------------	--	---	--

The principal regulatory foundations for this comparison are the WHO biosimilar guidance, the Indian CDSCO–DBT framework, and FDA materials concerning biosimilarity and interchangeability. [63-65] The WHO 2022 guidance emphasizes a scientifically based approach to biosimilar evaluation, while India's 2025 guideline updates the national framework in light of international scientific developments. [63,69]

11.2 Ethical strengths and challenges in India

India's biosimilar framework provides a regulatory foundation for the development and authorization of biological medicines through a structured comparability exercise. The Indian framework has evolved from the 2012 and 2016 guidelines to the revised 2025 framework, which emphasizes updated quality, nonclinical, clinical, and analytical considerations. [63,70]

The availability of a domestic and internationally active biopharmaceutical sector may support manufacturing capacity, competition, and the potential expansion of treatment access. However, ethical governance requires more than the existence of a regulatory pathway. Important challenges include healthcare infrastructure, affordability, access to specialist services, manufacturing oversight, pharmacovigilance capacity, and patient education. [70]

From a pharmacy ethics perspective, patient-centered counselling, product traceability, professional training, independent safety monitoring, and transparent procurement remain important areas for strengthening biosimilar governance. Such measures should be adapted to the Indian healthcare context rather than assuming that a foreign regulatory model can be transferred without modification. [63,70]

11.3 Ethical strengths and challenges in the United States

The US framework provides a defined statutory pathway for biosimilar approval under section 351(k) and a separate FDA designation for interchangeable biosimilars. [64,65] FDA defines a biosimilar as highly similar to its reference product with no clinically meaningful differences in safety, purity, or potency, while an interchangeable product must satisfy additional statutory requirements. [65]

The United States also has extensive experience with biological medicines and a complex healthcare financing system. Patients may experience different levels of access depending on insurance arrangements, reimbursement policies, formularies, and treatment settings. FDA notes that biosimilars may provide additional treatment options and potentially reduce costs, but FDA does not itself control medicine prices. [71]

Potential challenges include reimbursement complexity, unequal exposure to cost savings, administrative barriers, and the need for clear communication regarding product

switching. Ethical governance should ensure that financial incentives do not replace clinical appropriateness or compromise continuity of care. [62,71]

11.4 Similarities and differences in ethical priorities

Both countries share ethical objectives relating to patient safety, scientific rigor, and expanded access. Both require responsible manufacturing, appropriate scientific evidence, and post-marketing oversight. Nevertheless, differences in healthcare financing, institutional structure, regulatory terminology, and legal arrangements influence the practical implementation of these objectives. [63-65]

A comparative review should therefore avoid treating the regulatory system of either country as universally transferable. Ethical performance can instead be examined using measurable factors such as:

Safety-reporting effectiveness.

Manufacturing quality and inspection outcomes.

Timeliness of regulatory decisions.

Patient access to appropriate biological therapy.

Transparency of evidence.

Quality of professional counselling.

Appropriate documentation of product changes.

Fair distribution of financial benefits. [54,62-63]

A useful comparative framework should evaluate these outcomes rather than rely only on the presence or absence of a particular legal designation.

12. Major Ethical Challenges and Critical Discussion

12.1 The tension between affordability and patient autonomy

One of the central ethical tensions in biosimilar policy is the relationship between affordability and patient autonomy. A healthcare institution may seek to promote a less expensive biological medicine to reduce expenditure or improve access. Such a policy should be accompanied by evidence-based assessment and appropriate clinical consideration. [62,68]

Patients may nevertheless have concerns about changing established therapy. These concerns may involve fear of adverse effects, previous treatment experiences, differences in administration, or uncertainty about the new product. Evidence from systematic reviews has generally not identified major efficacy, safety, or immunogenicity problems associated with switching between reference biologics and biosimilars, although study limitations and treatment-context differences remain relevant. [72-73]

If a treatment change is implemented without adequate communication, patients may experience loss of trust even when the scientific basis for the switch is sound. Patient information should therefore explain the reason for a

treatment change, the regulatory status of the product, the available evidence, and the monitoring plan. [62,72]

The ethical approach is to establish transparent, clinically appropriate decision-making that explains the rationale for treatment changes and provides reasonable opportunities for questions and discussion. The World Medical Association's Declaration of Lisbon recognizes patients' rights to information, self-determination, and participation in decisions concerning their treatment. [62]

