

Beyond Regulatory Approval: Ethical Accountability, Pharmacovigilance, and Access to Biosimilars in India, the United States, Canada, and the European Union

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Abstract

Background

Biosimilars have become important components of contemporary biopharmaceutical care because they can increase competition and expand access to biological medicines. Their successful integration into healthcare systems, however, requires more than regulatory authorisation. Ethical challenges persist in post-marketing safety surveillance, product traceability, interchangeability, patient communication, reimbursement, and the distribution of healthcare resources.

Objective

This review critically examines the ethical and regulatory responsibilities associated with biosimilars in India, the United States (US), Canada, and the European Union (EU), focusing on patient safety, pharmacovigilance, equitable access, and accountability throughout the

product lifecycle.

Methods

A critical narrative review approach was adopted to examine international biosimilar guidance, regulatory documents, pharmacovigilance recommendations, and relevant peer-reviewed literature. The comparison was organised around five domains: regulatory authorisation, post-marketing safety surveillance, interchangeability and substitution, affordability and access, and ethical accountability. International guidance and jurisdiction-specific regulatory materials were considered alongside literature addressing traceability, immunogenicity, patient autonomy, and responsible biosimilar use. This approach supports a comparative policy analysis but does not constitute a systematic review or an exhaustive assessment of every national legal provision.

Results

The comparison identifies a shared scientific foundation for biosimilar authorisation but different approaches to implementation, interchangeability, healthcare financing, and product-level safety monitoring. India's framework is particularly relevant to the relationship between regulatory capacity, domestic manufacturing, and access. The US framework distinguishes biosimilarity from the additional designation of interchangeability under federal law, with pharmacy substitution governed by state law. The EU combines central scientific assessment with national decisions concerning pharmacy-level substitution and healthcare implementation. Canada provides federal authorisation and safety oversight, while provincial and territorial systems substantially influence interchangeability and formulary policies. Across all four jurisdictions, accurate product identification, effective adverse-event reporting, transparent patient communication, and equitable reimbursement remain important ethical priorities.

Conclusion

Responsible biosimilar governance should extend beyond market authorisation through lifecycle-based pharmacovigilance, reliable traceability, patient-centred communication, and fair access policies. A coordinated ethical governance framework could strengthen accountability while preserving regulatory flexibility and supporting sustainable healthcare.

Keywords: Biosimilars; bioethics; pharmacovigilance; patient safety; regulatory governance; equitable access; interchangeability; India; United States; Canada; European Union.

1. Introduction

Biological medicines have transformed the treatment of several chronic, inflammatory, autoimmune, metabolic, and malignant diseases. Advances in biotechnology have enabled the development of therapeutic proteins, monoclonal antibodies, hormones, and other complex biological products. However, their development and manufacture can involve substantial investment, specialised infrastructure, and complex quality-control requirements. These factors may contribute to high treatment costs and unequal access across healthcare systems [1,2].

Biosimilars offer a regulatory pathway through which a biological medicine can be authorised after demonstrating high similarity to an appropriate reference biological product, without clinically meaningful differences in safety, efficacy, and quality. Unlike conventional generic medicines, biosimilars are not expected to be exact molecular copies of their reference products. Biological medicines exhibit inherent molecular variability, and their characteristics depend on complex manufacturing processes, making a comprehensive comparability exercise central to biosimilar development [1,3].

The World Health Organization (WHO) provides internationally applicable principles for the

evaluation of biosimilars, supporting national regulatory authorities in developing scientifically justified approval pathways [1]. The US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, and India's Central Drugs Standard Control Organization (CDSCO), together with the Department of Biotechnology (DBT) where applicable, have developed frameworks addressing biosimilar quality, safety, efficacy, and authorisation [2–6].

Nevertheless, regulatory approval is only one stage in the lifecycle of a biological medicine. Once a biosimilar enters clinical practice, additional responsibilities arise. These include detecting adverse events, identifying the exact product administered, assessing possible immunogenicity, communicating changes in treatment, maintaining product quality, and ensuring that cost-saving policies do not undermine patient autonomy or continuity of care [7,8].

Pharmacovigilance is particularly important because biological medicines may be associated with immune responses and because safety information must be attributed to the correct product and, where possible, the relevant manufacturer and batch. Inadequate product identification can weaken the interpretation of safety signals and delay appropriate regulatory responses [7,8].

Ethical challenges also arise when healthcare institutions, insurers, public procurement agencies, or prescribing professionals encourage biosimilar use to reduce expenditure. Cost reduction can support distributive justice by allowing more patients to receive effective treatment. However, the ethical legitimacy of such policies depends on reliable evidence, transparent communication, clinically appropriate implementation, and mechanisms for monitoring outcomes.

India, the US, Canada, and the EU provide a useful comparative framework because they combine common scientific principles with different regulatory arrangements, healthcare financing structures, and approaches to interchangeability and substitution. A four-jurisdiction analysis can therefore help distinguish universal ethical responsibilities from policy choices shaped by national or regional institutions.

1.1 Rationale for the review

Existing regulatory frameworks establish the scientific basis for biosimilar authorisation, while pharmacovigilance guidance addresses the detection and assessment of safety concerns. However, ethical accountability extends across these domains and includes questions of transparency, patient choice, affordability, professional responsibility, and fair allocation of healthcare resources.

A critical review connecting these issues may help policymakers and healthcare professionals evaluate biosimilar governance beyond the approval decision itself. Such a review should not assume that differences in regulation automatically indicate differences in safety. Instead, it should examine how regulatory and healthcare-system arrangements influence the practical implementation of patient protection and equitable access.

1.2 Aim and objectives

The aim of this review is to critically analyse ethical accountability, pharmacovigilance, and access to biosimilars across India, the US, Canada, and the EU.

The specific objectives are:

1. To compare the principal regulatory arrangements for biosimilar authorisation in the four jurisdictions.
2. To examine ethical responsibilities associated with post-marketing surveillance, immunogenicity monitoring, and product traceability.
3. To analyse the ethical implications of interchangeability, switching, pharmacy

substitution, and patient communication.

4. To evaluate how reimbursement arrangements, affordability, and healthcare-system structures influence equitable access.
5. To propose a practical ethical governance framework for regulators, manufacturers, healthcare professionals, and policymakers.

2. Conceptual and ethical framework

2.1 Biosimilarity and regulatory responsibility

Biosimilarity is established through a structured comparison with an appropriate reference biological medicine. Analytical and functional characterisation forms the scientific foundation of this assessment, while pharmacokinetic, pharmacodynamic, non-clinical, and clinical evidence is selected according to the remaining uncertainties and applicable regulatory requirements [1,3,4].

This evidence-based approach avoids unnecessary duplication of studies while maintaining appropriate standards of quality, safety, and efficacy. It also creates a continuing responsibility to monitor the authorised product in clinical use. Regulatory confidence should therefore be understood as the foundation of responsible use rather than a substitute for post-marketing oversight.

