



Review

Biosimilars: Bridging the Gap in Biologics, Access, and Affordability

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Abstract

There is a growing global demand for cost-effective alternatives to high-priced biologic therapies, which has significantly accelerated the development of biosimilars and positioned them as sustainable and affordable treatment options. Biosimilars include therapeutic products such as monoclonal antibodies, soluble receptors, growth factors, and hormones that demonstrate comparable efficacy, safety, and quality to their reference biologics. By providing lower-cost alternatives, biosimilars play a vital role in bridging the affordability gap and expanding patient access to essential, life-saving treatments, particularly in low- and middle-income countries. This review focuses on current Good Manufacturing Practices (cGMPs) in biosimilar development, highlighting critical processes such as cell line engineering, glycosylation optimization, and bioprocess refinement aimed at improving cell culture productivity and product yield while ensuring consistent safety, efficacy, and quality across production batches. Advances in biotechnology, especially in proteomics and advanced analytical characterization, have improved understanding of cellular mechanisms influencing product quality and strengthened comparability with reference biologics. These scientific innovations have enhanced regulatory and clinical confidence, supporting wider acceptance and use amongst patients. In addition, this review examines the evolving global regulatory landscape governing biosimilars and its role in reducing development timelines and costs. Together, scientific innovation, standardized manufacturing practices, and harmonized regulatory frameworks foster competition, accelerate market entry, and ultimately help bridge the gap between innovation and affordability, ensuring equitable and sustainable global access to advanced biologic therapies.

Keywords: biosimilars; Good Manufacturing Practices; regulatory approval



Academic Editor: Robert Ancuceanu

Received: 17 August 2025

Revised: 8 January 2026

Accepted: 26 January 2026

Published: 5 February 2026

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1. Introduction

The ever-increasing cost of life-saving therapeutics has presented a significant challenge for both patients and the pharmaceutical industry in ensuring access to affordable, lower-cost options for those in need of critical care. Biopharmaceuticals are biological medicinal products whose active drug substance is made by a living organism or derived from a living organism by means of recombinant DNA and/or controlled gene expression methods. Biosimilars, on the other hand, are clinically similar to the original biologic; however, they are not the same as the originator biologic. As biosimilars are produced in living systems, which are inherently variable, a biosimilar is not a replica of its reference. Instead, it undergoes a thorough comparability process to confirm that its key characteristics align with those of the reference product within an acceptable range [1].

Since the first authorization for marketing of the biosimilar ‘Omnitrope’ in 2006 in Europe and 2015 in the United States, this sector has seen significant global momentum. Europe leads the way in building a strong regulatory pathway for approvals, and the United States has seen significant legislation for the approval of biosimilars. The USA is speeding approvals but faces patent disputes and slow adoption. India shows strong promising growth, yet regulatory uncertainty persists [2].

Cell lines form an essential tool for the production of biosimilars. Stable cell lines are particularly critical because they enable reproducible manufacturing of complex biologics across multiple production batches [3]. This stability ensures that biosimilars remain highly comparable to originator biologics in terms of structure, function, and therapeutic effect, which is a cornerstone of regulatory approval and patient safety [4].

Biosimilars do not undergo the same approval procedures as biologics, which is reflected in their cost. Biosimilars are comparatively cheaper than the originator biologic. However, in comparison to small molecules and generic drugs, biosimilars are still costlier. A prominent challenge associated with biosimilar production is establishing biosimilarity, which requires extensive analytical testing and clinical comparability studies to prove safety and efficacy [5,6]. Other challenges related to this innovation include the complex regulatory pathway, rigorous manufacturing standards, and hurdles in market adoption and commercialization to maintain critical quality attributes (CQAs) such as binding affinity, immunogenicity, and glycosylation profile [7,8]. In addition to this, originator biologic manufacturers create patent thickets of overlapping patents that delay biosimilar entry.

This review, therefore, discusses different aspects of biosimilar production, regulatory frameworks worldwide, and challenges in this important sector of biotherapeutics. We will focus on India as a representative of the challenges faced by lower-middle-income countries, contrasting them with the established pathways in the USA and EU.

2. Biosimilar Production

The production of biosimilars is a complex, multi-stage process that mirrors the conventional biopharmaceutical development pathway but incorporates additional analytical, comparability, and regulatory steps to confirm a high degree of similarity with an already approved reference biologic. Unlike originator biopharmaceuticals, which begin with the discovery of a novel therapeutic protein followed by characterization, preclinical testing, and clinical validation, biosimilars are developed through reverse engineering of an existing biologic. This process starts with a detailed analysis of the reference product’s structural, physicochemical, and functional properties to define the quality attributes that must be matched. The goal is not to replicate the reference molecule identically, as inherent biological variability makes this impossible, but to ensure that any differences are not clinically meaningful in terms of safety, purity, or potency.

Both biopharmaceuticals and biosimilars follow comparable upstream and downstream processes, including cell line development, process optimization, purification, formulation, and validation. However, biosimilar production requires greater precision and tighter control at each step, since even minor deviations in culture conditions, post-translational modifications, or purification parameters can alter critical quality attributes such as glycosylation profiles, binding affinity, or immunogenic potential. For this reason, biosimilar development heavily relies on advanced analytical tools, Quality by Design (QbD) frameworks, and Design of Experiments (DoE) strategies to maintain consistency and achieve equivalence with the originator biologic.

Figure 1 presents a comparative overview of the biopharmaceutical and biosimilar development workflows, showing how biosimilar production integrates analytical

comparability, process engineering, and regulatory alignment to achieve clinical and functional equivalence.

