

EVOLUTION OF THE BIOSIMILAR LANDSCAPE: A GLOBAL PERSPECTIVE

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ABSTRACT:

Biosimilars have evolved from a European regulatory innovation into a major component of the global biological-medicine ecosystem. This narrative review examines that evolution through a science-to-regulation framework, moving beyond a descriptive catalogue of approvals to consider how analytical similarity, a stepwise evidence-development strategy, interchangeability policies, regulatory reliance, and market competition influence biosimilar development and access. The review compares the regulatory approaches of the World Health Organization (WHO), the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and India. Particular attention is given to the increasing emphasis on sensitive orthogonal analytical methods, product-specific evidence requirements, reduction of unnecessary animal and clinical studies, post-marketing pharmacovigilance, and the distinction between scientific interchangeability and pharmacy-level substitution. The 2022 WHO guideline revision and India's 2025 revised Similar Biologics framework illustrate a broader international movement toward science-based flexibility, greater reliance on analytical and in-vitro evidence, and reduced duplication of studies. In the United States, the expanding biosimilar portfolio and evolution of interchangeability guidance demonstrate how regulatory experience can refine evidence requirements over time. The global landscape therefore appears to be shifting from an approval-centred model toward a lifecycle model in which analytical characterization, manufacturing consistency, clinical confidence, pharmacovigilance, and market implementation are considered together. A harmonized but scientifically flexible approach may reduce development duplication while preserving standards for quality, safety, and efficacy.

KEYWORDS: biosimilars; biological medicines; analytical similarity; interchangeability; regulatory science; FDA; EMA; WHO; India; pharmacovigilance

INTRODUCTION

Biological medicines have transformed the treatment of cancer, autoimmune disorders, endocrine diseases, inflammatory diseases, and other chronic conditions. Their development and manufacture, however, involve complex expression systems and process-dependent molecular characteristics that distinguish them from conventional small-molecule medicines. As patents and data-protection periods for reference biological medicines expire, biosimilars provide a regulatory route for introducing highly similar biological products without reproducing the entire development programme of the reference medicine.

A central scientific principle of biosimilar development is that similarity is established through a structured, comparative exercise rather than by demonstrating molecular identity. The objective is to determine whether the proposed product is highly similar to the reference product and whether any residual differences are clinically meaningful. This distinction is important because biological products naturally exhibit heterogeneity and manufacturing-process dependence. WHO's revised 2022 guidance explicitly emphasizes a stepwise approach and greater flexibility based on the strength of analytical and other evidence. [1,2]

The literature has extensively described individual regulatory systems and the history of biosimilars. The added value of the present review is a cross-regional synthesis that links four elements: (i) scientific evidence generation, (ii) regulatory decision-making, (iii) interchangeability and substitution, and (iv) post-approval access and competition. This framework helps explain why different jurisdictions can reach comparable scientific conclusions while using different legal terminology or evidence requirements.

2. REVIEW METHODOLOGY

This article was developed as a narrative regulatory-science review. The original manuscript references were retained where they remained relevant, while the regulatory sections were updated using authoritative documents from WHO, FDA, EMA, and the Central Drugs Standard Control Organization (CDSCO). Priority was given to primary regulatory documents and official agency material for definitions, approval pathways, interchangeability, and current policy developments. Peer-reviewed reviews were used for historical context and

broader interpretation. Because this is a narrative review rather than a systematic review, no pooled effect estimate or formal risk-of-bias assessment was performed.

The evidence was organized around five analytical questions: What constitutes biosimilarity? How has the evidence package evolved? How do major jurisdictions differ? How is interchangeability distinguished from biosimilarity? And which regulatory and market mechanisms may influence access? This structure is intended to make the review analytical rather than purely chronological.

3. Biosimilars: Scientific Basis

3.1 Biosimilar Versus Generic Medicine

A generic medicine is generally a chemically synthesized small-molecule product that can be demonstrated to have the same active ingredient as its reference medicine and, under the applicable regulatory framework, therapeutic equivalence through pharmaceutical and bioequivalence evidence. Biological medicines are different because their molecular structures and functional attributes depend on the biological source, expression system, manufacturing process, formulation, and analytical control strategy. Consequently, a biosimilar is not expected to be an exact molecular copy. Instead, regulatory evaluation focuses on demonstrating high similarity and excluding clinically meaningful differences. [2,3]

3.2 The totality-of-evidence and stepwise comparability model

Modern biosimilar development can be understood as a stepwise evidence-generation process. Analytical characterization is the foundation because it can directly interrogate structural and functional attributes. The results then inform the need, extent, and design of non-clinical and clinical studies. This is more efficient than treating every evidence category as an independent requirement. EMA describes biosimilar comparability as a tailored, head-to-head process in which the amount and type of evidence are determined by the characteristics of the individual product. [3]