2.2 Autonomy and informed decision-making

Respect for autonomy requires that patients receive understandable and relevant information about their treatment. In biosimilar care, this may include the reason for a proposed switch, expected therapeutic benefits, relevant uncertainties, available alternatives, monitoring arrangements, and the process for reporting adverse events.

Informed communication does not necessarily mean that every change between biological products requires a separate formal consent procedure under every jurisdiction. Legal requirements and clinical circumstances differ. Nevertheless, transparent communication is ethically important, particularly when patients are concerned about a change in a treatment that has previously controlled their disease.

2.3 Beneficence and non-maleficence

Beneficence requires decisions that promote patient welfare, while non-maleficence requires reasonable measures to prevent avoidable harm. In biosimilar practice, these principles support evidence-based prescribing, appropriate product selection, continuity of supply, quality assurance, and reliable safety surveillance.

These principles should not be used to imply that biosimilars are inherently less safe than reference products. Rather, they require that decisions about biosimilar use be supported by the relevant scientific evidence and that potential safety concerns be investigated systematically.

2.4 Distributive justice and equitable access

Distributive justice concerns the fair allocation of healthcare benefits and burdens. Biosimilars may contribute to improved access through competition, lower acquisition costs, and more efficient use of healthcare budgets. However, lower prices do not automatically ensure equitable treatment.

Access may also depend on insurance coverage, reimbursement criteria, procurement systems, geographical availability, specialist services, and continuity of supply. An ethically responsible policy should assess whether savings translate into meaningful improvements in patient access rather than treating price reduction as the sole measure of success.

2.5 Transparency and accountability

Accountability requires clear responsibilities for manufacturers, regulators, prescribers, pharmacists, healthcare institutions, and payers. These responsibilities include maintaining

product quality, reporting safety concerns, communicating material risks, protecting patient information, and explaining decisions that affect treatment access.

Transparency should also extend to the basis for procurement decisions, the management of conflicts of interest, and the communication of safety information. Where responsibilities are distributed among several institutions, mechanisms for coordination and corrective action become especially important.

3. Review methodology

3.1 Review design

This manuscript uses a critical narrative review design with a comparative regulatory-policy component. It integrates official regulatory guidance and relevant scientific literature to examine ethical challenges in biosimilar governance. It is not presented as a systematic review, meta-analysis, or completed exhaustive legal review.

3.2 Information sources and search approach

Relevant information sources include PubMed/MEDLINE, regulatory publications, international guidance documents, and official websites of the WHO, CDSCO, DBT, FDA, EMA, and Health Canada. Literature searches should cover biosimilar authorisation, pharmacovigilance, product traceability, interchangeability, substitution, immunogenicity, affordability, patient autonomy, and equitable access.

Suggested search concepts include combinations of the following terms:

- “biosimilar” AND “pharmacovigilance”
- “biosimilar” AND “traceability” OR “product identification”
- “biosimilar” AND “interchangeability” OR “switching”
- “biosimilar” AND “patient safety” OR “immunogenicity”
- “biosimilar” AND “access” OR “affordability” OR “reimbursement”
- “biosimilar” AND “ethics” OR “accountability”
- “biosimilar regulation” AND “India” OR “United States” OR “Canada” OR “European Union”

3.3 Eligibility and synthesis

Priority should be given to official regulatory documents, WHO guidance, peer-reviewed reviews, and relevant comparative policy studies. Sources should be selected for their relevance to at least one of the five analytical domains: authorisation, pharmacovigilance, interchangeability, access, and accountability.

The synthesis should distinguish formal legal requirements from non-binding regulatory guidance, professional recommendations, and ethical interpretations. Where a policy is administered at a subnational level, the review should identify that distinction rather than treating a country or regional jurisdiction as a uniform system.

3.4 Methodological limitations

Because the present manuscript is a narrative review draft, it does not report a completed systematic search, duplicate screening, formal risk-of-bias assessment, or exhaustive extraction of every applicable legal instrument. A journal-ready version should document the actual databases searched, search dates, complete search strings, inclusion and exclusion criteria, and source-verification process. If a systematic or scoping review is intended, the methods and reporting framework should be redesigned accordingly.

4. Comparative regulatory governance across four jurisdictions

4.1 India

India’s biosimilar framework has developed through regulatory collaboration involving CDSCO and DBT. The 2016 Similar Biologics Guidelines were revised through a 2025 document intended to reflect advances in analytical characterisation, functional assessment, and

international scientific practice [2]. The precise publication and implementation status of the 2025 document should be confirmed against the applicable final official notification before submission.

The Indian framework is important in the context of domestic biopharmaceutical manufacturing and the potential for biosimilars to improve access to biological treatment. Regulatory responsibility includes ensuring product quality, evaluating evidence of similarity, and maintaining appropriate post-marketing safety oversight.

India's Pharmacovigilance Programme of India (PvPI), supported by the Indian Pharmacopoeia Commission, provides a national structure for adverse drug reaction reporting. CDSCO guidance also describes pharmacovigilance responsibilities for marketing authorisation holders, including safety reporting, risk management, and periodic safety evaluation [9].

From an ethical perspective, the principal challenge is to combine scientifically credible regulatory standards with practical implementation across a diverse healthcare system. Differences in healthcare infrastructure, access to specialist care, product availability, and reporting practices may affect how safety and access policies operate in practice.

India should not be characterised as having lower safety standards solely because it is a middle-income country. Instead, the review should examine the documented requirements and evidence available for implementation, surveillance capacity, and access outcomes.

4.2 United States

The US biosimilar pathway was established under the Biologics Price Competition and Innovation Act of 2009. The FDA evaluates biosimilar applications using a totality-of-evidence approach in which comparative analytical and functional studies form the foundation, supported by other studies appropriate to the remaining scientific uncertainties [3,4].

US regulation distinguishes a biosimilar designation from an interchangeable biosimilar designation. The latter is subject to additional statutory requirements concerning expected clinical outcomes and, where applicable, switching evidence. Pharmacy substitution is also governed by state law, meaning that federal authorisation does not create a single uniform substitution rule for all states [3].

The US system illustrates how regulatory authorisation, insurance arrangements, pharmacy practice, and commercial incentives can interact. Biosimilar competition may support affordability, but the extent to which savings reach patients depends on coverage, reimbursement, distribution, contracting, and other market arrangements.

Ethical accountability therefore involves more than determining whether a product meets the regulatory definition of biosimilarity. It also involves clear communication about product identity, appropriate substitution practices, accurate safety reporting, and transparency regarding the financial incentives influencing treatment decisions.

4.3 European Union

The EU has an established biosimilar authorisation framework coordinated through the EMA and the European medicines regulatory network. Authorisation is based on evidence that the proposed biosimilar is highly similar to its reference medicine and has no clinically meaningful differences in quality, safety, and efficacy [5].