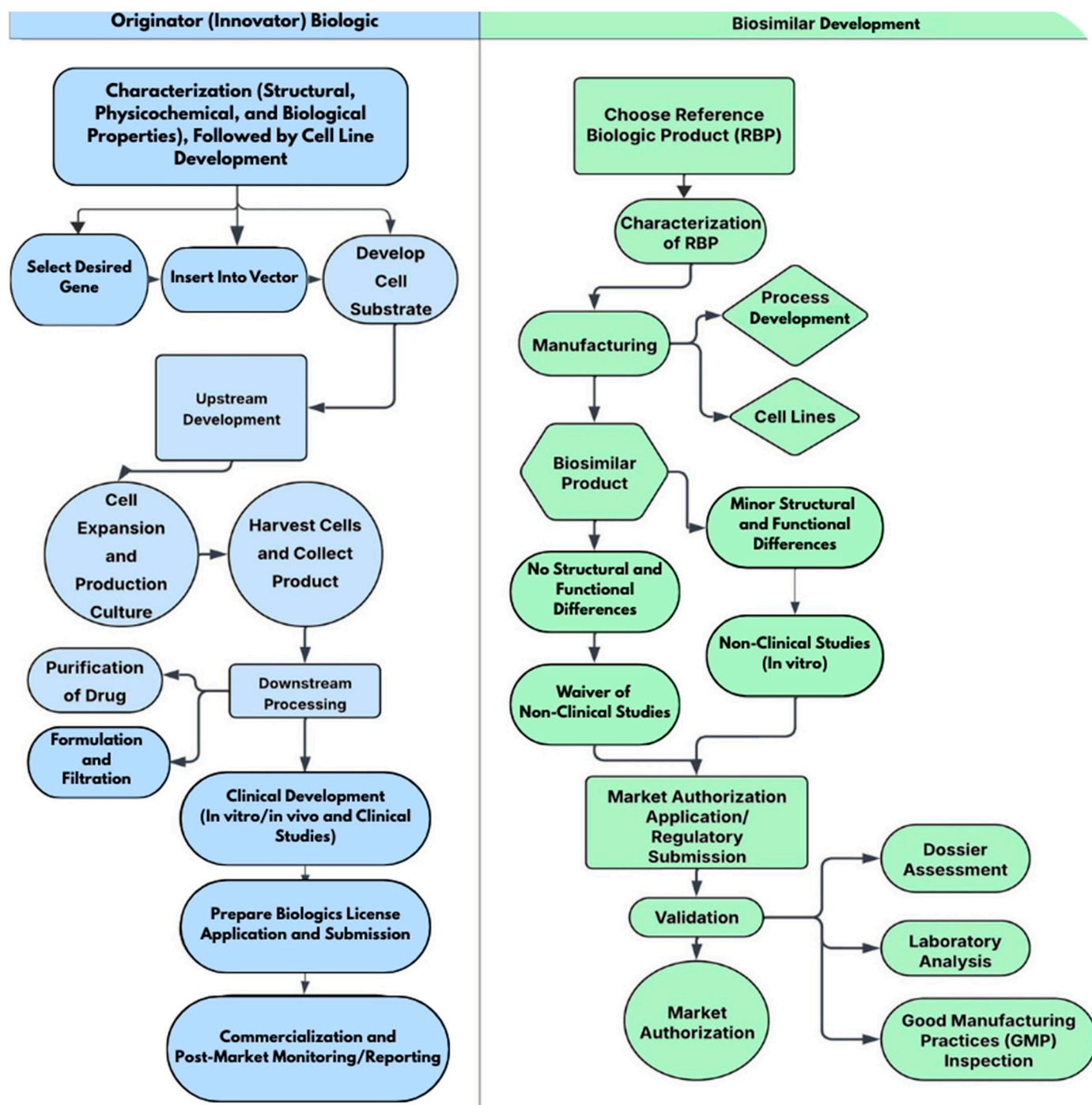


Figure 1. Comparative flowchart depicting comparative details of biopharmaceutical and biosimilar development.

2.1. Characterization of Originator Biologic

Characterizing an originator biologic is the first step in understanding the molecular and functional complexity of therapeutic proteins. This process involves a comprehensive evaluation of the originator product's structural, physicochemical, and biological properties to prepare a fingerprint and build a detailed quality profile for the proposed biosimilar. Analytical studies typically assess the primary amino acid sequence, higher-order structure, post-translational modifications such as glycosylation, charge variants, and aggregation

tendencies. In addition, functional assays are conducted to examine biological activity, binding interactions, and the mechanism of action, ensuring that the therapeutic protein performs as intended. Such in-depth characterization is not only essential for understanding the relationship between structure and function but also for setting quality benchmarks that future products, including biosimilars, must meet. These data form the scientific basis for regulatory assessment, quality control, and lifecycle management of biopharmaceutical products [9,10].

2.2. Cell Line Development

Developing an optimal biosimilar cell line and design and identifying proper vectors that deliver the desired gene is the foundation of success of biosimilar production. Mammalian expression systems, particularly Chinese Hamster Ovary (CHO) cells, are widely used for recombinant protein production, including mAbs. CHO cells are preferred due to their ability to carry out complex post-translational modifications and proper protein folding, which are essential for the functionality of therapeutic proteins. Other mammalian cell lines, like mouse myeloma cell lines (NS0 and Sp2/0) and human embryonic kidney (HEK293) cells, are also used, although their use is less common.

CHO cells stand out because of their high cell density, robust growth, and superior protein expression capabilities. These features have made them the leading cell line for industrial mAb production. Recent and continuous advancements in CHO cell line engineering, such as enhancing metabolic efficiency, improving specific productivity, and refining glycosylation pathways, directly reduce upstream production costs because of increased volumetric yield and decreasing batch-to-batch variability [10]. Lower manufacturing costs cascade through the biomanufacturing pipeline and enable developers to price biosimilars more competitively while maintaining quality and regulatory compliance. Such cost-effectiveness is significant for healthcare systems and patients, as it helps in expanding access to biologic therapies that would otherwise remain prohibitively expensive [11].

3. Process Development

Process development is the methodical and iterative approach to establishing and optimizing the manufacturing processes to produce biosimilars, such as mAbs. Early-stage development and late-stage development are the two primary stages that make up the normal biosimilar process development. During the early stages of product development, the primary focus is on developing a process that is both robust and scalable and that satisfies the requirements for the ideal product. This goes beyond conventional objectives due to the requirement of these products to demonstrate a high degree of structural, functional, analytical, and clinical similarity to an approved originator biologic. Even subtle variations introduced during the cell culture, purification, or formulation can alter CQAs such as patterns of glycosylation, protein misfolding aggregation behavior, and binding affinity, potentially triggering additional comparability studies or regulatory delays. Therefore, optimization strategies in biosimilar development are designed not only to maximize yield and efficiency but also to maintain molecular equivalence, ensuring regulatory acceptance and clinical interchangeability. This requires performing a screening and selecting the relevant cell lines, optimizing the conditions of the cell growth, and determining appropriate purification methods. In the later stages of product development, as the product is nearing completion, the focus switches to process characterization, scale-up, and validation [12]. During this phase, the process parameters that were determined during the earlier stages of development are subjected to further optimization and refining. Establishing robust control strategies and validating process consistency ensures both product quality and regulatory compliance. It also improves manufacturing economics. Well-defined control ranges reduce

batch failures, minimize reprocessing needs, and enhance the process reproducibility, all of which significantly lower the cost of goods (COGs). COGs are a critical factor in delivering biosimilars as cost-effective therapeutic alternatives to originator biologics and defining the primary process parameters and conditions that, when optimized, will produce the product quality, yield, and productivity levels that are sought [13].

The process parameters are an extremely important part of the overall development of the process. These parameters consist of cell culture conditions, the optimization of the nutrients and feed, the design of the bioreactor, harvesting and purification processes, and the development of formulations. The optimization of these factors is necessary to achieve excellent product quality, maximize production, and reduce the amount of unpredictability that the process exhibits. When it comes to process development, product quality is of the utmost significance [14]. The therapeutic criteria and regulatory guidelines serve as the basis for defining the product quality characteristics that are optimally sought. The goal of process development is to build control techniques and process conditions that will ensure the product quality is maintained as per the Quality Target Product Profile (QTPP) throughout the manufacturing process [15].

3.1. Host Cell Growth Requirements

In biosimilar manufacturing, such as mAbs, optimizing the growth of host cells is necessary for high productivity and product quality. By precisely modulating nutrient composition and feed timing, researchers can control metabolic flux within the culture, limiting accumulation of by-products such as lactate and ammonia that negatively impact protein structure and stability. This metabolic control is especially critical in biosimilar production, where even a minor deviation can lead to altered higher-order structure or glycan heterogeneity, potentially compromising comparability to the reference biologic. Additionally, improved nutrient utilization enhances volumetric productivity, reducing the number of production runs required and thereby lowering overall manufacturing costs [16,17].

Key parameters for optimal growth include temperature, pH, dissolved oxygen (DO) levels, and agitation. Mammalian cells are typically cultured at 37 °C, while the pH is maintained between 6.8 and 7.4 to support cell growth and protein production. In biosimilar manufacturing, the acceptable operating ranges for these variables are much narrower than in novel biologic production because even the slightest of deviations can influence post-translational modifications, protein conformation, and glycan heterogeneity. These attributes are CQAs that are subjected to strict regulatory comparability assessments. Stringent control of such parameters ensures that biosimilar candidates remain structurally and functionally equivalent to their reference products, reducing the risk of any additional analytical or clinical comparability studies. By adjusting nutrients, growth, and environmental conditions, researchers can achieve high cell density, viability, and productivity [18].

3.2. Clone Selection

Clone selection is a critical step in mAb production, involving the evaluation of numerous parameters to identify clones with desirable characteristics. For biosimilars, selecting clones is not just about maximizing titers but also about ensuring that the selected clones yield products with structural and functional similarity to the originator biologic. To achieve biosimilarity, clones that consistently produce antibodies with comparable higher-order structure, glycosylation profile, and biological activity to the reference product are selected, as even minor variations can impact the safety and efficacy of the product [19]. Therefore, clone selection strategies must integrate detailed analytical and functional

assessments early in development to confirm the comparability of critical quality attributes with the originator molecule [20].

