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Review Article

Biologics And Biosimilars

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ABSTRACT

Biologics and biosimilars represent a transformative advancement in modern therapeutics, offering targeted and highly effective treatment options for complex diseases such as cancer, autoimmune disorders, and metabolic conditions. Derived from living systems, biologics are structurally complex, which makes their development and regulation more challenging compared to conventional drugs. Biosimilars, designed to be highly similar to approved biologics, provide cost-effective alternatives while maintaining comparable safety and efficacy. This review highlights the scientific principles underlying their development, including molecular characterization and immunogenicity assessment, along with evolving regulatory pathways that ensure quality, safety, and interchangeability. It also explores their expanding clinical applications across diverse therapeutic areas. Overall, biologics and biosimilars hold significant potential to improve global healthcare accessibility. Future perspectives focus on advancing analytical technologies, streamlining regulatory processes, and enhancing clinician and patient confidence to promote wider adoption and sustainable healthcare solutions.

INTRODUCTION

Unlike conventional medicines that are chemically synthesized in a laboratory, biopharmaceuticals are produced using living cells and that single distinction changes almost everything about how they are made, copied, and regulated. When companies attempt to develop biosimilar versions of these complex therapies, they quickly encounter a fundamental reality: you cannot make a perfect replica of a molecule produced by a biological

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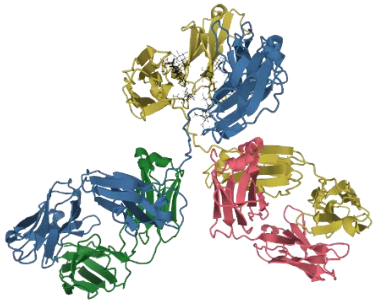
system. What you can do is demonstrate, through rigorous side-by-side testing, that your version behaves in essentially the same way. Regulators have built a framework around this reality — one that demands thorough quality comparisons but reduces the clinical evidence bar once similarity has been convincingly shown. Still, the biological complexity of these molecules and the relatively short track record of biosimilars in clinical practice mean regulators remain cautious about declaring them fully interchangeable with the original products, a position that carries real implications for how doctors prescribe and how pharmacists dispense them. [1] When patents on blockbuster biologics eventually expire, the door opens for biosimilar competitors — and the effects on healthcare markets can be substantial. Competition drives prices down, and the savings have accumulated to billions of dollars globally. More importantly for patients, therapies that were once unaffordable have become accessible to a far wider population. Nowhere is this more vividly illustrated than in Eastern Europe. In countries like Bulgaria, the Czech Republic, and Romania, access to epoetin treatments had long been out of reach for most patients who needed them. The arrival of biosimilar alternatives cut prices nearly in half and drove utilization up by more than 250% a remarkable demonstration of what happens when economic barriers to biological therapies are removed. [2] This review sets out to unpack all of this in depth. It examines what makes biologics so fundamentally different from ordinary generic drugs, and why those differences matter so much in practice. It walks through the regulatory pathways that govern biosimilar approvals around the world, the manufacturing challenges that make biological production so demanding, and the clinical questions around safety, effectiveness, immune responses, and substitutability that remain actively debated. The economic landscape, including how biosimilar adoption is reshaping global healthcare spending, receives close attention as well. Throughout, the aim is to give readers a clear-eyed view of where the field stands today, what obstacles remain, and what a more accessible and scientifically mature biosimilar landscape might look like in the years ahead. [3]

Table 1. The Differences Between Small-Molecule Medicines & Biological Medicines

	Small- molecule medicines (chemical-based)	Biological medicines (protein-based)
Example	 Acetylsalicylic acid (anti-inflammatory & pain Relief)	 Monoclonal antibody (Treats cancer & autoimmune diseases)
Molecular Weight	180 daltons	-144000 daltons
Size	Small	Large
Structure	Simple and well defined.	Complex
Manufacturing	Predictable chemical process; Identical copies can be made.	Each Manufactured In a unique living cell line; similar-but-not-identical copies can be made.
Characterisation	Easy to fully characterise	Difficult to fully characterise

Stability	Usually Stable	More sensitive than small molecule medicines to handling
Immunogenicity	Usually Unexpected	Higher Potential; always need to be tested during development

Overview of biologics

Definition and characteristics

Biopharmaceuticals, also known as biological medicines, are a specialized class of therapies derived from living systems or produced using recombinant DNA and gene expression technologies. Unlike conventional small-molecule drugs, they are composed of large and complex macromolecules such as proteins, glycoproteins, and nucleic acids, which contribute to their high specificity and therapeutic effectiveness. Their production is highly complex and influenced by multiple factors, including the choice of expression system, cell culture conditions, purification processes, and storage methods. Additionally, post-translational modifications like glycosylation and phosphorylation introduce natural variability that can affect their biological activity. Biopharmaceuticals are also more sensitive to environmental conditions, making them prone to instability such as degradation or aggregation. In contrast, small-molecule drugs are simpler, chemically synthesized, and more stable, with predictable properties and easier manufacturing. Due to these differences, biopharmaceuticals require more stringent development, characterization, and regulatory approaches. [4, 5]