The EU also distinguishes between scientific interchangeability and pharmacy-level substitution. EMA and the Heads of Medicines Agencies have stated that EU-approved biosimilars are scientifically interchangeable with their reference products, subject to consideration of product information. Decisions about whether automatic substitution is permitted at pharmacy level remain with individual member states [5].

This structure combines common scientific standards with national differences in healthcare delivery and implementation. Reimbursement, procurement, prescribing arrangements, and

substitution practices can therefore vary across the EU.

The principal ethical questions concern consistent patient protection, transparent implementation, continuity of treatment, and the equitable distribution of benefits from biosimilar competition. A critical review should avoid treating the EU as if it were a single national reimbursement or pharmacy-substitution system.

4.4 Canada

Health Canada evaluates biosimilar submissions through a comparative framework intended to establish a high degree of similarity to an authorised Canadian reference biologic. Its guidance addresses analytical characterisation, quality, non-clinical and clinical evidence, and risk-management requirements [6].

Health Canada also requires appropriate post-market safety oversight. Manufacturers are responsible for monitoring adverse reactions, maintaining risk-management activities, and evaluating new safety information. Product-specific identification is important because biosimilars and their reference products may share a common non-proprietary name [7].

Interchangeability and substitution are distinct from federal authorisation. Decisions affecting interchangeability and formulary coverage are influenced by provincial and territorial arrangements. This creates a governance structure in which federal scientific assessment coexists with subnational decisions affecting practical access.

The ethical issues include maintaining product traceability, communicating treatment changes, ensuring continuity of care, and examining whether reimbursement policies distribute the benefits of biosimilar competition fairly.

4.5 Comparative overview

Table 1. Comparative ethical and regulatory governance of biosimilars in four jurisdictions

S.N O	Domain	India	United States	European Union	Canada
1.	Principal regulatory authority	CDSCO, with DBT involvement in the relevant framework	FDA	EMA and national competent authorities	Health Canada
2.	Authorisation approach	Comparative similarity assessment under the applicable Similar Biologics framework	Biosimilar pathway under the Public Health Service Act	Centralised EU authorisation framework for applicable products	Comparative assessment under the Food and Drug Regulations and Health Canada guidance
3.	Pharmacovigilance	PvPI and relevant marketing authorisation holder	FDA safety-reporting and surveillance systems	EU pharmacovigilance system and national competent	Canada Vigilance and manufacturer obligations

		obligations		authorities	
4.	Interchangeability	Must be assessed in the context of applicable product requirements and relevant legal and clinical arrangements	Separate FDA interchangeability designation; substitution depends on state law	Scientific interchangeability supported at EU level; pharmacy substitution is determined nationally	Provincial and territorial policy plays a substantial role
5.	Reimbursement and access	Influenced by public and private provision, affordability, procurement, and availability	Influenced by insurance, reimbursement, contracting, and market competition	Varies among member states and their reimbursement systems	Influenced by provincial and territorial formularies and public/private coverage
6.	Central ethical priority	Consistent implementation, safety oversight, and equitable access	Transparent substitution, product identification, and fair distribution of savings	Consistent scientific standards with transparent national implementation	Traceability, continuity of care, and fair access across subnational systems

Source: Synthesis of WHO guidance and official jurisdictional regulatory information [1–9]. The table is a qualitative comparison, not a formal assessment of regulatory performance or patient outcomes.

5. Ethical accountability beyond market authorisation

5.1 Product quality and lifecycle responsibility

Biological medicines are produced through complex processes, and manufacturing changes can influence relevant product characteristics. Biosimilar development therefore requires appropriate analytical and functional comparability, together with a scientifically justified evaluation of any observed differences [1,3,6].

Ethical accountability continues after approval. Manufacturers should maintain quality systems, investigate deviations, assess the implications of manufacturing changes, and communicate safety-relevant information to regulators and healthcare professionals. Regulators should have appropriate mechanisms to evaluate emerging evidence and take proportionate corrective action.

A responsible governance model should make clear which party is accountable for each stage of product quality and safety. Contract manufacturing, distribution arrangements, and complex supply chains should not create gaps in responsibility.

5.2 Pharmacovigilance and immunogenicity

Immunogenicity is a relevant consideration in biological therapy because immune responses

can influence safety, efficacy, and treatment outcomes. The clinical significance of an immune response depends on the product, patient population, treatment context, and nature of the response. It should not be assumed that every detected immune response produces clinically significant harm.

Pre-authorisation studies may not identify every rare or delayed adverse event. Post-marketing surveillance is therefore needed to identify potential safety signals in broader and more diverse populations [7,8].

Spontaneous adverse-event reporting is valuable, but it has limitations, including under-reporting, incomplete clinical information, duplicate reports, and difficulty establishing causality. Active surveillance, registries, observational studies, and other real-world evidence methods can complement spontaneous reporting where appropriate.

Ethically responsible pharmacovigilance requires timely reporting, adequate follow-up, assessment of emerging signals, and communication of relevant findings. Surveillance should be proportionate to the product's characteristics and known or potential risks rather than based on the assumption that all biosimilars have identical risk profiles.

5.3 Traceability and product identification

Accurate identification is essential when several biological products share a non-proprietary name. A safety report that identifies only the active substance may be insufficient to determine which product was administered, particularly when multiple manufacturers supply related products.

Traceability should, where feasible, capture the brand or product name, manufacturer, batch or lot number when relevant, and details of the administration or dispensing event. Electronic prescribing and dispensing systems can support this process if product identifiers are retained and transferred accurately.

Traceability is not merely an administrative requirement. It is an ethical responsibility because incomplete product information can delay the investigation of safety signals and weaken the evidence used to protect future patients.

5.4 Switching, interchangeability, and substitution

Switching between a reference biological medicine and a biosimilar may be clinically appropriate when supported by the relevant evidence and regulatory framework. Nevertheless, the terminology and legal consequences of biosimilarity, interchangeability, and pharmacy substitution should be clearly distinguished.

Interchangeability refers to the possibility of using a biosimilar in place of its reference product under the applicable scientific and regulatory framework. Pharmacy substitution concerns whether a pharmacist may dispense an alternative product without obtaining a new prescription or additional prescriber authorisation under the relevant law.

These concepts are related but not identical. A scientific conclusion about interchangeability does not automatically establish a universal legal right to substitute a product in every jurisdiction.

Ethically responsible switching should involve clinically appropriate decision-making, accurate documentation, clear communication, and a plan for monitoring treatment outcomes. Patients should be able to raise concerns and understand whom to contact if a change is associated with a suspected adverse event or a deterioration in disease control.

5.5 Patient autonomy and communication

Communication about biosimilars should be accurate, balanced, and understandable. Patients should not be told that a biosimilar is inferior simply because it is not an identical molecular copy of the reference product. Equally, patients should not be given absolute assurances that exclude the possibility of individual adverse events or uncertainties relevant to a specific

treatment.