12.2 Scientific similarity and public confidence

The term "biosimilar" may be misunderstood by patients who interpret "similar" as meaning "less effective" or "inferior." Conversely, promotional communication may incorrectly imply that biosimilars are identical in every molecular and manufacturing characteristic. Biological products may exhibit inherent variability, and biosimilars are not required to be molecularly identical to their reference products. [71]

The ethical responsibility of regulators, manufacturers, pharmacists, and prescribers is to communicate the scientific meaning of biosimilarity accurately. FDA describes biosimilars as highly similar to their reference products without clinically meaningful differences in safety and effectiveness. [65,71]

Public confidence should therefore be based on evidence and transparency rather than exaggerated reassurance or unnecessary fear. Trust is strengthened when safety concerns are acknowledged, investigated, and communicated appropriately. [54,57]

12.3 Commercial competition and ethical pharmaceutical practice

Competition may support affordability and increase treatment options. FDA identifies biosimilars as products that can potentially increase access and reduce costs through competition. [71]

Commercial incentives can nevertheless create conflicts of interest. Manufacturers may emphasize favourable evidence, institutions may prioritize procurement savings, and payers may design policies that encourage particular products. Conflicts of interest should be disclosed and appropriately managed. [59-60]

Commercial interests are not inherently unethical. The ethical concern arises when financial considerations distort scientific information, restrict patient choice without appropriate justification, or create incentives for inappropriate prescribing or substitution. [59,60,62]

Ethically responsible competition should therefore be accompanied by:

Accurate scientific communication.

Transparent financial arrangements.

Independent clinical decision-making.

Appropriate conflict-of-interest management.

Reliable product monitoring.

Protection of patient welfare. [54,59-60]

12.4 Regulatory efficiency versus regulatory rigor

Biosimilar pathways are designed partly to avoid unnecessary duplication of research and to facilitate access to biological medicines. WHO's revised biosimilar guidance emphasizes greater regulatory flexibility while maintaining standards for quality, safety, and efficacy. [69]

A scientifically proportionate regulatory process may reduce unnecessary studies while maintaining a rigorous assessment of the evidence needed to address uncertainty. The 2025 Indian guideline similarly emphasizes updated analytical and *in vitro* approaches and a more scientifically informed approach to the need for additional studies. [63]

Excessive regulatory burdens may delay access and increase development costs, whereas insufficient requirements may compromise patient protection. Ethical regulation should therefore continually assess whether evidence requirements are scientifically justified and proportionate to the remaining uncertainty. [63,69]

12.5 Ethical implications of treatment switching

Evidence concerning switching should be evaluated at the product and clinical-context level. It is inappropriate to assume that every switch has the same implications for every patient or every biological product. Systematic reviews have reported no major overall efficacy, safety, or immunogenicity concerns associated with switching between reference biologics and biosimilars, while also noting limitations in the available evidence. [72-73]

The ethical assessment should consider:

The available clinical evidence.

The product's approved indications.

The patient's clinical condition.

The number and type of previous switches.

The monitoring plan.

The patient's ability to access follow-up care.

The legal and institutional framework. [72-73]

A responsible switch should be supported by appropriate clinical judgment and documentation. Where uncertainty remains, additional monitoring or consultation may be appropriate rather than assuming that switching is universally beneficial or universally harmful. [72-73]

12.6 Ethical implications of healthcare inequality

Biosimilars may contribute to healthcare justice by increasing the availability of biological treatments. However, access remains influenced by income, healthcare infrastructure, procurement, insurance, reimbursement, and geographical factors. [67-68]

The ethical challenge is to ensure that biosimilar policy does not primarily benefit institutions or insurers while leaving vulnerable patients with substantial financial or logistical barriers. Evaluation should include patient-level outcomes such as treatment initiation, treatment continuation, out-of-pocket expenditure, and access to monitoring. [68]