Assessing antibody titers is a common initial step. Clones with high titers are preferred, as they produce larger quantities of the desired mAb. Clones with consistently high titers are prioritized for further evaluation [21].

The objective is to identify clones that exhibit product quality attributes comparable to the originator biologic. This involves assessing critical parameters such as size and charge heterogeneity, glycosylation profiles, post-translational modifications, and other quality-defining characteristics. Clones whose product quality closely aligns with that of the originator biologic are prioritized for further development.

Equally important is ensuring batch-to-batch consistency. A stable cell line is essential to achieve reproducibility and uniformity during large-scale manufacturing. Stability is evaluated by monitoring cell growth and productivity over multiple passages and extended culture periods [22]. Clones that maintain robust growth, high viability, and consistent productivity are considered stable and suitable for progression.

In addition, metabolic performance is a key selection criterion. Clones with high viable cell concentrations are preferred, as they enable higher cell densities in bioreactors and thereby enhance productivity. Clones producing low levels of lactate are also favored, since excessive lactate can impair cell growth and reduce overall production yields.

3.3. Media Feed Screening

Screening of media in biosimilar development is crucial for optimizing cell growth, productivity, and product quality. This process involves evaluating various media compositions, amino acids, vitamins, and feed strategies to identify the best combination for high yields, desirable titers, and product quality comparable to the innovator drug. Chemically defined and serum-free media are often explored to optimize nutrient availability for robust cell growth and development.

By standardizing feed concentrations, timing, and frequency, researchers ensure consistent production and high yields. The DoE approach is often used to optimize media-feed conditions. DoE allows researchers to systematically analyze multiple factors—such as process parameters, feed schemes, and media components—simultaneously. This method helps pinpoint critical variables that significantly impact productivity and product quality, enabling fine-tuning for optimal performance [23]. Linking DoE specifically to biosimilars, such optimization not only improves yields but also ensures that CQAs match the reference biologics, which is essential for establishing biosimilarity [24]. This is achieved through the application of QbD principles. Systematic control of the entire manufacturing process ensures control between process parameters and product quality.

3.4. Media Optimization

Media optimization boosts culture growth and yield that also directly impacts cost, which is central to the affordability aspect of the biosimilar [25]. Media optimization is a critical strategy for reducing the high cost of manufacturing biosimilars. It entails fine-tuning the components of cell culture media and process conditions to maximize product yield and quality while minimizing waste. This optimization impacts productivity as well as ensures comparability to the originator biologic, as nutrient conditions can affect glycosylation and protein folding, which are critical for maintaining structural and functional biosimilarity [26,27]. By combining a high-performing cell line with an optimized media-feed strategy, productivity can be enhanced and biosimilarity can be ensured, leading to reliable mAb production for commercial use [6]. The reliability of the product also ensures faster regulatory approvals and cost-effectiveness of the biosimilar.

3.5. Vial Thaw and Seed Expansion

The process for the synthesis of mAbs requires several phases, two of the most important of which are vial thawing and seed expansion. In most cases, this procedure is broken up into a few steps, beginning with the defrosting of the vials and continuing through a series of flask stages before entering the bioreactors. Controlled methods of thawing of cryopreserved host cells, typically CHO cells, are essential to minimize cellular stress and maintain high viability. Any variability introduced at this stage can propagate through subsequent culture steps, leading to alterations in growth kinetics or protein expression profiles that compromise biosimilar comparability [28]. The thawing of cells kickstarts their growth. Seed expansion is carried out through sequential scale-up in increasingly larger vessels, which helps to not only generate the required biomass but also stabilize the cellular phenotypes and maintain consistent productivity. Stringent control of culture conditions during this phase helps preserve key CQAs such as glycosylation patterns, higher-order structure, and bioactivity parameters that are required to closely match those of the reference product to meet regulatory requirements [29]. Early process control during expansion reduces the risk of batch-to-batch variability and downstream deviations, thereby enhancing process robustness and lowering the likelihood of extended analytical or clinical comparability assessments [30]. This stage is essential for growing the cell population and establishing a sufficient number of cells to scale-up the process further. Figure 2 is a visual representation of the vial thawing process [31].

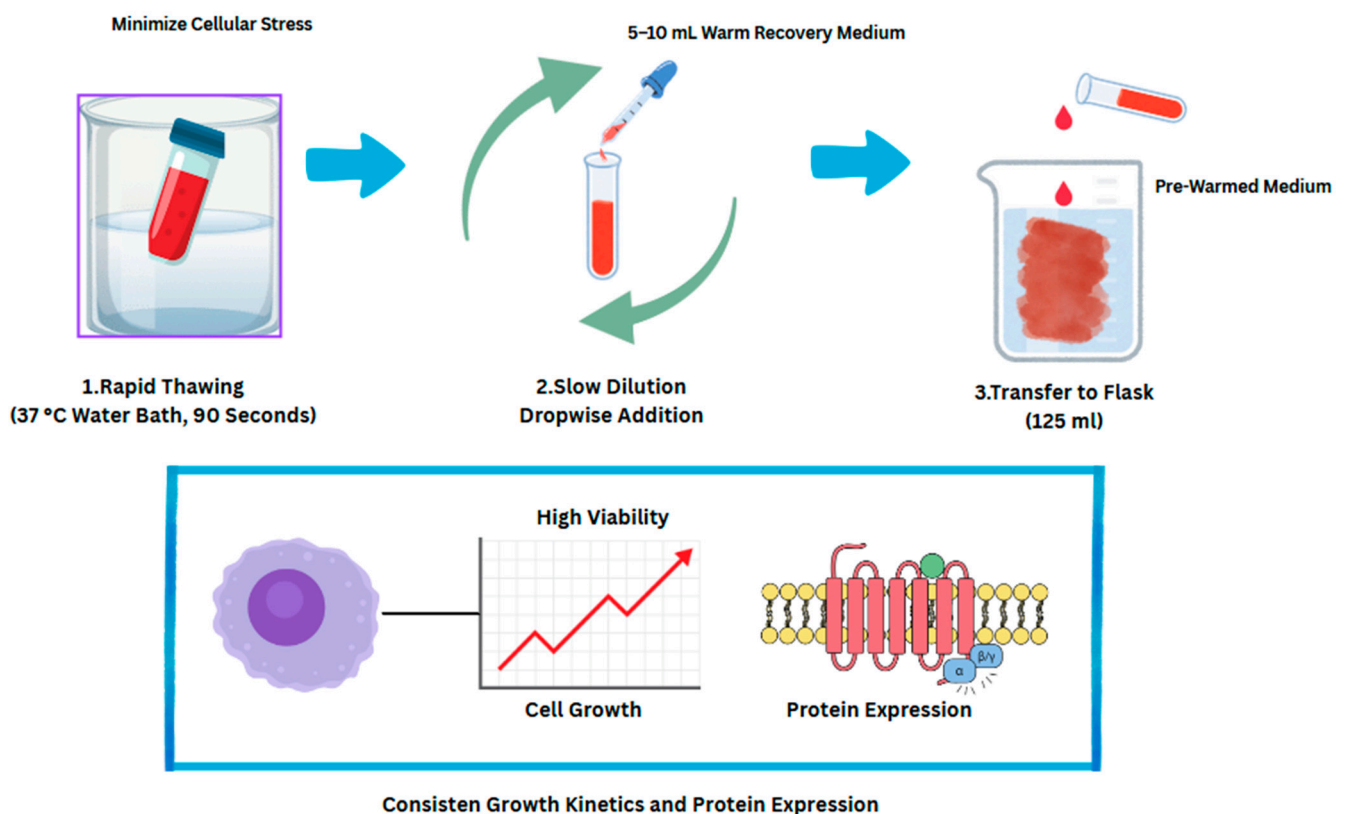


Figure 2. Illustration depicting the controlled vial thawing stage that is essential for growing the cell population to scale-up the process.