Healthcare professionals should explain why a biosimilar is being prescribed or substituted, the expected therapeutic purpose, any relevant monitoring arrangements, and how safety concerns can be reported. The depth of communication should reflect the clinical context and the patient's needs.

Patient autonomy also requires attention to language, health literacy, cultural context, and access to reliable information. Where treatment changes are driven by procurement or reimbursement policies, transparent explanations can help preserve trust in the healthcare system.

6. Pharmacovigilance as an ethical and regulatory obligation

6.1 Limitations of passive surveillance

Spontaneous reporting systems can detect important safety signals, but they cannot reliably estimate incidence without additional data and appropriate methods. Reporting rates may differ because of awareness, prescribing volume, publicity, or access to reporting mechanisms. Comparisons between biosimilars and reference products should therefore account for exposure, reporting quality, product identification, and other relevant factors. A higher number of reports does not necessarily demonstrate a higher risk, and a low number of reports does not establish the absence of harm.

6.2 Integrating real-world evidence

Real-world data can complement regulatory evidence by examining product use in routine clinical practice. Depending on the question, relevant sources may include electronic health records, claims databases, patient registries, and disease-specific observational cohorts.

These methods require careful attention to confounding, missing data, changes in prescribing practices, and differences between patient populations. Real-world evidence should complement rather than automatically replace well-designed comparative studies or established pharmacovigilance procedures.

6.3 Shared responsibilities

A lifecycle-based approach distributes responsibilities across several stakeholders:

- **Manufacturers:** Maintain product quality, collect and assess safety information, report adverse events as required, and implement risk-management activities.
- **Regulators:** Evaluate evidence, monitor safety signals, require appropriate corrective measures, and communicate important safety information.
- **Prescribers and pharmacists:** Document the product used, communicate relevant treatment information, and report suspected adverse reactions.
- **Healthcare institutions:** Maintain appropriate dispensing, administration, storage, and record-keeping systems.
- **Patients and caregivers:** Receive accessible information and have practical opportunities to report suspected problems.

The allocation of these responsibilities must follow applicable law and professional standards. Ethical accountability is strongest when each participant understands their obligations and has the information and infrastructure necessary to fulfil them.

7. Affordability, access, and distributive justice

7.1 Biosimilars and the potential for improved access

Biosimilar competition can create opportunities for lower treatment costs and wider availability. Savings may allow healthcare systems to treat additional patients, expand access to biologic therapies, or reallocate resources to other clinical needs [3,5].

However, the relationship between biosimilar entry and actual patient affordability is not automatic. The final cost to patients may depend on procurement arrangements,

reimbursement rules, insurance design, distribution margins, discounts, and prescribing incentives.

Accordingly, access should be evaluated using several dimensions: availability, affordability, geographic reach, continuity of supply, reimbursement eligibility, and the ability to receive clinically appropriate treatment without unreasonable financial burden.

7.2 India: affordability and implementation

In India, the ethical discussion should consider the potential contribution of domestic manufacturing and biosimilar competition to access, alongside the requirements for reliable quality assurance and safety monitoring. The analysis should be supported by product-specific price data, procurement information, and evidence about patient access rather than broad assumptions about national affordability.

Differences in healthcare infrastructure and the distribution of specialist services may affect the practical availability of biological treatments. These factors make implementation and monitoring important components of ethical governance.

7.3 United States: coverage and financial incentives

In the US, biosimilar affordability is influenced by the structure of insurance coverage, reimbursement, pharmacy and medical benefit arrangements, and commercial contracting. A lower acquisition price does not necessarily translate into an equivalent reduction in a patient's out-of-pocket expenditure.

A comparative ethical analysis should therefore distinguish manufacturer prices, payer expenditure, provider incentives, and patient costs. It should also examine whether substitution policies and financial incentives are communicated transparently and implemented in ways that protect clinically appropriate choice.

7.4 European Union: national variation

The EU's common scientific authorisation framework coexists with national differences in reimbursement, procurement, and healthcare organisation. Consequently, the availability and financial accessibility of a biosimilar may vary between member states even when the product has been authorised under a common framework.

Ethical assessment should examine whether national policies support equitable access, transparent implementation, and continuity of treatment. It should also distinguish observed policy outcomes from assumptions about the benefits of competition.

7.5 Canada: provincial and territorial differences

Canadian access is influenced by provincial and territorial formularies, public drug programmes, private insurance, and product-specific policies. Federal authorisation does not guarantee identical reimbursement or substitution arrangements across the country.

The relevant ethical question is whether differences in coverage and implementation create avoidable barriers to clinically appropriate treatment. Such a question requires jurisdiction-specific evidence on coverage criteria, patient costs, and access outcomes.

7.6 Ethical evaluation of cost-saving policies

Cost-saving policies are ethically defensible when they are supported by relevant evidence, protect patient safety, and distribute benefits fairly. A policy that reduces acquisition costs but causes avoidable treatment interruption, inadequate monitoring, or disproportionate burdens for vulnerable patients requires further scrutiny.

Conversely, rejecting biosimilars without evidence-based justification may restrict access and divert resources from other healthcare needs. Ethical governance must therefore avoid both unjustified resistance to biosimilars and indiscriminate substitution based solely on cost.

8. Cross-jurisdictional challenges and opportunities for policy learning

The four jurisdictions illustrate several shared challenges.

First, all require scientifically credible evidence for authorisation, but they differ in the institutional arrangements governing substitution, reimbursement, and implementation. These differences should be described precisely rather than interpreted as direct evidence of superior or inferior patient safety.

Second, pharmacovigilance depends on the quality of product identification and reporting. International cooperation may improve signal detection, but differences in databases, identifiers, reporting practices, and legal requirements can complicate the interpretation of evidence across jurisdictions.

Third, healthcare access is shaped by more than regulatory approval. Affordability, reimbursement, procurement, prescribing practices, and supply continuity determine whether authorised products are available to the patients who need them.

Fourth, patient trust depends on the credibility of communication. Transparent explanations of biosimilarity, switching, safety monitoring, and financial considerations can reduce misunderstanding and support shared decision-making.

A useful comparative review should therefore identify transferable practices without assuming that a policy can be transplanted unchanged from one jurisdiction to another. Recommendations should be adapted to each system's legal structure, resources, healthcare organisation, and patient population.

9. Recommendations for Ethical Biosimilar Governance

Ethical biosimilar governance requires a coordinated approach that extends beyond regulatory authorisation to encompass product traceability, lifecycle pharmacovigilance, patient-centred communication, appropriate switching practices, equitable access, institutional transparency, and international regulatory cooperation. Although India, the United States (US), Canada, and the European Union (EU) share a scientific commitment to the quality, safety, and efficacy of authorised biosimilars, differences in their regulatory structures and healthcare financing systems influence how these principles are implemented in clinical practice [16–21]. Accordingly, governance recommendations should establish common ethical objectives while allowing implementation to reflect the applicable legal requirements, healthcare infrastructure, and patient needs of each jurisdiction.