13. Recommendations for Ethical Biosimilar Governance

13.1 Recommendations for India

1. Strengthen implementation of regulatory standards. Regulatory authorities should support consistent application of quality, safety, clinical, and post-marketing requirements, with appropriate inspection and enforcement. [73]
2. Improve product traceability. Healthcare institutions and pharmacies should maintain accurate records of biological products, including relevant product identifiers and batch information where appropriate. [54-55]
3. Promote patient-centered counselling. Pharmacists and prescribers should receive training on biosimilarity, treatment switching, adverse-event reporting, and communication of scientific uncertainty. [61,72]
4. Improve access-oriented procurement. Public and institutional procurement should evaluate both product quality and the actual effect of purchasing decisions on patient affordability. [67-68]
5. Strengthen pharmacovigilance. Reporting systems should be accessible to healthcare professionals and patients, and relevant product information should be recorded accurately. [54-55]
6. Support ethical industry conduct. Manufacturers should maintain transparency in clinical evidence, quality information, promotional communication, and post-marketing responsibilities. [57,59]
7. Encourage evidence-based public education. Educational materials should explain biosimilars in clear language and should not equate biosimilarity with either molecular identity or inferiority. [71]

13.2 Recommendations for the United States

1. Improve communication concerning regulatory status. Patients and healthcare professionals should understand the distinction between biosimilar approval and interchangeable biosimilar designation. [65-66]
2. Promote transparent transmission of savings. Policymakers and institutions should evaluate whether reductions in medicine expenditure benefit patients through lower out-of-pocket costs and improved access. [68,71]
3. Reduce inappropriate administrative barriers. Payer policies should not unnecessarily delay clinically appropriate treatment or create avoidable interruptions in biological therapy. [68]
4. Strengthen professional education. Pharmacists and prescribers should be supported with current, evidence-based information on biosimilars, switching, substitution law, and pharmacovigilance. [54,65,72]
5. Maintain accurate product identification. Dispensing and administration records should facilitate product-specific adverse-event investigation.
6. Safeguard independent clinical judgment. Institutional and payer incentives should be designed so that cost considerations do not replace clinical appropriateness.
7. Continue transparent regulatory communication. The FDA and relevant professional bodies should communicate regulatory decisions, evidence, and safety information in a manner understandable to healthcare professionals and patients. [57,65]

13.3 Recommendations applicable to both countries (Table 4)

Priority	Recommended action	Ethical justification
Patient safety	Strengthen manufacturing quality, clinical evaluation, and post-marketing monitoring. [54-55,63-64]	Non-maleficence
Patient autonomy	Provide understandable information about treatment changes and clinically relevant risks. [62,72]	Autonomy
Accessibility	Evaluate patient expenditure and availability, not only market prices. [68]	Justice
Professional practice	Train pharmacists and prescribers in biosimilar evidence and applicable law. [62,65,72]	Beneficence and accountability
Transparency	Communicate regulatory status and evidence accurately. [54,65]	Trust and informed decision-making
Traceability	Maintain reliable product identification and adverse-event records. [54-55]	Patient protection
Industry ethics	Disclose and manage conflicts of interest and avoid misleading promotion.	Integrity and accountability
Regulatory governance	Maintain proportionate, scientifically defensible, and enforceable standards. [54,69]	Public-health responsibility

13.4 Proposed ethical governance model

An ethically responsible biosimilar system can be conceptualized as a continuous cycle involving:

scientific evidence → regulatory assessment → authorization → clinical use → patient communication → pharmacovigilance → outcome evaluation → regulatory learning and improvement.

The model emphasizes that ethical governance is not limited to approval. It is a continuing process involving scientific evidence, clinical practice, patient participation, safety monitoring, and institutional accountability. [54,57,63-70]

14. Future Research Directions

Further research is required to strengthen the evidence base for ethical biosimilar governance in India and the United States.

14.1 Patient-centered research

Future studies should examine patient knowledge, perceptions, preferences, and trust concerning biosimilars. Research should assess whether patients understand the meaning of biosimilarity and whether communication affects treatment acceptance and adherence[62,71-72].