3.6. Inoculum Propagation (Seed Expansion) in Shake Flasks and Bioreactors

The process of inoculum propagation, also known as seed expansion, is an essential stage in the scaling-up of cell cultures for the manufacture of mAbs. The inoculum propagation process involves a series of scale-up steps from small flasks to large bioreactors [26].

On achieving desired cell density, the process is upscaled [19], which makes it possible to produce higher cell densities as well as larger amounts of cells [20,21]. Scaling from shake flasks to production bioreactors is a critical step that directly influences both process economics and product quality. As illustrated in Figure 3, after the completion of the bioreactor stage, the cells are moved to the production bioreactor, which is intended for upscaling the culture. Before the actual manufacture of mAbs can begin, the seed expansion process is completed in its entirety in the last bioreactor of the production chain [32]. Following the completion of the previous bioreactor stage, the cells are moved on to the production bioreactor, which is intended for culture on a much larger scale. This bioreactor has sophisticated control systems built into it, which allow for optimal growth conditions to be maintained. Factors such as temperature, pH, DO, and agitation are maintained through sophisticated control systems. The production bioreactor is used to cultivate the cells to attain the high cell density and productivity required for the manufacture of mAbs [33].

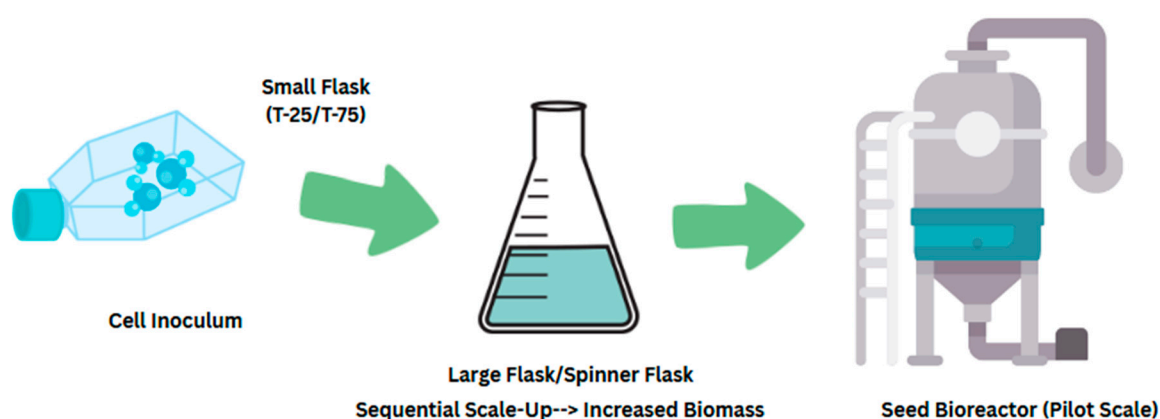


Figure 3. Illustration of the seed expansion stage, which involves seed expansion in the bioreactor stage, following which the cells are moved to the production bioreactor for upscaling the culture.

Efficient and predictable scale-up enhances volumetric productivity, reduces batch failures, and lowers the cost of goods, thereby cost-effectively enabling more competitive pricing and improving patient access to biosimilars [22]. It is equally important to maintain consistent cell growth and product quality across scales, as these are essential for achieving the desired CQAs and demonstrating structural and functional equivalence to the originator biologic, which is a key hallmark for biosimilar approval [34].

3.7. Process Parameter Optimization

Process parameter optimization is crucial in biosimilar production to align product quality with regulatory scrutiny and extensive analytical comparability. As illustrated in Figure 4, careful adjustment and optimization of various process factors can ensure that the biosimilar meets specified quality criteria, ensuring comparability with the originator biologic. QTPP is a prospective summary of the desired quality characteristics of the biosimilar product. To achieve this, reverse engineering of the originator biologic to define the target ranges for all CQAs that affect the product's safety and efficacy must be carried out. Importantly, matching the originator's profile is required not just to achieve the desired product quality, but also to satisfy regulatory comparability criteria that govern biosimilar approvals [35]. The following are crucial process parameters that require optimization for successful biosimilar production.

1. **Culture Conditions:** Optimizing culture conditions, including temperature, pH, DO levels, and nutrient availability, is essential for achieving the desired product quality. These variables affect mAb post-translational modifications, cell productivity, and

cell proliferation. Carefully regulating these parameters is especially critical for biosimilars, as deviations can lead to structural or functional differences from the reference biologic, potentially impacting clinical performance [36].

2. **Fermentation Parameters:** To achieve a high-quality biosimilar product, parameters such as agitation, aeration, and feeding techniques significantly impact the CQAs, including proper protein folding, disulfide bond formation, and the reduction of aggregates and contaminants. Proper oxygen delivery, effective mixing, and controlled nutrition input are essential for maintaining cell health and appropriate protein properties. Optimization of these parameters can lead to proper disulfide bond formation, adequate protein folding, and reduced aggregates and contaminants [37].
3. **Purification parameters:** The purification process is crucial for achieving the desired product quality by removing impurities and obtaining the appropriate purity levels. Selecting the right chromatographic techniques, filtration procedures, and other purification methodologies is essential to eliminate process-related contaminants and ensure the final product meets the necessary quality requirements [38].
4. **Formulation Considerations:** Formulation affects both the quality and properties of the finished product. Optimizing formulation parameters, such as buffer composition, pH, and excipient choice, is crucial to maintain stability, reduce degradation, and ensure compatibility with the intended product. The quality of a biosimilar is profoundly influenced by its stabilizers and excipients, which must meet the strictest standards. These components directly impact the biosimilar's biopharmaceutical profile, affecting its shelf life, administration, clinical efficacy, and potential for causing an immune response. Stable formulations help reduce wastage, extend shelf life, and enable wider distribution—directly impacting affordability and patient accessibility [39].

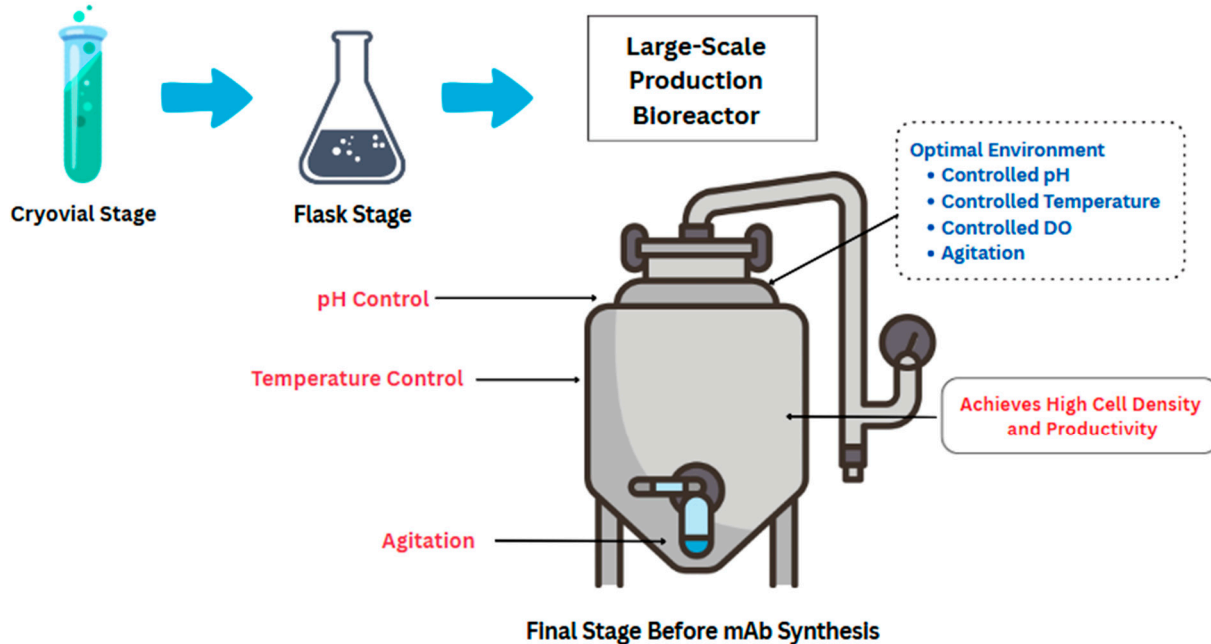


Figure 4. Illustration of key steps in process parameter optimization.