- □ Step 1 — Reference-product knowledge and quality target: identify critical quality attributes (CQAs), relevant variability, and a scientifically justified reference-product strategy.
- □ Step 2 — Analytical similarity: use orthogonal structural, physicochemical, biological, and functional assays to detect differences in CQAs.
- □ Step 3 — Non-clinical assessment: use in-vitro and, when scientifically justified, in-vivo studies to resolve remaining uncertainty.
- □ Step 4 — Clinical pharmacology and immunogenicity: generate the clinical evidence needed to address residual uncertainty, with study requirements tailored to the molecule and indication.
- □ Step 5 — Confirmation and lifecycle monitoring: integrate the evidence package and continue pharmacovigilance and manufacturing control after authorization.

This framework increases scientific efficiency because the evidence is cumulative: stronger analytical similarity can reduce the residual uncertainty that must be addressed by later stages. WHO's 2022 guidance and India's 2025 revision both reflect this direction. [1,4]

3.3 Analytical similarity and critical quality attributes

Analytical characterization is increasingly central to biosimilar development. Relevant attributes may include primary structure, higher-order structure, purity and impurities, charge variants, glycosylation, aggregation, potency, and other product-specific functional characteristics. The appropriate analytical package depends on the molecule and its mechanism of action. No single assay can establish biosimilarity; rather, multiple sensitive and orthogonal methods are used to build a coherent similarity assessment. This analytical emphasis is particularly important as regulatory agencies seek to reduce unnecessary duplication of non-clinical and clinical studies.

4. Global Regulatory Evolution

4.1 Who

WHO's 2022 Guidelines on Evaluation of Biosimilars replaced the earlier framework and expanded its scope beyond biotherapeutic products. The revision emphasizes a science-based, stepwise comparability approach, greater flexibility in data requirements, updated treatment of pharmacovigilance and labeling, and consideration of the 3Rs in animal studies. The guideline is intended to provide globally acceptable principles that national regulatory authorities can adapt to their own frameworks. [1]

4.2 European Union

The European Union pioneered a dedicated biosimilar regulatory framework and authorized its first biosimilar in 2006. EMA evaluates biosimilars using comprehensive comparability studies and requires high similarity with no clinically meaningful differences in quality, safety, and efficacy. The current European position is also notable for its distinction between scientific interchangeability and national rules governing pharmacy-level substitution. EMA and the Heads of Medicines Agencies have stated that EU-approved biosimilars are scientifically interchangeable with their reference medicines, while individual Member States determine substitution policy. [3,5]

4.3 United States

The US biosimilar pathway was established through the Biologics Price Competition and Innovation Act of 2009 and implemented through section 351(k) of the Public Health Service Act. FDA defines a biosimilar as a

biological product that is highly similar to the reference product and has no clinically meaningful differences in safety and effectiveness. An interchangeable biosimilar must meet additional statutory and regulatory requirements and may be substituted at the pharmacy level subject to state law. [6,7]

The US pathway is also evolving. FDA reported 18 new biosimilar approvals for 10 reference products in 2025, illustrating continued expansion of the market. FDA has also revised its scientific approach to interchangeability, noting that accumulated evidence has reduced concern about switching risk and that modern analytical tools can provide highly sensitive assessments of biological products. [8,9]

4.4 India

India's regulatory framework for similar biologics was originally developed through CDSCO and the Department of Biotechnology and was revised in 2016. Importantly, the 2016 framework already required a comparability exercise covering quality, preclinical and clinical aspects. Therefore, the statement in the earlier manuscript that Indian assessment involved 'no comparative testing' should be removed. [10]

A major recent development is India's 2025 revised Guidelines on Similar Biologics. The revised framework replaces the 2016 guidance and aligns more closely with contemporary international principles. Its stated emphasis includes next-generation analytical methodologies, reference standards, expanded in-vitro studies, clearer criteria for in-vivo animal studies, and implementation of the 3Rs. This is a significant scientific evolution and should be a central part of any contemporary review claiming to describe the global biosimilar landscape. [4]

5. Comparative Regulatory Framework

Table 1. High-level comparison of major biosimilar regulatory approaches. The table summarizes the regulatory-science direction rather than reproducing legal text. [1,3,4,6,7]