Types of biologics:-

Unlike conventional drugs which are chemically synthesized and yield well-defined, predictable molecules biologics are produced from or within living biological systems, making them far more structurally complex. They broadly fall into three functional categories: monoclonal antibodies, receptor modulators, and enzyme-replacement or enzyme-modulating agents. Manufacturing them is a technically demanding process that typically involves gene isolation, recombinant DNA engineering, and advanced protein purification, carried out using platforms ranging from mammalian cell lines to microbial and plant-based systems. Because of their size and structural sensitivity, biologics also require carefully designed formulations containing stabilizers and preservatives components that can meaningfully influence the drug's pharmacokinetics, pharmacodynamics, and overall biological activity. [6, 7] Biologics span several major therapeutic categories, each with a distinct mechanism of action:

Monoclonal antibodies are laboratory-engineered proteins designed to bind with high precision to specific targets — such as cancer cell antigens or infectious pathogens triggering their destruction or modulating immune responses. Well-known examples include rituximab and adalimumab.

Recombinant proteins are produced via recombinant DNA technology to replace proteins the body is missing or unable to produce correctly. Recombinant insulin and various growth factors are among the most widely used examples.

Vaccines prepare the immune system to recognize and fight specific pathogens, conferring lasting protection through immunological memory.

Cell-based therapies involve introducing living cells particularly stem cells into patients to repair or regenerate damaged tissues, representing one of the most rapidly advancing areas of regenerative medicine.

Gene therapies work at the genetic level, correcting, replacing, or modifying defective DNA or RNA sequences to address the root cause of disease rather than just its symptoms. Together, these agents primarily work by targeting components of the immune system or restoring proteins that are absent or dysfunctional in patients.

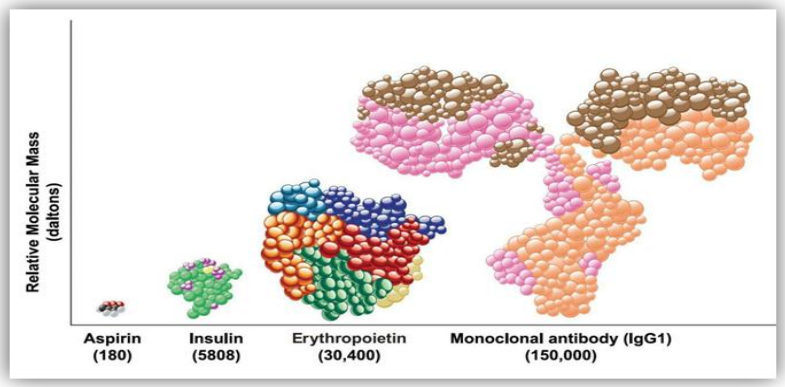


Figure 1. Types of Biologics

Because biopharmaceuticals come from living biological systems, the risk of triggering an immune response is an ever-present concern in clinical practice. These reactions can cause two distinct problems: they may provoke allergic or hypersensitivity reactions in some patients, and they can interfere with how the drug works sometimes to a serious degree. When the immune system mounts a response against the biologic itself, or against components of its formulation, the drug's effectiveness can gradually erode, leading to reduced efficacy or, in some cases, complete treatment failure. A particularly worrying though relatively rare scenario arises when the antibodies generated against the biologic cross-react with the body's own naturally occurring proteins. This phenomenon, sometimes described as molecular mimicry, can produce serious clinical consequences. A well-documented example is pure red cell aplasia, a severe blood disorder seen in some patients receiving epoetin therapy. In these cases, neutralizing antibodies raised against the recombinant protein also attack the patient's endogenous erythropoietin, effectively shutting down red blood cell production. Though uncommon, this illustrates just how consequential immunogenic responses to biologics can be when they extend beyond the drug itself. [8]