By systematically analyzing and optimizing key process parameters, the desired product CQA's comparable to the originator biologic can be achieved. A combination of experimental design, statistical analysis, and iterative refinement is necessary to achieve the desired product attributes. It is important to note that the originator biologic and the biosimilar product must be compared in terms of structure, function, efficacy, and safety to be compliant with regulatory guidelines. This involves thorough analytical characterization

and comparative studies [40]. The goal is to ensure that any differences in the biosimilar are not clinically meaningful in terms of safety, purity, and potency.

3.8. Scale-Up and Optimization of Bioreactor

To ensure successful biosimilar production, bioreactors must be scaled up and optimized. This process involves transferring batch data from smaller-scale bioreactors to larger production bioreactors while maintaining process consistency and maximizing output. For biosimilars, scaling is not only about maintaining process consistency but also managing the regulatory risk that any inconsistency can undermine comparability with the originator biologic, potentially resulting in delayed approval or rejection by regulatory authorities [41]. The factors that have to be kept in consideration are mentioned below.

- (a) **Scale-Up Methodology:** Volumetric mass transfer coefficient (kLa) and power per unit volume (p/v) scaling are common methods. These techniques ensure that desired parameters are maintained during scale-up by considering factors like oxygen transfer rates, mixing effectiveness, and power usage. For biosimilars, maintaining these parameters within strict limits is critical to ensure product quality and biosimilarity, reducing the risk of costly regulatory delays [42].
- (b) **Process Consistency:** Demonstrating process consistency at the pilot scale is essential before transferring to production. This involves running multiple batches and carefully tracking process variables, product quality, and yield. For biosimilars, demonstrating this consistency is a key regulatory requirement to confirm comparability with the originator and to support cost-effective manufacturing as well as timely regulatory approvals [43].
- (c) **Development Batch:** A development batch is conducted at the production scale to validate the functionality of the bioreactor and establish the scalability of the optimized process. Key factors evaluated include cell growth, productivity, product quality, and process robustness. Ensuring these parameters align with the originator QTPP profile minimizes regulatory risk and supports timely market entry for affordable biosimilars [44].

4. Process Validation

Process validation is a critical step in biopharmaceutical production, ensuring that the manufacturing process consistently produces high-quality products [45]. This is a multi-step approach that requires detailed analytical comparison to the originator product and includes a series of qualifications and verifications to ensure the manufacturing process consistently produces a high-quality product. Biosimilar process validation uses QbD based on QTPP to build quality into the product from the earliest stages of development, rather than solely relying on end-product testing. Process validation includes process qualification, process characterization, and ongoing process verification. The overarching goal is to build confidence in the consistency, reliability, and control of the manufacturing process. This is achieved through data collection, risk analysis, and control measures. Conducted in accordance with regulatory requirements, the validation process involves creating validation protocols, conducting tests, collecting data, statistical analysis, and generating validation reports. The procedures are carried out in compliance with GMPs and other relevant regulations [46]. In addition, a biosimilar's drug substance and drug product being consistent and highly comparable to the innovator biologic is fundamental to the entire regulatory approval process. This principle governs the "totality of evidence" approach for biosimilar approval and differs significantly from the process for generic drugs.

5. Manufacturing Under cGMP

Manufacturing of biosimilars under cGMP involves two key processes: batch fabrication for toxicological investigations and clinical trial material generation. These steps ensure the product is produced in a regulated and controlled environment, meeting quality, similarity to the original biopharmaceutical, and safety standards [47].

5. **Production Scale and Unit:** The manufacturing process is conducted in a cGMP-compliant facility equipped with production-scale bioreactors, ensuring both scalability to produce large volumes and the reproducibility of the process. For biosimilars, however, adherence to cGMP is not just a regulatory requirement; it is the foundation of their value proposition. The rigorous quality control mandated by cGMP ensures the strict batch-to-batch consistency required for a product to be considered a reliable substitute. This consistency is critical for building the trust of physicians and patients, which ultimately allows biosimilars to be accepted as interchangeable and affordable alternatives to innovator drugs [48].
6. **Batches for Toxicological Studies:** Batches for toxicological studies are produced in the production facility, adhering to cGMP standards. These early batches must be consistent with the batches made later for clinical trials. If they are not, regulators may question if the safety data truly applies to the final product. This can force the manufacturer to repeat expensive studies, causing major delays in the approval timeline and adding significant unnecessary costs [49].
7. **Clinical Trial Material Generation:** Following successful toxicological investigations, the manufacturing process continues to produce clinical trial material, adhering to cGMP regulations. Unlike novel biologics, biosimilars must undergo head-to-head trials designed against a reference product. Therefore, ensuring unwavering consistency between the clinical trial material and the final commercial product is essential. Any variation could invalidate the results of these sensitive comparative studies, jeopardizing the entire approval pathway [47,49].
8. **The cGMP Compliance Process:** The production unit operates in a controlled environment with rigorous procedures for personnel hygiene, equipment cleaning, and maintenance. The manufacturing process, including raw material processing, cell culture, purification, formulation, and filling, follows established protocols and undergoes quality control inspections [50].
9. **Regular Sampling and Testing:** Quality control measures include regular sampling and testing of raw materials, in-process samples, and finished goods. The primary objective is not merely to meet predefined specifications but to rigorously demonstrate comparability to a reference product. Consequently, regulators place intense focus on assays for critical quality attributes that serve as sensitive indicators of similarity. Among these, potency and purity are intensely scrutinized. Potency assays are fundamental to confirming an equivalent biological activity, while the comparison of purity profiles is crucial for ensuring comparable safety and immunogenicity risk [47].
10. **Documentation:** Documentation and record-keeping are integral parts of the cGMP manufacturing process. All manufacturing activities are meticulously documented, including batch records, equipment logs, cleaning records, and quality control test results [51].

6. Biosimilar Regulatory Approvals and Status

Europe and the USA represent major, high-value markets for these products, with Europe having 50% of the revenue share in 2022. Asia Pacific is projected to grow with the second-highest Compound Annual Growth Rate between 2022 and 2030.

Keeping in view the tremendous growth potential for Asia Pacific in this sector, individual roles for Asia Pacific, the USA, and Europe, although distinct, collectively have the potential to drive the global biosimilar landscape. India in the Asia Pacific region has a distinct edge due to a combination of manufacturing expertise and already established markets and regulatory environments [52].

6.1. Product Filing

Regulatory approvals are the cornerstone for the introduction of a given biosimilar in different regions worldwide. A streamlined system can result in a robust supply chain and contribute to the accessibility and cost of biosimilars.

Figure 5a outlines India's multi-step regulatory pathway, designed to balance patient safety with access to more affordable medicines. The Central Drugs Standard Control Organisation (CDSCO) acts as the central gatekeeper, relying on recommendations from an independent Subject Expert Committee (SEC), which provides its scientific opinion to the Drugs Controller General of India (DCGI). A defining feature of this process is the requirement for local clinical trials, which confirms the biosimilar's performance specifically in the Indian population and helps build crucial trust with doctors. Securing this domestic marketing authorization is a critical milestone that establishes the product's manufacturing process and initial data, positioning Indian companies to then seek approval and enter the international market. Recently, in May 2025, CDSCO published draft revisions to the biosimilar guidelines to align with international standards and streamline the approval process.