Dimension	WHO	EU/EMA	US/FDA	India
Core concept	High similarity; no clinically meaningful differences	Comprehensive comparability	High similarity + no clinically meaningful differences	Similarity based on comparability
Analytical evidence	Foundational and product-specific	Central to stepwise assessment	Central to biosimilarity determination	Strengthened with next-generation methods
Clinical evidence	Tailored to residual uncertainty	Tailored to product and evidence	Condition-of-use evidence; extrapolation possible with justification	Revised toward science-based, flexible requirements
Interchangeability	Principles for national authorities	Scientific interchangeability supported at EU level; substitution is national	Separate interchangeable designation	Regulatory/substitution rules require jurisdiction-specific interpretation
Animal studies	Use when scientifically justified; 3Rs	Product-specific	Product-specific	2025 framework emphasizes criteria and 3Rs

6. Interchangeability, Extrapolation And Clinical Confidence

Interchangeability should not be treated as synonymous with biosimilarity. Biosimilarity concerns the scientific demonstration that a proposed product is highly similar to its reference product and has no clinically meaningful differences. Interchangeability addresses whether switching can occur under the relevant regulatory and legal framework. The terminology and legal consequences therefore differ between jurisdictions. In the EU, EMA/HMA have endorsed scientific interchangeability, whereas decisions about pharmacy-level substitution remain within Member State competence. In the US, interchangeability is a specific FDA designation with additional requirements and state-law implications. [5,7]

Another important efficiency mechanism is extrapolation of indications. A biosimilar may be authorized for indications that were not directly studied in a clinical trial when the totality of evidence and scientific justification support the conclusion. FDA explicitly recognizes this possibility, provided the applicant addresses relevant scientific factors. This illustrates why the regulatory question is not simply whether every indication has been separately tested, but whether residual uncertainty has been adequately addressed. [7]

7. Therapeutic And Market Impact

Biosimilars have become particularly important in oncology, immunology, rheumatology, endocrinology, ophthalmology, and hematology. The clinical value of biosimilars is not based solely on lower acquisition price; competition can expand treatment options and influence prescribing, reimbursement, procurement, and patient access. However, the magnitude of savings varies by molecule, country, procurement system, competition, and

market maturity. Claims of universal or fixed cost savings should therefore be avoided unless supported by a defined economic analysis.

The US experience demonstrates the scale of recent market expansion. FDA's current product information records approvals across an increasingly broad range of reference products, including monoclonal antibodies, insulins, growth factors, and ophthalmic biologics. [8] In Europe, long-term clinical experience has supported confidence in the safety and effectiveness of approved biosimilars. [3,5] These developments suggest that the next stage of biosimilar policy is less about proving the basic feasibility of biosimilars and more about improving competition, uptake, manufacturing resilience, and equitable access.

8. Pharmacovigilance And Lifecycle Management

Biosimilar evaluation does not end at marketing authorization. Pharmacovigilance remains essential because biological medicines can be affected by manufacturing changes, immunogenicity, product-specific risks, and patterns of use that become clearer after wider exposure. A contemporary biosimilar framework should therefore integrate pre-authorization comparability with post-authorization safety monitoring, traceability, manufacturing consistency, and signal detection. WHO and EMA explicitly include pharmacovigilance within their biosimilar regulatory frameworks. [1,3]

9. Key Regulatory Challenges

- ☐ Global terminology and legal definitions are not fully harmonized, especially for interchangeability and substitution.
- ☐ Differences in reference-product requirements and bridging approaches can create duplicated development work.
- ☐ Evidence requirements continue to evolve as regulators gain experience with analytical methods, switching data, and post-market evidence.
- ☐ Market uptake depends on factors beyond regulatory approval, including procurement, reimbursement, clinician confidence, patient information, and competition.
- ☐ Rapid scientific progress requires regulatory frameworks to remain flexible without weakening standards for quality, safety, and efficacy.

These challenges indicate that international harmonization should focus on common scientific principles rather than identical legal procedures. WHO's framework can support convergence, while regional agencies can retain product- and jurisdiction-specific requirements. [1,4]

10. Novel Synthesis: From 'Approval Pathway' To 'Global Biosimilar Ecosystem'

The evolution of biosimilars can be interpreted as a transition through three stages. The first stage was regulatory establishment, in which authorities created a legal pathway for products that could not be evaluated using conventional generic-drug principles. The second stage was evidence maturation, characterized by increasing reliance on sensitive analytical methods, accumulated clinical experience, and scientifically justified extrapolation. The emerging third stage is ecosystem optimization, in which regulators, manufacturers, clinicians, payers, and patients collectively determine whether scientific approval translates into access.