14.2 Comparative pharmacoeconomic research

Studies should evaluate the relationship between biosimilar competition and actual patient expenditure. Important outcomes include treatment initiation, treatment continuation, out-of-pocket costs, and access among economically disadvantaged populations. [68,71]

14.3 Pharmacist-led interventions

Research should assess whether pharmacist counselling, medication reconciliation, traceability systems, and structured switching protocols improve patient understanding, medication safety, and treatment continuity. [54,62,72]

14.4 Long-term safety and immunogenicity

Long-term pharmacovigilance studies are needed to evaluate uncommon adverse events, repeated switching, product-specific safety signals, and the clinical implications of manufacturing changes. Immunogenicity remains an important component of biosimilar safety assessment because anti-drug antibodies may affect pharmacokinetics, efficacy, and safety. [54,74]

14.5 Regulatory and policy evaluation

Comparative policy studies should evaluate the effectiveness of regulatory implementation, substitution arrangements, procurement policies, reimbursement systems, and reporting mechanisms. Such research should focus on measurable patient outcomes rather than regulatory terminology alone. [63,65,68]

14.6 Ethical frameworks for digital and AI-assisted governance

Emerging digital systems may support product traceability, pharmacovigilance, medicine procurement, and patient education. However, the use of artificial intelligence and automated decision-making introduces additional questions concerning transparency, accountability, data protection, and professional oversight. Future research should consider how such technologies can be integrated without weakening human

clinical judgment.

15. Conclusion

Biosimilars represent an important development in biopharmaceutical care and have the potential to expand access to biological therapies, support competition, and contribute to affordability. Their ethical significance extends beyond scientific similarity and regulatory approval. Responsible biosimilar use requires attention to patient safety, treatment continuity, informed communication, professional autonomy, healthcare justice, commercial integrity, and regulatory accountability. [54,62-69]

India and the United States have established scientific and regulatory approaches for biosimilar medicines, but differences in terminology, healthcare financing, legal substitution arrangements, institutional capacity, and medicine distribution create distinct implementation considerations. India's 2025 regulatory framework represents an updated approach to similar biologics, while the US framework distinguishes biosimilarity from the separate FDA designation of interchangeability. [63,65]

An ethically responsible biosimilar policy should consider affordability and patient safety together. Properly designed regulation, responsible manufacturing, evidence-based clinical practice, robust pharmacovigilance, and transparent procurement can support these objectives. Pharmacists and prescribers have a central role in translating scientific evidence into safe, patient-centered care. [1,9,10,19]

Ultimately, biosimilar governance should be assessed not only by the number of products approved or the degree of market competition, but also by measurable patient outcomes, including safety, treatment effectiveness, affordability, continuity of care, appropriate monitoring, and equitable access. A comparative ethical framework can therefore assist India and the United States in strengthening patient protection and responsible use of biological medicines. [54,63-65].

REFERENCES

- 1) World Health Organization. Guidelines on evaluation of biosimilars. Geneva: World Health Organization; 2022. Technical Report Series No. 1043, Annex 3.
- 2) Central Drugs Standard Control Organization, Department of Biotechnology. Guidelines on similar biologics: regulatory requirements for marketing authorization in India. New Delhi: Ministry of Health and Family Welfare, Government of India; 2016.
- 3) US Food and Drug Administration. Development of therapeutic protein biosimilars: comparative analytical assessment and other quality-related considerations: guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2025.
- 4) Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Giezen TJ, et al. Biosimilars: what clinicians should know. *Blood*. 2012;120(26):5111-7.
- 5) . Simoens S. Biosimilar medicines and cost-effectiveness. *Clinicoecon Outcomes Res*. 2011;3:29-36.