In Europe, the European Medicines Agency (EMA) establishes a framework for the approval of biosimilars, and individual countries within the European Union create laws and regulations governing how those drugs are dispensed, as illustrated in Figure 5b. In the EU, a Marketing Authorisation Application (MAA) is submitted by the manufacturer to the EMA to obtain permission to market a medicinal product. Products can proceed with commercial manufacturing following successful audits and regulatory assessments by their country's respective agencies [53]. The EMA conducts an MAA. The primary purpose of the MAA is for the EMA to scientifically evaluate the medicinal product's quality, safety, and efficacy to ensure it has a positive risk–benefit balance. It also evaluates the manufacturers' capabilities in distribution and marketing procedures. A successful MAA conclusion is essential for product approval in the E.U. [54]. It is important to mention that EMA does not have a separate formal designation of interchangeability.

In contrast to this, for the USA, a Biological License Application (BLA) must be submitted to the FDA requesting permission to market biological products in the USA, as illustrated in Figure 5c. The BLA contains comprehensive information on the product, including safety profiles, preclinical and clinical trial results, manufacturing procedures, and quality control tests. It displays compliance with regulatory standards for quality, safety, and efficacy [55]. In contrast to the EU, the FDA's stance on interchangeability allows a biosimilar product to be substituted for a biological product at the pharmacy level, without the need for the prescriber's intervention [56].

6.2. Regulatory Audits

Regulatory bodies conduct audits to verify compliance with current cGMP. These inspections assess factors like facility design, equipment qualification, process validation, documentation, and quality control processes. For biosimilars, documents have different burdens compared to generics or novel biologics, since they must include extensive analytical comparison data and sometimes head-to-head clinical trials. Successful audits examining all these aspects are crucial for obtaining regulatory approval [55]. India's regulatory audit for biosimilars is overseen by the CDSCO, which evaluates quality, safety,

and efficacy for market approval. In the USA, this task is assigned to the FDA, and in Europe, the EMA is responsible for the quality, safety, and efficacy of the biosimilar.

6.3. Drug Manufacturing License

The manufacturing facility must obtain a drug manufacturing license, which certifies compliance with legal specifications for producing medications. This involves inspections, documentation reviews, and cGMP compliance checks [57]. Upon successful completion of the BLA, regulatory audits, MAA, and CDSCO and obtaining a drug manufacturing license, regulatory authorities approve commercial manufacture. This approval indicates compliance with legal requirements for quality, effectiveness, and safety, allowing for commercial production and distribution of the biosimilar [58].

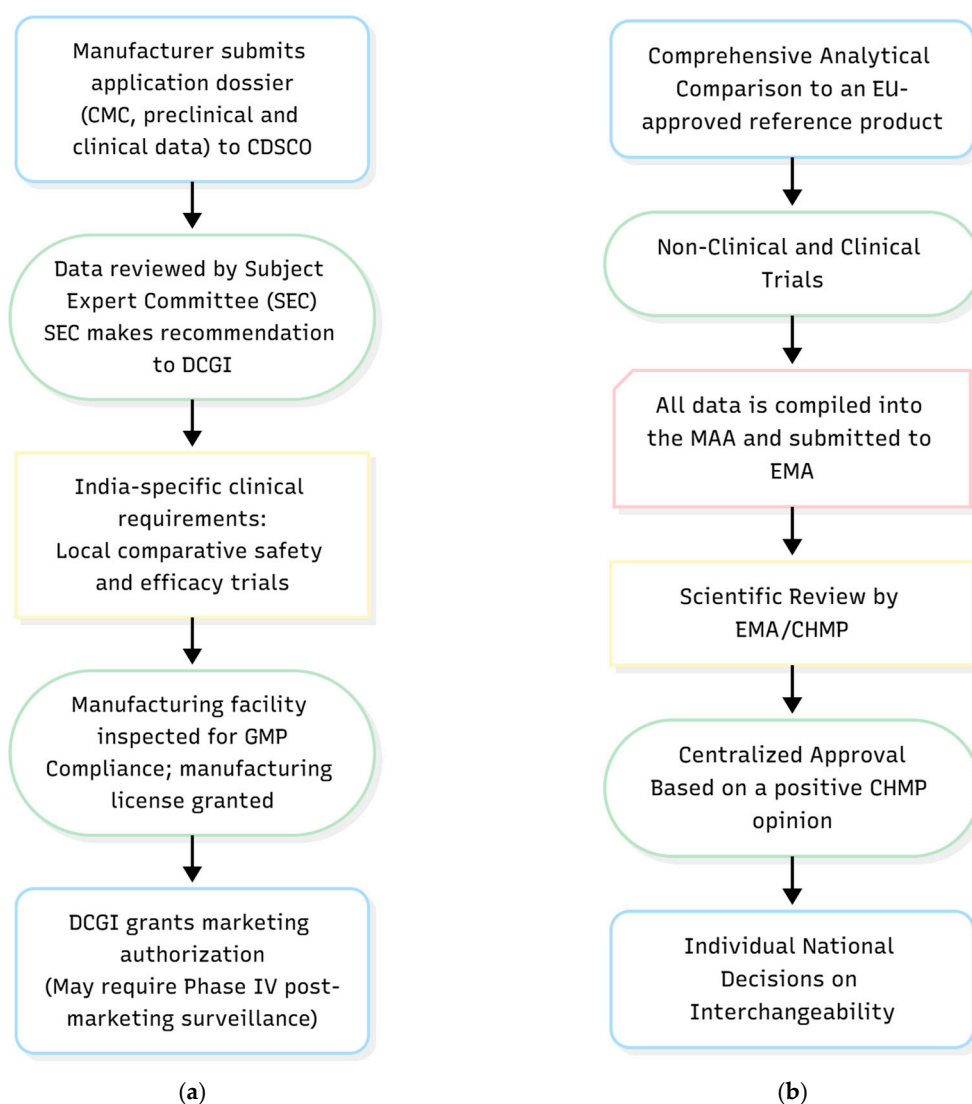


Figure 5. Cont.