This three-stage interpretation provides a novel organizing framework for the global literature. It also explains why current reforms increasingly target evidence efficiency rather than simply adding clinical studies. When analytical similarity is demonstrated with greater sensitivity, unnecessary downstream studies may be reduced; when real-world switching experience accumulates, interchangeability policies can be refined; and when competition expands, the policy focus shifts toward sustainable access and market functioning. Thus, the scientific and economic evolution of biosimilars are interconnected rather than separate topics.

11. Future Directions

- ☐ Advanced analytical technologies are likely to strengthen the ability to resolve small structural and functional differences between biological products.
- ☐ Regulatory reliance and work-sharing may reduce duplicated assessments while preserving national oversight.
- ☐ Real-world evidence and pharmacovigilance will become increasingly important for monitoring switching, immunogenicity, and long-term safety.
- ☐ The role of biosimilars in lower- and middle-income countries may expand as regulatory capacity and manufacturing capability mature.
- ☐ Future policy should distinguish scientific interchangeability from legal substitution and communicate that distinction clearly to clinicians, pharmacists, and patients.

India is particularly important in this context because its 2025 revised framework explicitly moves toward stronger analytical characterization, more extensive in-vitro assessment, and a science-based determination of the need for animal studies. [4] This makes India a useful case study of how emerging regulatory systems can evolve in parallel with international biosimilar science.

12. CONCLUSION

The biosimilar field has progressed from a pioneering European regulatory concept to a global system supported by increasingly mature analytical science and regulatory experience. The central scientific principle remains high similarity with no clinically meaningful differences, but the evidence used to establish that principle is becoming more analytical, product-specific, and risk-based. WHO's 2022 framework, the continuing evolution of FDA policy, EMA's experience with interchangeability, and India's 2025 revised Similar Biologics guideline collectively illustrate this shift. [1,4,5,7]

The major opportunity for the next phase of biosimilar development is not simply to increase the number of approvals. It is to build an efficient global ecosystem in which scientifically appropriate evidence requirements, regulatory reliance, manufacturing quality, pharmacovigilance, and market competition work together to improve access. Future research should therefore evaluate biosimilars not only by regulatory approval counts but also by analytical robustness, switching evidence, uptake, affordability, and real-world patient access.

REFERENCES

1. World Health Organization. Guidelines on evaluation of biosimilars. WHO Technical Report Series 1043, Annex 3. Geneva: WHO; 2022.
2. World Health Organization. Biosimilars: Standards and specifications. Geneva: WHO. Updated resource accessed 2026.
3. European Medicines Agency. Biosimilar medicines: overview and marketing authorisation. Amsterdam: EMA. Updated 2026.
4. Central Drugs Standard Control Organization; Department of Biotechnology, Government of India. Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India. Revised 2025.
5. European Medicines Agency; Heads of Medicines Agencies. Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU. EMA/627319/2022; updated 2023.
6. US Congress. Biologics Price Competition and Innovation Act of 2009. Public Law 111-148, as amended.
7. US Food and Drug Administration. Review and Approval: Biosimilars and Interchangeable Biosimilars. FDA. Updated 2026.
8. US Food and Drug Administration. Biosimilar Product Information. FDA. Updated 2026.
9. US Food and Drug Administration. FDA updates guidance on interchangeability. FDA. 2024.
10. Central Drugs Standard Control Organization; Department of Biotechnology. Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India. 2016.
11. Farhat F, Torres A, Park W, de Lima Lopes G, Mudad R, Ikpeazu C, et al. The concept of biosimilars: from characterization to evolution—a narrative review. 2018;23(3):346-352.
12. Gherghescu I, Delgado-Charro MB. The biosimilar landscape: an overview of regulatory approvals by the EMA and FDA. 2020;13(1):48.
13. Schiestl M, Zabransky M, Sörgel F. Ten years of biosimilars in Europe: development and evolution of the regulatory pathways. Drug Discov Today. 2017;1509-1515.
14. Niazi SK. Biosimilars: harmonizing the approval guidelines. 2022;2(3):171-195.
15. Kirchhoff CF, Wang XZM, Conlon HD, Anderson S, Ryan AM, Bose A. Biosimilars: key regulatory considerations and similarity assessment tools. 2017;114(12):2696-2705.
16. Kang HN, Thorpe R, Knezevic I, et al. Regulatory challenges with biosimilars: an update from 20 countries. 2021;1491(1):42-59.
17. Hock SC, Kian SM, Wah CLG. Global challenges in the manufacture, regulation and international harmonization of GMP and quality standards for biopharmaceuticals. 2020;9(2):52-64.
18. Humphreys SZ. Real-world evidence of a successful biosimilar adoption program. 2022;18(16):1997-2006.
19. Malhotra H. Biosimilars and non-innovator biotherapeutics in India: an overview of the current situation. 2011;39(5):321-324.