- 6) Moorkens E, et al. A systematic literature review of gaps and challenges in value assessment of biosimilars: an ISPOR Special Interest Group report. *Value Health*. 2023;26(8):1137-44. doi:10.1016/j.jval.2023.04.007.
- 7) . Beauchamp TL, Childress JF. Principles of biomedical ethics. 8th ed. New York: Oxford University Press; 2019.
- 8) . McKinnon RA, Cook M, Liauw W, Marabani M, Marschner I, Packer NH, et al. Biosimilarity and interchangeability: principles and evidence: a systematic review. *BioDrugs*. 2018;32(1):27-52. doi:10.1007/s40259-017-0256-z.
- 9) . US Food and Drug Administration. Background information: list of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations (Purple Book). Silver Spring (MD): US Food and Drug Administration; 2026.
- 10) . Strand V, Gonçalves J, Hickling TP, Jones HE, Marshall L, Isaacs JD. Immunogenicity of biosimilars for rheumatic diseases, plaque psoriasis, and inflammatory bowel disease: a review from clinical trials and regulatory documents. *BioDrugs*. 2020;34(1):27-37. doi:10.1007/s40259-019-00394-x.
- 11) Casadevall N, et al. Pharmacovigilance and biosimilars: considerations, needs and challenges. *BioDrugs*. 2013;27(4):319-27.
- 12) Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. *Clin Pharmacol Ther*. 2020;108(4):734-55. doi:10.1002/cpt.1836.
- 13) US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2019.
- 14) Ascef BO, et al. Health technology assessment of biosimilars worldwide: a scoping review. *Health Res Policy Syst*. 2020;18:95.
- 15) US Food and Drug Administration. Promotional labeling and advertising considerations for prescription biological reference products, biosimilar products, and interchangeable biosimilar products: questions and answers. Silver Spring (MD): US Food and Drug Administration; 2025.
- 16) Casadevall N, et al. Pharmacovigilance and biosimilars: considerations, needs and challenges. *BioDrugs*. 2013;27(4):319-27.
- 17) Gerard JS, Ramachandran V. Navigating regulatory complexities in biosimilar approvals and imports for autoimmune disorder management: a comparative analysis of FDA (US), EMA (EU), and CDSCO (India) guidelines. *Recent Adv Drug Deliv Formul*. 2025. doi:10.2174/0126673878360952250715031025.
- 18) US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: update. Draft guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2024.
- 19) World Health Organization. Guidelines on evaluation of biosimilars. WHO Technical Report Series, No. 1043, Annex 3. Geneva: World Health Organization; 2022.
- 20) Central Drugs Standard Control Organization, Department of Biotechnology. Guidelines on similar biologics: regulatory requirements for marketing authorization in India. New Delhi: CDSCO, Ministry of Health and Family Welfare, Government of India; Department of Biotechnology, Ministry of Science and Technology, Government of India; 2016.
- 21) US Food and Drug Administration. Questions and answers on biosimilar development and the BPCI Act: guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2026.
- 22) US Food and Drug Administration. Overview for health care professionals: biosimilars and interchangeable biosimilars. Silver Spring (MD): US Food and Drug Administration; 2024-2026.
- 23) Markus R, Liu J, Ramchandani M, Landa D, Born T, Kaur P. Developing the totality of evidence for biosimilars: regulatory considerations and building confidence for the healthcare community. *Bio-Drugs*. 2017;31(3):175-187. doi:10.1007/s40259-017-0218-5.
- 24) Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. *Clin Pharmacol Ther*. 2020;108(4):734-755. doi:10.1002/cpt.1836.
- 25) Herndon TM, Ausin C, Brahme NN, Schrieber SJ, Luo M, Andrada FC, et al. Safety outcomes when switching between biosimilars and reference biologics: a systematic review and meta-analysis. *PLoS One*. 2023;18(10). doi:10.1371/journal.pone.0292231.
- 26) Strand V, Gonçalves J, Hickling TP, Jones HE, Marshall L, Isaacs JD. Immunogenicity of biosimilars for rheumatic diseases, plaque psoriasis, and inflammatory bowel disease: a review from clinical trials and regulatory documents. *BioDrugs*. 2020;34(1):27-37. doi:10.1007/s40259-019-00394-x.
- 27) Mikhail A, et al. Assessing immunogenicity of biosimilar therapeutic monoclonal antibodies: regulatory and bioanalytical considerations. *Bioanalysis*. 2013;5(5):519-534. doi:10.4155/bio.13.6.
- 28) Jois R, Mukherjee S, Rajeswari S, Rath PD, Goyal V, Gupta D. Similar biologics in India: a story of access or potential for compromise? *Indian J Med Res*. 2020;152(5):456-467. doi:10.4103/ijmr.IJMR_43_18.
- 29) Beauchamp TL, Childress JF. Principles of biomedical ethics. 8th ed. New York: Oxford University Press; 2019.
- 30) Mulcahy AW, Buttorff C, Callahan S, et al. Comparison of uptake and prices of biosimilars in the US,

Germany, and Switzerland. *JAMA Netw Open*. 2023;6(1). doi:10.1001/jamanetworkopen.2022.54770.

31) Reddy SK, et al. Economic perspective of cancer treatment in India. *Mol Clin Oncol*. 2020;13(6):1-8. doi:10.3892/mco.2020.2144.