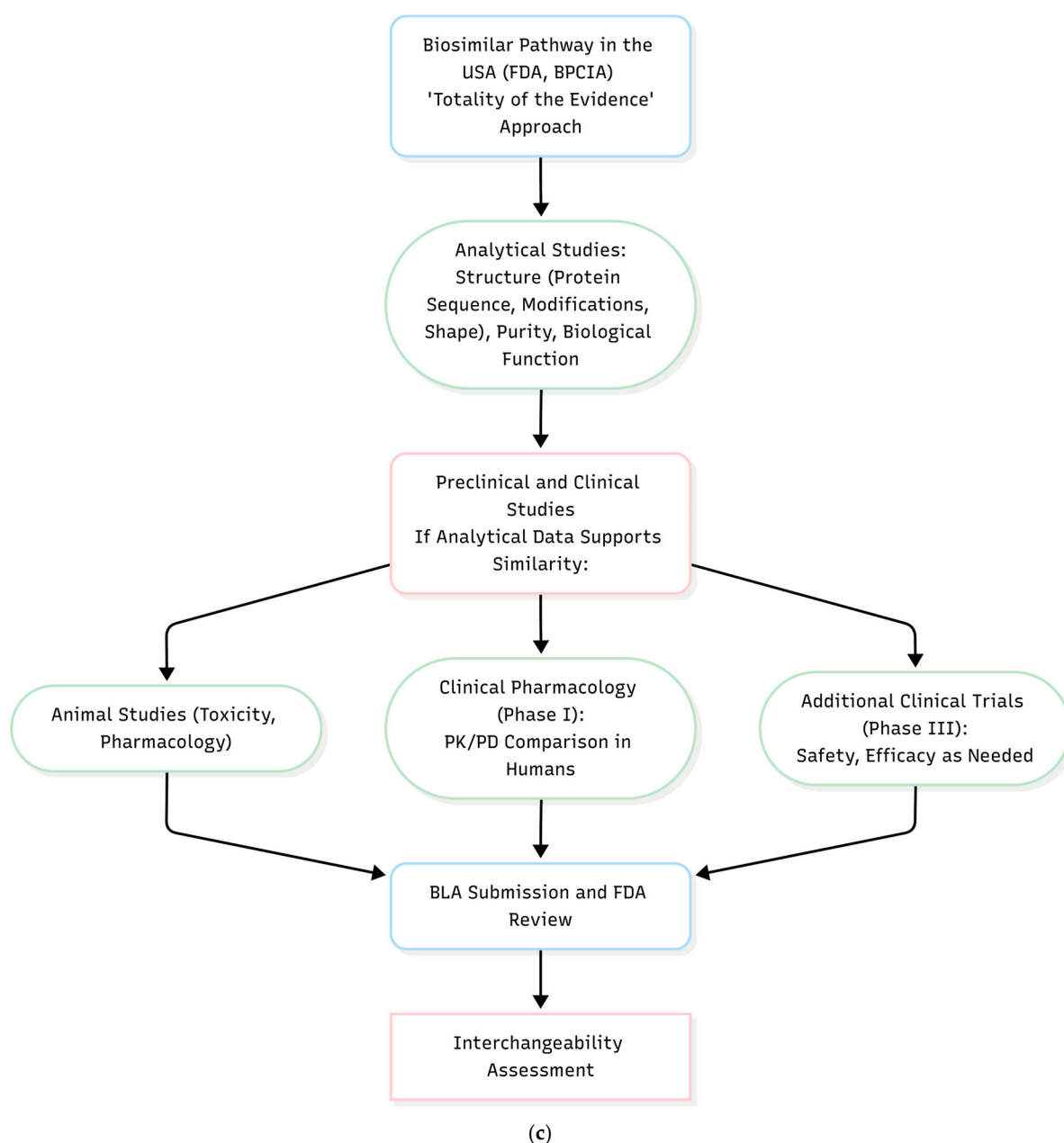


Figure 5. Regulatory framework for biosimilar approval in different countries: (a) India; (b) EU; (c) USA.

6.4. Current Status of Approved Biosimilars in Different Geographic Regions

6.4.1. Biosimilars Approved in India

Biosimilars have become a significant part of the pharmaceutical market in India, driven by companies like Biocon and Dr Reddy's. The CDSCO ensures biosimilars meet stringent safety, efficacy, and quality standards, positioning India as a global leader. Out-of-patent biologics offer opportunities for biosimilar development. By using the original drug's formula, manufacturers can reduce costs and price biosimilars 30–70% lower, making treatments more accessible. India approved its first biosimilar in 2000 for hepatitis B [59,60]. A study identified 304 follow-on biologics, 78 of which were manufactured in India [61].

Table 1 provides a list of approved biosimilars in India. These are now widely available in India for conditions like cancer, chronic kidney disease, autoimmune disease, and diabetes. Despite challenges associated with regulatory mechanisms, some of these biosimilars

have received regulatory approval in the USA and Europe. These include Filgrastim and Bevacizumab, to name a few.

Table 1. Biosimilars approved in India.

Reference (Originator) Biologic	Biosimilar (India)	Active Drug	Indications	Therapeutic Class	References
Lantus	Basalog	Insulin glargine	Diabetes mellitus	Insulin analog	[62]
Neupogen	Accofil	Filgrastim	Neutropenia	Granulocyte colony-stimulating factor (G-CSF)	[63]
Epogen	Shanpoietin	Epoetin alfa	Anemia	Erythropoiesis-stimulating agent (ESA)	[61]
Humira	Exemptia	Adalimumab	Rheumatoid arthritis, Crohn's disease	TNF-alpha inhibitor	[64]
Erbitux	Cetuxa	Cetuximab	Colorectal carcinoma	EGFR inhibitor	[65]
Avastin	Bevacirel	Bevacizumab	Colorectal cancer	VEGF inhibitor	[66]
Herceptin	Hertraz	Trastuzumab	Breast cancer	HER2 inhibitor	[67]
Enbrel	Nepexto	Etanercept	Rheumatoid arthritis	TNF-alpha inhibitor	[68]
Rebif	Relibeta	Interferon beta-1a	Multiple sclerosis	Immunomodulator	[69]
Lucentis	Razumab	Ranibizumab	Wet macular degeneration	Anti-VEGF agent	[70]
Forteo	Teriparatide	Teriparatide	Osteoporosis	Parathyroid hormone analog	[71]
Victoza	Lirafit	Liraglutide	Type 2 diabetes mellitus	GLP-1 receptor agonist	[72]

6.4.2. Biosimilars Approved in the USA and Europe

The United States and Europe represent the two largest markets for biosimilars, each with a robust regulatory framework but markedly different post-approval landscapes.

In the US, the FDA oversees the approval of biosimilars under the 2009 Biologics Price Competition and Innovation Act (BPCIA). Extensive testing is required to demonstrate a high degree of similarity to a product to receive approval. Fifty-one biosimilars, including six interchangeable ones that can be used in place of a prescription drug without a doctor's approval, were approved as of April 2025 [73]. While approval is a major hurdle, the actual market uptake of biosimilars has been comparatively slow. This is not due to a lack of quality but rather to significant commercial and legal barriers. These include protracted patent litigation from innovator companies that delays market entry, the additional clinical and regulatory hurdles required to achieve interchangeability, and complex payer dynamics where rebate structures can disincentivize the adoption of lower-cost biosimilars.

In contrast, biosimilars can be sold in all EU nations due to Europe's centralized approval process, which is carried out through the EMA. Quality, safety, and efficacy are guaranteed by the EMA's stringent regulations. With 115 biosimilars approved by December 2024, Europe has maintained its position as a leader since the first approval in 2006. This success, however, has created a different kind of challenge: intense competition has driven severe price competition. This has pushed prices so low that it threatens the long-term commercial sustainability for manufacturers, risking future competition. Together, they uphold strong biosimilar approval processes that facilitate greater accessibility to biologic treatments that are safe, efficient, and reasonably priced, but the ultimate success

of biosimilars hinges on navigating distinct post-approval challenges, from market-access barriers in the USA to sustainability pressures in Europe [7]. Table 2 lists the biosimilars approved in the USA and Europe. Out of these, several biosimilars, including infliximab, etanercept, and adalimumab, have been approved in both the USA and Europe and are available in India. Notably, Cipla's etanercept biosimilar has been launched in India at a considerably lower price.

Table 2. Biosimilars approved in the USA and Europe.

Reference (Originator) Biologic	Biosimilar (US)	Biosimilar (EU)	Active Drug	Indications	Therapeutic Class	References
Genotropin	Omnitrope	Omnitrope	Somatropin	Growth hormone deficiency	Human growth hormone	[74]
Neupogen	Zarxio	Nivestym	Filgrastim	Neutropenia	Granulocyte colony-stimulating factor (G-CSF)	[75]
Enbrel	Erelzi	Benepali	Etanercept	Rheumatoid arthritis, psoriasis	TNF-alpha inhibitor	[76]
Humira	Amjevita	Idacio	Adalimumab	Rheumatoid arthritis, Crohn's disease	TNF-alpha inhibitor	[77]
Avastin	Mvasi	Mvasi	Bevacizumab	Colorectal cancer, lung cancer	VEGF inhibitor	[78]
Rituxan	Truxima	Riximyo	Rituximab	Non-Hodgkin's lymphoma, rheumatoid arthritis	Monoclonal antibody	[79]
Herceptin	Herzuma	Herzuma	Trastuzumab	Breast cancer, gastric cancer	HER2 inhibitor	[80]
Lantus	Semglee	Basaglar	Insulin glargine	Diabetes mellitus	Insulin analog	[81]
Lucentis	Cimerli	Byooviz	Ranibizumab	Wet macular degeneration	Anti-VEGF agent	[82]
Prolia	Jubbonti	Jubbonti	Denosumab	Osteoporosis, bone metastases	Monoclonal antibody	[83]
Xolair	Omlyclo	Omlyclo	Omalizumab	Allergic asthma, chronic urticaria	Monoclonal antibody	[84]
Remicade	Inflectra	Inflectra	Infliximab	Crohn's disease, rheumatoid arthritis	TNF-alpha inhibitor	[85]

7. Ethical and Economic Concerns for Biosimilars

Advances in technology have paved the path for the introduction of biosimilars, which are similar to the originator biologics. Although biosimilars offer significant cost savings by providing affordable alternatives to existing biopharmaceuticals and improve patient access, reducing healthcare costs, biosimilar adoption faces significant barriers that place physicians in ethical dilemmas.