9.1 Strengthen Product-Level Traceability

Reliable product-level traceability is fundamental to the safe use of biosimilars because several biological medicines may have similar therapeutic indications while differing in manufacturer, formulation, manufacturing process, or product-specific characteristics. Although biosimilars undergo rigorous comparative evaluation before authorisation, the identification of the precise product administered remains important for investigating suspected adverse drug reactions, evaluating safety signals, and identifying potential batch-related quality concerns [16,22–23].

Regulators and healthcare institutions should promote prescribing, dispensing, administration, and pharmacovigilance systems that record the brand or product name, manufacturer, and other appropriate product identifiers. Batch or lot numbers should be captured when required by applicable regulations or when clinically and operationally relevant, particularly during investigations of suspected adverse reactions, quality defects, or product recalls. Recording the active substance alone may be insufficient when several products containing the same substance are available.

Electronic health records, electronic prescribing systems, hospital pharmacy software, and adverse-event reporting platforms should support consistent recording and transfer of product-identification information. Healthcare institutions should also establish procedures for retaining dispensing and administration records so that relevant information remains

available during safety investigations. Manufacturers and distributors should maintain appropriate records that facilitate the identification of affected products and batches.

The implementation of these measures should reflect the different institutional arrangements in the four jurisdictions. In India, strengthening product-level documentation and the integration of pharmacovigilance reporting with clinical records could support the investigation of suspected adverse reactions. In the US, product identification should be considered alongside FDA safety-reporting requirements and the applicable state-level rules governing substitution. In Canada, product-level identification can support the assessment of adverse reactions reported through national pharmacovigilance arrangements. In the EU, traceability practices should be consistent with applicable EU pharmacovigilance requirements and national implementation arrangements [16–23].

From an ethical perspective, traceability supports non-maleficence, transparency, and accountability. Its purpose is not to imply that biosimilars are inherently less safe than reference biological medicines; rather, it ensures that safety concerns can be investigated using sufficiently specific information. Regulators and healthcare institutions should therefore evaluate traceability measures through indicators such as the completeness of product identifiers in clinical records, the availability of batch information when required, and the proportion of adverse-event reports containing sufficient information for product identification.

9.2 Integrate Pharmacovigilance Throughout the Product Lifecycle

Pharmacovigilance should be regarded as a continuing responsibility throughout the lifecycle of a biosimilar rather than as an activity limited to the period immediately following regulatory authorisation. Pre-authorisation studies provide essential evidence of biosimilarity, safety, and efficacy; however, the size and duration of clinical studies may limit the detection of rare adverse reactions, delayed effects, or events occurring in patient populations that are underrepresented in clinical trials. Post-marketing surveillance is therefore necessary to complement the evidence available at the time of authorisation [16,22–23].

Regulators and marketing authorisation holders should maintain pharmacovigilance systems that comply with applicable legislation and product-specific risk-management requirements. These systems should facilitate the collection, assessment, documentation, and reporting of suspected adverse reactions, as well as the evaluation of emerging safety signals. Where appropriate, spontaneous adverse-event reporting should be complemented by active surveillance, patient registries, observational studies, and other suitable real-world evidence approaches.

The selection of surveillance methods should be proportionate to the characteristics of the biological product, the seriousness of potential adverse reactions, the extent of clinical exposure, and the uncertainties identified during development. Particular attention may be warranted when investigating suspected immunogenicity-related events, loss of therapeutic response, unexpected adverse reactions, or possible quality defects. Nevertheless, the presence of an immune response should not automatically be interpreted as evidence of clinically significant harm; its implications depend on the nature of the response and the clinical context [16,22–23].

An important limitation of spontaneous reporting is that reports may be incomplete, under-reported, duplicated, or insufficient to establish causality. Differences in reporting frequency may also reflect variations in prescribing volume, awareness, and reporting practices rather than differences in the underlying risk of a product. Consequently, regulators should interpret safety reports using appropriate scientific methods and should avoid concluding comparative safety from unadjusted report counts alone.

In India, pharmacovigilance measures should support effective implementation of applicable marketing authorisation holder obligations and the national adverse-event reporting framework. In the US, FDA surveillance and reporting mechanisms should be supported by accurate product identification. In Canada, manufacturers and healthcare professionals should contribute to appropriate post-market safety monitoring and reporting. In the EU, pharmacovigilance responsibilities should be implemented through the relevant EU and national systems [16–23].

Ethical accountability requires that significant safety signals be assessed promptly, relevant findings be communicated to appropriate stakeholders, and corrective measures be implemented when warranted. Useful indicators include the completeness and timeliness of adverse-event reports, the time required to assess safety signals, the implementation of risk-minimisation measures, and the availability of product-specific information. These indicators should be interpreted alongside exposure data and other relevant evidence rather than used as simple rankings of regulatory performance.

9.3 Improve Patient-Centred Communication

Patient-centred communication is essential for maintaining trust in biosimilar treatment and supporting informed decision-making. Although regulatory authorisation establishes the required evidence of biosimilarity, patients may remain uncertain about whether a biosimilar will provide the expected therapeutic benefit, whether switching is clinically appropriate, or why a healthcare institution has recommended a different biological medicine. Such concerns should be addressed through accurate, balanced, and accessible information [16,20,23].

Healthcare professionals should explain the rationale for prescribing a biosimilar or changing treatment, the expected therapeutic benefits, the relevant safety information, and any monitoring arrangements appropriate to the individual patient. Where a change is associated with a formulary decision, procurement policy, or reimbursement arrangement, the reason should be communicated transparently. Patients should also know how to report suspected adverse reactions and whom to contact if they experience new symptoms or concerns about treatment effectiveness.

Communication should avoid two opposing errors. First, biosimilars should not be portrayed as inferior solely because their molecular structures are not necessarily identical to those of their reference products. Second, patients should not be given absolute assurances that disregard the possibility of individual adverse reactions or product-specific uncertainties. The objective is to communicate the scientific basis for biosimilar use without exaggerating either risk or benefit.

Information should be adapted to patients' health literacy, language preferences, cultural context, and clinical circumstances. Written information, verbal counselling, translated materials, and accessible digital resources may be used as appropriate. For patients receiving long-term biological treatment, additional explanation may be helpful when switching could affect their confidence in treatment continuity. Shared decision-making should be encouraged where clinically appropriate and consistent with the applicable legal framework.

The legal requirements for consent, notification, and substitution differ among jurisdictions. Therefore, ethical recommendations for transparent communication should not be presented as a universal statutory requirement for a separate consent procedure before every biosimilar switch. Rather, the appropriate communication process should be determined by applicable law, clinical circumstances, and professional standards [18–21].

Patient-centred governance can be assessed through patient understanding of treatment changes, access to understandable product information, the availability of counselling, and patient-reported confidence in the treatment process. These measures should be designed to

improve communication rather than create unnecessary barriers to the appropriate use of biosimilars.