32) Casadevall N, Edwards IR, Felix T, Graze PR, Litten JB, Strober BE, et al. Pharmacovigilance and biosimilars: considerations, needs and challenges. *Expert Opin Biol Ther*. 2013;13(7):1039-1047. doi:10.1517/14712598.2013.783560.

33) Ebberts HC, Mantel-Teeuwisse AK, Moors EHM, Simoons S, Schellekens H. The role of pharmacovigilance in the biosimilars market. *BioDrugs*. 2012;26(1):1-9.

34)

35) World Health Organization. Guidelines on evaluation of biosimilars. WHO Technical Report Series, No. 1043, Annex 3. Geneva: World Health Organization; 2022.

36) Kwon O, Joung J, Park Y, Kim CW, Hong SH. Considerations of critical quality attributes in the analytical comparability assessment of biosimilar products. *Biologicals*. 2017;48:101-108. doi:10.1016/j.biologicals.2017.04.005.

37) Kwon H, et al. Rational selection, criticality assessment, and tiering of quality attributes and test methods for analytical similarity evaluation of biosimilars. *AAPS J*. 2018;20(4):68. doi:10.1208/s12248-018-0230-9.

38) US Food and Drug Administration. Questions and answers on biosimilar development and the BPCI Act: guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2026.

39) US Food and Drug Administration. Review and approval: biosimilar and interchangeable biosimilar products. Silver Spring (MD): US Food and Drug Administration; 2026.

40) Barbier L, Ebberts HC, Declerck P, Simoons S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. *Clin Pharmacol Ther*. 2020;108(4):734-755. doi:10.1002/cpt.1836.

41) Herndon TM, Ausin C, Brahme NN, Schrieber SJ, Luo M, Andrada FC, et al. Safety outcomes when switching between biosimilars and reference biologics: a systematic review and meta-analysis. *PLoS One*. 2023;18(10). doi:10.1371/journal.pone.0292231.

42) Strand V, Gonçalves J, Hickling TP, Jones HE, Marshall L, Isaacs JD. Immunogenicity of biosimilars for rheumatic diseases, plaque psoriasis, and inflammatory bowel disease: a review from clinical trials and regulatory documents. *BioDrugs*. 2020;34(1):27-37. doi:10.1007/s40259-019-00394-x.

43) Casadevall N, Edwards IR, Felix T, Graze PR, Litten JB, Strober BE, et al. Pharmacovigilance and biosimilars: considerations, needs and challenges. *Expert*

Opin Biol Ther. 2013;13(7):1039-1047. doi:10.1517/14712598.2013.783560.

44) Beauchamp TL, Childress JF. Principles of biomedical ethics. 8th ed. New York: Oxford University Press; 2019.

45) Central Drugs Standard Control Organization, Department of Biotechnology. Guidelines on similar biologics: regulatory requirements for marketing authorization in India. New Delhi: Ministry of Health and Family Welfare, Government of India; Department of Biotechnology, Ministry of Science and Technology, Government of India; 2016.

46) Central Drugs Standard Control Organization, Department of Biotechnology. Guidelines on similar biologics: regulatory requirements for marketing authorization in India. New Delhi: Ministry of Health and Family Welfare, Government of India; Department of Biotechnology, Ministry of Science and Technology, Government of India; 2025.

47) United States Congress. Biologics Price Competition and Innovation Act of 2009. In: Patient Protection and Affordable Care Act, Pub L No. 111-148, §7002. Washington (DC): US Government; 2010.

48) US Food and Drug Administration. Background information: list of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations (Purple Book). Silver Spring (MD): US Food and Drug Administration; 2026.

49) US Food and Drug Administration. Biosimilars basics for patients. Silver Spring (MD): US Food and Drug Administration; 2026.

50) World Medical Association. WMA Declaration of Lisbon on the rights of the patient. Ferney-Voltaire: World Medical Association; 2022.

51) Mulcahy AW, Buttorff C, Callahan S, et al. Comparison of uptake and prices of biosimilars in the US, Germany, and Switzerland. *JAMA Netw Open*. 2023;6(1). doi:10.1001/jamanetworkopen.2022.54770.

52) Jois R, Mukherjee S, Rajeswari S, Rath PD, Goyal V, Gupta D. Similar biologics in India: a story of access or potential for compromise? *Indian J Med Res*. 2021;153(5-6):608-616.