Clear government policies are essential to ensure patients benefit from biosimilars. These policies must guide every stage, from setting regulatory standards for approval, interchangeability, and switching to managing supply chain issues like manufacturing and traceability. Furthermore, strong policies are needed for post-market activities, including pharmacoeconomic evaluations, physician education, and long-term pharmacovigilance.

Currently, formularies have become one of the biggest barriers to realizing the cost-saving potential of biosimilars. Biosimilars currently require a complex evaluation process by insurance providers that differs from traditional generics due to their complexity as large-molecule drugs. Pharmaceutical companies also use tactics like rebate traps and discount strategies with insurers and pharmacy benefit managers to maintain dominance of original biologics. Many insurance providers require patients to try the more expensive

original drug first or financially incentivize its use. Physicians are often mandated to prescribe the original biologic first due to better reimbursement margins, even if biosimilars would be more cost-effective. This may create conflict between financial incentives and the goal of delivering affordable treatment [86].

Commercial and policy-related barriers also continue to limit the full realization of biosimilar benefits. In the USA, market access is constrained by payer dynamics and patent strategies, while in Europe, aggressive price erosion threatens long-term market sustainability. In India and other emerging markets, challenges include physician education, pharmacovigilance infrastructure, and balancing domestic affordability with global regulatory expectations. These issues underscore the ethical concerns faced by healthcare providers, who must navigate financial incentives, reimbursement policies, and patient welfare when prescribing biosimilars. Equally important is the need for coherent and inclusive health policies that promote biosimilar adoption through fair reimbursement, insurance coverage, and transparent interchangeability guidelines. Ultimately, the long-term success of biosimilars will depend not only on scientific and technological progress but also on policy reforms that address ethical and economic concerns, ensuring that biosimilars translate into meaningful improvements in patient access and healthcare affordability.

8. Challenges

The transition from a selected cell line to a validated commercial product involves overcoming several key production challenges, like scale-up. A significant technical hurdle is controlling complex details like glycosylation, which must precisely match the originator's efficacy. Proteins are only stable in a limited range of concentrations, temperatures, ionic strengths, and acidity conditions and are very prone to physical and chemical destabilizations. Many recombinant proteins also become unstable and lose their correct folding. Structural instability caused by unfolding, misfolding, or covalent/non-covalent modifications, as well as aggregation, can degrade drug efficacy and greatly overshadow the low cost and speedy regulatory approvals of biosimilars, making it a formidable challenge for manufacturing these products. The entire manufacturing process then must be successfully scaled up from a small lab batch to large-scale commercial production without changing the final product's quality. This difficulty with glycosylation extends beyond the manufacturing process, as it also creates a major regulatory bottleneck. Because these sugar patterns can affect how the body's immune system reacts to the drug, regulators require extensive data to prove similarity. Any small difference can lead to questions, slow down the approval process, and increase costs, which impacts the final affordability of the biosimilar.

Apart from production-based challenges, the growth of the domestic market is tempered by significant adoption hurdles. Overcoming physician hesitancy and building patient trust remain crucial, as confidence is often impacted by a lack of long-term, real-world data for newer products and the challenge of differentiating among multiple biosimilars for the same biologic. Simultaneously, the market is characterized by intense pricing pressures driven by a crowded field of local manufacturers, a dynamic that can squeeze profit margins and affect long-term sustainability. Although Indian biosimilars are entering global markets, their path is complicated by the complexity and high cost of meeting the stringent regulatory standards of regions like the USA and EU. This requires extensive and costly analytical and clinical data packages that go far beyond domestic requirements, representing a substantial barrier to entry for firms seeking to help reduce healthcare costs worldwide [8,59]. In addition to this, patents and patent litigation have a significant role to play in determining biosimilar competition and its entry into the market. Therefore,

working in tandem with international partners, keeping in view international regulations, will go a long way in establishing a steady supply of these lifesaving therapeutics.

9. Discussion

From a scientific perspective, biosimilar development is a complex and resource-intensive industry. Establishing comparability with the reference biologic requires extensive analytical characterization, robust cell line development, and tightly controlled upstream and downstream processes. Scale-up and process optimization pose significant risks to product quality, necessitating rigorous validation and consistent cGMP-compliant manufacturing. The substantial documentation burden, including head-to-head clinical and analytical comparability studies, is essential for building trust among regulators, clinicians, and patients, but it also contributes to high development costs and long timelines. The presence of multiple biosimilars derived from the same originator across different regions underscores the importance of understanding both the manufacturing variability of biologics and the regulatory interpretation of biosimilarity to improve patient access worldwide.

Regulatory decision-making for biosimilars differs significantly across regions, as shown in Figure 5a–c. While the EMA emphasizes extensive analytical comparability with limited clinical data, the FDA introduces an additional interchangeability designation, and Indian regulators often mandate local clinical trials. These regional regulatory expectations influence biosimilar development strategies, including selection of manufacturing processes and comparability endpoints, ultimately contributing to region-specific biosimilar approvals for the same originator biologic.

It is evident that the global biosimilars' market predictions for the next decade reflect increasing demand in the healthcare sector. With the market projected to grow from USD 37.73 billion in 2025 to USD 116.90 billion by 2034, biosimilars are becoming central to long-term healthcare sustainability. Europe's leadership is supported by strong regulatory frameworks, contrasting with the U.S. market, where exceptionally high growth rates are tempered by post-approval challenges such as patent litigation and delayed physician adoption. These regional differences highlight that regulatory approval alone is insufficient to guarantee market penetration or equitable patient access. The Asia Pacific region is poised towards incremental growth as per market forecasts and predictions. India's expanding bioindustry illustrates a distinct growth pathway driven by cost-efficient manufacturing, global collaborations, and supportive government initiatives such as the National Biopharma Mission. While India is emerging as a major hub for biosimilar development and production, it continues to face challenges related to physician confidence, regulatory harmonization, and meeting stringent international quality expectations for export markets.

Taken together, harmonizing regulatory standards, advancing manufacturing technologies, and strengthening physician confidence and policy support worldwide are essential to realize the full clinical and economic potential of biosimilars.

10. Conclusions

In conclusion, biosimilars represent a transformative pathway toward improving the accessibility and affordability of advanced biologic therapies worldwide. Scientific advancements, standardized manufacturing protocols, and rigorous quality controls can ensure the production of high-quality biosimilars without compromising safety or efficacy. Strict adherence to cGMP and consistent vial-to-vial quality further ensure reliability. Streamlined regulatory frameworks and global harmonization can accelerate approvals and promote market competition. Increased competition among manufacturers directly drives down prices and improves patient access. In resource-limited settings, biosimilars help bridge the gap between innovation and affordability. Wider adoption also supports

sustainable healthcare spending by reducing the economic burden of chronic diseases. Continued investment in technology and capacity building is essential to maintain supply reliability. Collectively, these efforts position biosimilars as a cornerstone of affordable and equitable global healthcare.

Author Contributions: Conceptualization, S.B.; writing—original draft preparation, A.R., K.D., and V.M.; writing—review and editing, A.R., K.D., and V.M.; supervision, S.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Some data will be shared on request.

Acknowledgments: We acknowledge Amity Institute of Biotechnology for providing us with the infrastructure required.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

mAbs—Monoclonal Antibodies; CQA—Critical Quality Attributes; CHO—Chinese Hamster Ovary; Dissolved Oxygen (DO); COGs—Cost of Goods; DoE—Design of Experiments; QTPP—Quality Target Product Profile; QbD—Quality by Design; FDA—Food and Drug Administration; EMA—European Medicines Agency.

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