9.4 Clarify Interchangeability and Substitution Rules

Interchangeability, switching, and pharmacy-level substitution are related but distinct concepts. Interchangeability concerns the use of a biosimilar in place of its reference biological product within the relevant scientific and regulatory framework. Switching generally describes a change from one biological product to another, whereas pharmacy substitution concerns the legal and professional circumstances in which a pharmacist may dispense an alternative product without obtaining a new prescription or additional prescriber authorisation. The precise meaning and legal consequences of these terms depend on the applicable jurisdiction [18–21].

Regulators, professional organisations, pharmacists, prescribers, and healthcare institutions should provide clear guidance explaining these distinctions. Policies should identify who is authorised to initiate or approve a change, what information must be documented, whether the prescriber must be notified, and how the patient should be informed. They should also clarify the relationship between product authorisation, any applicable interchangeability designation, pharmacy substitution, and reimbursement-driven switching.

In the US, the FDA's designation of a biosimilar as interchangeable is distinct from biosimilar authorisation, and pharmacy substitution remains subject to applicable state law. In the EU, the scientific position supporting interchangeability of EU-approved biosimilars does not establish a single uniform pharmacy-substitution rule across all member states. In Canada, federal authorisation should be distinguished from interchangeability and substitution policies administered at the provincial or territorial level. In India, switching and substitution should be assessed according to applicable regulatory requirements, prescribing arrangements, and professional standards rather than inferred solely from the general concept of biosimilarity [2–6].

Clinically appropriate switching policies should support continuity of treatment, accurate documentation, and suitable follow-up. Where a change is implemented, the product administered should be identifiable in the clinical record, and patients should receive information relevant to their treatment and monitoring. If a suspected adverse reaction or deterioration in disease control occurs, the relevant product information should be available to facilitate clinical assessment and pharmacovigilance reporting.

Ethically, clear rules protect patient safety, support professional accountability, and reduce avoidable uncertainty. At the same time, unnecessary administrative restrictions may delay appropriate treatment or limit access to more affordable medicines. Policies should therefore balance patient protection with the potential public-health benefits of biosimilar competition. Evaluation should consider clarity of professional guidance, documentation of product changes, treatment continuity, and compliance with the applicable legal framework.

9.5 Link Access Policies to Measurable Outcomes

The potential of biosimilars to improve affordability and expand access is an important ethical justification for encouraging their appropriate use. Competition between biological medicines may reduce treatment expenditure and allow healthcare systems to allocate resources to additional patients or other clinical priorities. However, reductions in acquisition costs do not automatically translate into lower patient expenditure or equitable access [3,5,6].

Policymakers should evaluate biosimilar access through a multidimensional framework that includes product availability, reimbursement eligibility, out-of-pocket expenditure, geographical accessibility, continuity of supply, and the ability of patients to receive clinically appropriate treatment. These indicators provide a more informative assessment than price

reduction alone. Where feasible, evaluations should also examine differences in access across income groups, geographical areas, insurance categories, and clinically relevant patient populations.

In India, access assessments should consider the relationship between product availability, healthcare infrastructure, affordability, procurement arrangements, and the distribution of specialist services. In the US, analyses should distinguish manufacturer prices, payer expenditure, insurance coverage, contracting arrangements, and patients' out-of-pocket costs. In the EU, comparisons should recognise variation in national reimbursement and procurement policies despite the common scientific authorisation framework. In Canada, evaluations should consider provincial and territorial formularies, public drug programmes, private insurance, and product-specific coverage policies [17–21].

Cost-saving initiatives should be assessed for their effects on patients rather than assumed to be beneficial solely because they reduce institutional expenditure. For example, a procurement policy that lowers acquisition costs but creates avoidable treatment interruptions or places disproportionate financial burdens on vulnerable patients may fail to achieve its intended ethical objectives. Conversely, unjustified resistance to appropriately authorised biosimilars may restrict access and divert resources from other healthcare needs.

A transparent evaluation framework should therefore combine economic indicators with patient-centred and clinical measures. Potential indicators include changes in patient expenditure, reimbursement coverage, waiting times, treatment initiation, supply interruptions, treatment continuity, and relevant safety outcomes. Where possible, these outcomes should be compared before and after policy implementation and interpreted in light of other changes in healthcare delivery. Such evaluation can help determine whether biosimilar-related savings produce meaningful and fairly distributed benefits.

9.6 Improve Transparency and Accountability

Effective governance requires clear allocation of responsibilities among manufacturers, regulators, prescribers, pharmacists, healthcare institutions, procurement agencies, and payers. These stakeholders influence different stages of the biosimilar lifecycle, and uncertainty about their respective obligations can weaken product-quality oversight, adverse-event reporting, patient communication, and corrective action [17–24].

Manufacturers should maintain appropriate quality-management and pharmacovigilance systems, fulfil applicable reporting obligations, and provide relevant safety information to regulators. Regulatory authorities should assess submitted evidence, monitor safety information, communicate significant findings, and take proportionate action when justified. Prescribers and pharmacists should follow applicable professional and legal requirements, maintain appropriate treatment records, and report suspected adverse reactions through the relevant mechanisms. Healthcare institutions should support reliable storage, dispensing, administration, documentation, and continuity of supply.

Payers, procurement agencies, and healthcare institutions should use transparent criteria when selecting products or introducing biosimilar-switching policies. Relevant considerations may include regulatory authorisation, clinical suitability, product availability, supply reliability, total treatment costs, and arrangements for monitoring outcomes. Where financial incentives or commercial relationships may influence decisions, conflicts of interest should be identified and managed according to applicable rules and institutional policies.

Transparency does not require the disclosure of confidential commercial information that is lawfully protected. Rather, it requires that decision-making criteria, relevant clinical considerations, and responsibilities for patient protection be sufficiently clear to permit appropriate scrutiny. Patients and healthcare professionals should be able to understand the

principal reasons for treatment or procurement decisions that materially affect care.

Accountability should be supported by auditable records, defined reporting pathways, appropriate performance indicators, and procedures for responding to identified problems. Potential indicators include the timeliness of safety reporting, completion of corrective actions, availability of product-identification information, compliance with relevant quality requirements, and implementation of patient-communication procedures. These indicators should be adapted to the responsibilities of each stakeholder and should not be treated as interchangeable measures of overall regulatory performance.

9.7 Support International Regulatory Cooperation

International regulatory cooperation can improve scientific consistency, facilitate the efficient assessment of evidence, and support the identification of safety concerns that may emerge across different healthcare systems. The World Health Organization (WHO) provides internationally relevant guidance for biosimilar evaluation, while regulatory authorities in India, the US, Canada, and the EU maintain jurisdiction-specific frameworks for authorisation, pharmacovigilance, and implementation [16–21].