53) US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: update. Draft guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2024.

54) US Food and Drug Administration. 9 things to know about biosimilars and interchangeable biosimilars. Silver Spring (MD): US Food and Drug Administration; 2025.

55) Casadevall N, Edwards IR, Felix T, Graze PR, Litten JB, Strober BE, et al. Pharmacovigilance and biosimilars: considerations, needs and challenges. *Expert Opin Biol Ther*. 2013;13(7):1039-47. doi:10.1517/14712598.2013.783560.

56) Casadevall N, Gherardi RK, et al. Pharmacovigilance considerations for biosimilars in the

- USA. BioDrugs. 2014;28(5):439-44. doi:10.1007/s40259-014-0099-9.
- 57) World Health Organization. Guidelines on evaluation of biosimilars. WHO Technical Report Series, No. 1043, Annex 3. Geneva: World Health Organization; 2022.
- 58) US Food and Drug Administration. Questions and answers on biosimilar development and the BPCI Act: guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2026.
- 59) US Food and Drug Administration. Review and approval: biosimilar products and interchangeable biosimilar products. Silver Spring (MD): US Food and Drug Administration; 2026.
- 60) World Medical Association. Declaration of Lisbon on the rights of the patient. Ferney-Voltaire: World Medical Association; reaffirmed 2015.
- 61) Beauchamp TL, Childress JF. Principles of biomedical ethics. 8th ed. New York: Oxford University Press; 2019.
- 62) World Health Organization. Medicines shortages: global approaches to addressing shortages of medicines and other health products. Geneva: World Health Organization; relevant guidance.
- 63) World Medical Association. Declaration of Lisbon on the rights of the patient. Ferney-Voltaire: World Medical Association; 2015.
- 64) Central Drugs Standard Control Organization, Department of Biotechnology, Government of India. Guidelines on similar biologics—regulatory requirements for marketing authorization in India. New Delhi: Ministry of Health and Family Welfare, Government of India; 2025.
- 65) US Food and Drug Administration. Background information: list of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations (Purple Book). Silver Spring (MD): US Food and Drug Administration; 2026.
- 66) US Food and Drug Administration. Purple Book: lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Silver Spring (MD): US Food and Drug Administration; 2026.
- 67) US Food and Drug Administration. Biosimilars basics for patients. Silver Spring (MD): US Food and Drug Administration; 2024.
- 68) Jois R, Mukherjee S, Rajeswari S, Rath PD, Goyal V, Gupta D. Similar biologics in India: a story of access or potential for compromise? *Indian J Med Res*. 2020;152(5):456-67. doi:10.4103/ijmr.IJMR_43_18.
- 69) Mulcahy AW, Buttorff C, Callahan S, et al. Comparison of uptake and prices of biosimilars in the US, Germany, and Switzerland. *JAMA Netw Open*. 2023;6(1). doi:10.1001/jamanetworkopen.2022.54770.
- 70) World Health Organization. Guidelines on evaluation of biosimilars. WHO Technical Report Series. Geneva: World Health Organization; 2022.
- 71) Jois R, Mukherjee S, Rajeswari S, Rath PD, Goyal V, Gupta D. Similar biologics in India: a story of access or potential for compromise? *Indian J Med Res*. 2020;152(5):456-67. doi:10.4103/ijmr.IJMR_43_18.
- 72) US Food and Drug Administration. Biosimilars basics for patients. Silver Spring (MD): US Food and Drug Administration; 2024.
- 73) Barbier L, Ebberts HC, Declercq P, Simoens S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. *Clin Pharmacol Ther*. 2020;108(4):734-55. doi:10.1002/cpt.1836.
- 74) Herndon TM, et al. Safety outcomes when switching between biosimilars and reference biologics: a systematic review and meta-analysis. *PLoS One*. 2023;18(10). doi:10.1371/journal.pone.0292231.
- 75) Strand V, Gonçalves J, Hickling TP, Jones HE, Marshall L, Isaacs JD. Immunogenicity of biosimilars for rheumatic diseases, plaque psoriasis, and inflammatory bowel disease: a review from clinical trials and regulatory documents. *BioDrugs*. 2020;34(1):27-37. doi:10.1007/s40259-019-00394-x.