Cooperation may include scientific information exchange, dialogue concerning analytical and functional comparability, sharing of relevant safety signals, collaboration on pharmacovigilance methods, and discussion of approaches to product identification and risk management. Where legally permissible, cooperation may also support the efficient use of existing scientific evidence and reduce unnecessary duplication without compromising the requirements of the relevant regulatory authority.

However, international harmonisation should not be interpreted as requiring identical legislation or healthcare policies across jurisdictions. Differences in legal authority, healthcare financing, pharmacy practice, procurement, and reimbursement mean that the same scientific principles may be implemented through different institutional arrangements. For example, federal authorisation in the US and Canada coexists with important state, provincial, or territorial roles in substitution and access, while the EU combines common scientific assessment with national implementation decisions. India's regulatory framework must likewise be interpreted in the context of its applicable national requirements and healthcare system [2–6].

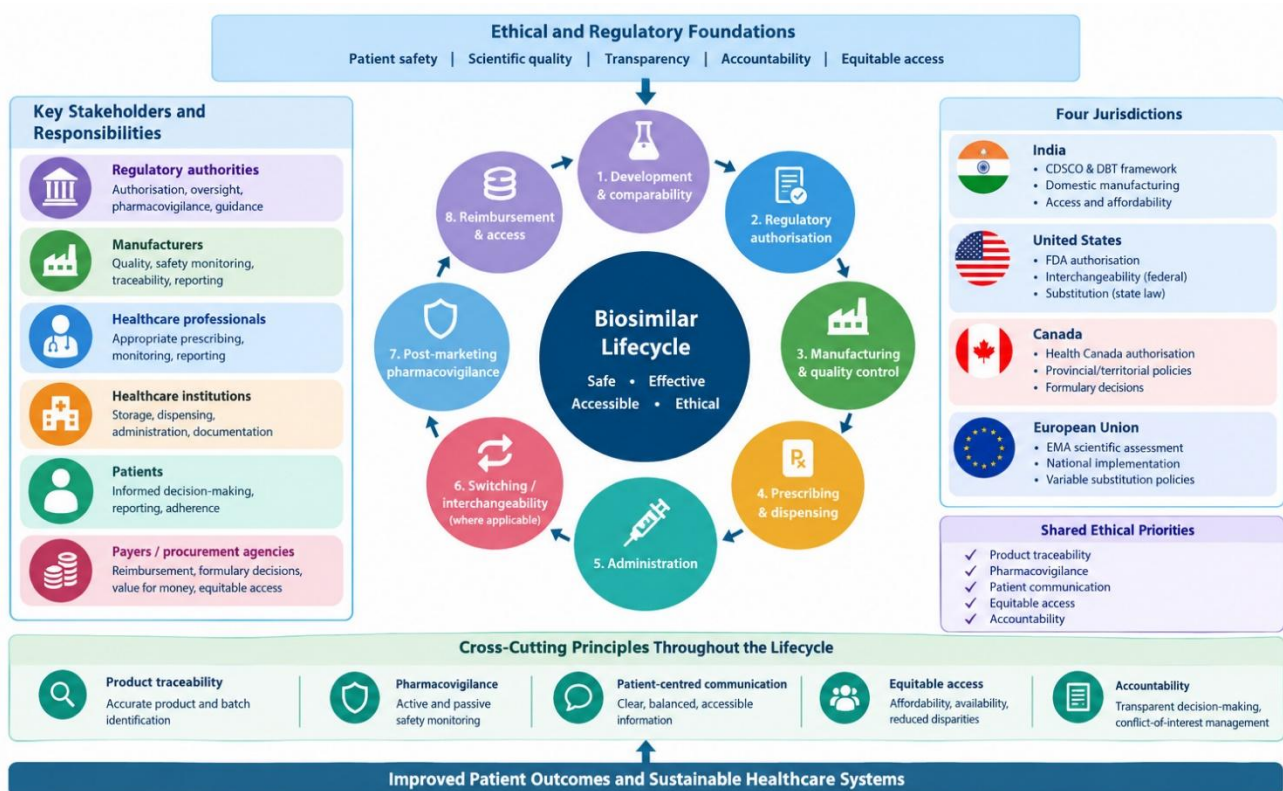


Figure 1. Lifecycle-based ethical governance framework for biosimilars: integrating regulatory authorisation, pharmacovigilance, product traceability, patient safety, and equitable access across India, the United States, Canada, and the European Union.

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Ethical cooperation should therefore focus on shared objectives: maintaining product quality, protecting patients, improving the usefulness of safety information, promoting responsible use of resources, and supporting equitable access. Regulators should exchange relevant information through appropriate mechanisms while respecting applicable confidentiality, privacy, and data-protection requirements.

Progress could be assessed through the timeliness of cross-jurisdictional safety communication, the use of compatible product-identification practices where feasible, the exchange of relevant regulatory information, and the adoption of scientifically justified improvements in regulatory practice. International cooperation should remain evidence-based, transparent, and responsive to local needs rather than pursuing uniformity as an end in itself.

9.8 Implementation and Evaluation of the Recommendations

The recommendations above should be translated into measurable actions rather than remain general ethical principles. Regulatory authorities can clarify applicable requirements and reporting pathways; manufacturers can strengthen product-quality and safety-monitoring systems; healthcare institutions can improve product documentation and communication procedures; and payers and procurement agencies can assess the effects of biosimilar policies on affordability and continuity of care.

A practical implementation strategy should identify the responsible stakeholder, the action required, an appropriate indicator, and a review period. Indicators should have clearly defined numerators, denominators, data sources, and reporting intervals wherever quantitative assessment is intended. Differences in data availability and regulatory responsibilities should be acknowledged when comparing jurisdictions.

Importantly, differences in reporting rates, substitution practices, or reimbursement policies should not automatically be interpreted as evidence that one jurisdiction provides better or worse patient protection. Such conclusions require appropriately designed empirical research that accounts for relevant differences in exposure, healthcare organisation, reporting practices, and patient populations.

Taken together, these recommendations provide a lifecycle-based approach to ethical biosimilar governance. Their central objective is to ensure that regulatory authorisation is accompanied by continuing safety oversight, reliable product identification, informed patient communication, transparent decision-making, and demonstrable improvements in access to clinically appropriate treatment.

10. Proposed ethical governance framework

Table 2. Proposed lifecycle-based ethical governance framework for biosimilars

S.NO	Lifecycle stage	Ethical risk	Proposed safeguard	Potential indicator
1.	Development and authorisation	Inadequate characterisation or unjustified evidence gaps	Robust analytical and functional comparability assessment	Completeness of required evidence and regulatory findings
2.	Manufacturing and distribution	Quality deviations or supply interruptions	Quality management, change control, and supply-risk planning	Quality deviations, recalls, and interruption frequency
3.	Prescribing and substitution	Inadequate communication or inappropriate substitution	Clear policies and documented clinical communication	Documentation and patient-information measures
4.	Administration and follow-up	Incomplete product identification	Product-specific recording and appropriate batch traceability	Completeness of product identifiers in records
5.	Post-marketing surveillance	Under-reporting or delayed signal detection	Accessible reporting and proportionate active surveillance	Reporting completeness and time to signal assessment
6.	Reimbursement and procurement	Unequal access or opaque financial incentives	Transparent criteria and distributional assessment	Patient costs, coverage, availability, and treatment continuity

7.	Regulatory response	Delayed action or unclear responsibility	Defined accountability and timely risk communication	Response time and implementation of corrective measures
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This framework is a proposed analytical model. The indicators require operational definitions and validation before use in empirical research or regulatory performance comparisons.

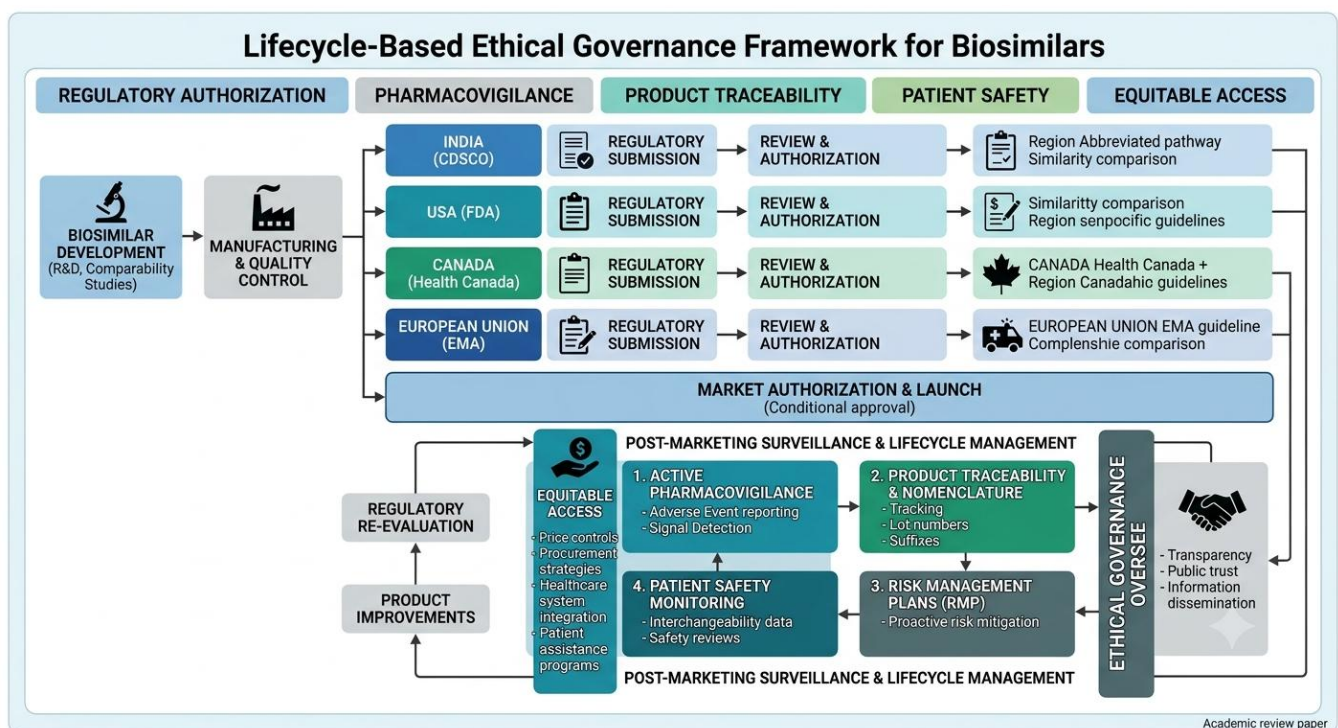


Figure 1. Lifecycle-Based Ethical Governance Framework for Biosimilars: Integrating Regulatory Authorisation, Pharmacovigilance, Product Traceability, Patient Safety, and Equitable Access Across India, the United States, Canada, and the European Union.

11. Research gaps and future directions

Several areas warrant further investigation.

First, comparative empirical studies are needed to evaluate whether differences in product traceability and adverse-event reporting influence the completeness and usefulness of biosimilar safety data.

Second, patient-centred research could examine how treatment-switch communication, health literacy, and trust influence patient understanding and treatment continuity. Such research should distinguish reported concerns from demonstrated clinical outcomes.

Third, comparative health-policy studies should assess whether biosimilar competition translates into lower out-of-pocket costs, wider coverage, and reduced treatment inequalities. Price comparisons alone may be insufficient to establish equitable access.

Fourth, research should examine the implementation of substitution and interchangeability policies across US states, EU member states, and Canadian provinces and territories, as well as the relevant arrangements in India. Such work should use a consistent set of criteria and identify the applicable legal and policy instruments.

Fifth, digital pharmacovigilance tools may improve product identification and signal detection, but their implementation raises questions about data quality, interoperability, privacy, access, and algorithmic transparency. Their value should be demonstrated through appropriate validation rather than assumed from technological novelty.

Finally, future reviews should investigate how international regulatory convergence can reduce unnecessary duplication while preserving robust quality, safety, and efficacy standards. Particular attention should be given to the relationship between regulatory efficiency, patient protection, and access in healthcare systems with differing resources.

12. Limitations

This review has several limitations. The narrative approach does not provide a reproducible quantitative estimate of the effects of biosimilar policies on safety or access. The four jurisdictions differ in legal structure, healthcare financing, and the organisation of pharmaceutical regulation, limiting direct comparisons of policy outcomes.

The review also focuses on general governance principles rather than a single therapeutic class or biosimilar product. Product-specific safety questions, clinical indications, manufacturing characteristics, and patterns of use may require separate analysis.

Finally, regulatory guidance changes over time. The applicable status of national and regional policies, particularly recent revisions, should be verified against official sources immediately before submission. A subsequent systematic or scoping review could address these limitations through predefined searches, transparent screening, and structured extraction of legal and empirical evidence.

13. Conclusion

Ethical biosimilar governance extends beyond the demonstration of similarity and the granting of regulatory authorisation. It requires continuing accountability for product quality, pharmacovigilance, traceability, appropriate switching and substitution, patient communication, and equitable access.

India, the United States, Canada, and the European Union share a scientific commitment to the quality, safety, and efficacy of authorised biosimilars, but differ in their institutional arrangements and implementation of substitution, reimbursement, and healthcare access policies. These differences provide opportunities for comparative policy learning, provided that legal requirements and patient outcomes are not conflated.

A lifecycle-based framework integrating regulatory oversight, manufacturer responsibility, professional practice, patient autonomy, and distributive justice can help identify practical improvements. Future policy should aim not only to authorise high-quality biosimilars but also to ensure that their use is appropriately monitored, transparently communicated, and translated into meaningful and equitable patient benefit.

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