Manufacturing of Biologics

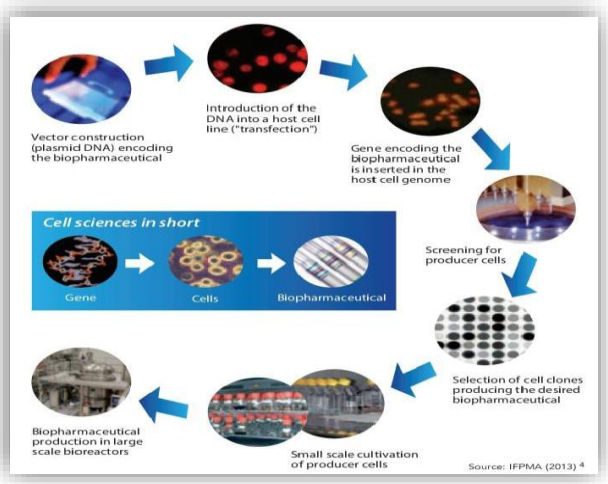


Figure 2. The process of producing biologics today

Cell line Development

Building a stable, high-yielding cell line is one of the most technically demanding steps in biopharmaceutical manufacturing — and one of the most important. The process begins with genetic engineering: the gene responsible for producing the target therapeutic protein is inserted into mammalian host cells in a way that ensures it is expressed reliably and consistently over time. From there, large numbers of candidate cell clones are screened and compared to identify those that produce the protein at the highest levels with the greatest stability. The most promising clones are then thoroughly characterized to confirm their genetic integrity, expression consistency, and biological function. Finally, the validated cell lines are preserved through a structured banking system comprising both master and working cell banks ensuring they remain available for future production runs and that manufacturing remains reproducible batch after batch.

Table 2. Key stages in monoclonal antibody cell line development include:-

Stage	Description
1. Selection of host cell line	Choosing an appropriate cell line that is amenable to genetic manipulation and capable of high-yield protein production.
2. Transfection	This initial step involves integrating the gene of interest into the host genome. Transfection can be achieved through physical methods like electroporation or chemical methods such as lipofection or methods using calcium phosphate
3. Stable pool generation	Post-transfection, cells incorporating the gene of interest are selected using selection markers and antibiotic markers. Common systems used include methotrexate (MTX) or the glutamine synthetase (GS) system.
4. Single-cell cloning	Ensuring the monoclonality of cell lines is crucial. This step involves isolating single cells to establish monoclonal cell lines, which guarantee consistent production of the target protein. Regulatory authorities require stringent standards of monoclonality. Advanced equipment like the Beacon from Berkeley Lights utilizes microfluidics and Opti Electro Positioning (OEP) technology to move cells in and out of nanopens, significantly reducing development timelines compared to traditional methods like limiting dilution.

5. Screening and isolation	This step involves assessing a large number of clones for yield, quality, and manufacturability. High-throughput equipment like the ambr250 system is typically used to screen multiple clones efficiently.
6. Cell line stability studies	The stability of established cell lines is evaluated to ensure that clones can maintain consistent titer and quality of the product over multiple generations.
7. Master cell banking and characterization	Master cell banks of the lead clones are created to ensure an adequate source of cells for future large-scale production. These banks are comprehensively characterized to meet regulatory requirements.

Cell line development is the backbone of biologics manufacturing, directly determining the efficiency and scalability of monoclonal antibody and recombinant protein production. Each stage host cell selection, genetic modification, clone screening, and cell banking is critical to achieving stable, high-yield protein expression. Chinese Hamster Ovary (CHO) cells have become the undisputed industry standard, thanks to continuous engineering advances that have delivered higher production titres, better genomic stability, and smoother regulatory pathways. Their versatility makes them the go-to platform for producing complex biologics, particularly monoclonal antibodies. Next-generation CHO-K1 systems are pushing boundaries further still. Technologies like transposase-mediated gene integration enable more precise, stable transgene insertion translating into more consistent expression, greater scalability, and stronger overall manufacturing performance. These advances are steadily reshaping expectations across the biologics industry. [9]

Upstream / downstream processing

Upstream processing is the first major phase of biologics manufacturing, covering everything that happens before purification begins cell line banking, culture media preparation, and the controlled cultivation of cells in bioreactors, culminating in harvest. The goal is straightforward: establish a stable, reproducible bioprocess that generates the target protein in sufficient quantities while meeting the quality standards required for regulatory approval and clinical use. The process typically starts from a single frozen vial of the engineered production cell line. This seed stock is gradually expanded through successive culture stages, with critical parameters temperature, pH, dissolved oxygen, and nutrient levels carefully monitored and adjusted throughout. Once the cells reach the required density and viability, they are transferred into progressively larger bioreactors for full-scale production. Scientists continually refine feeding strategies to maximize protein yield while keeping cells healthy enough to sustain productivity across the entire production run. Striking the right balance matters: while rapid cell growth is desirable early on, overly dense cultures can exhaust nutrients and accumulate toxic waste products, undermining productivity. Downstream processing picks up where upstream leaves off its purpose is to isolate and purify the target biologic from the complex mixture of cells, proteins, and impurities produced during cultivation. Using a sequence of techniques including depth filtration, tangential flow filtration, and multi-step chromatography, this phase systematically removes host cell proteins, residual nucleic acids, and other contaminants. The end result is a highly purified, appropriately concentrated product ready for therapeutic use, further formulation, or analytical testing much like how a chemist purifies

a reaction mixture to obtain a compound of defined quality and composition. [10, 11]

Figure 3. Upstream and downstream processing

Quality Attributes and Variability

Biosimilar development hinges on one core requirement: proving the candidate is highly similar to the reference product in both structure and function. Even minor manufacturing deviations can alter the product's properties, making rigorous process optimization non-negotiable from the outset. Development begins with transfecting a host cell line often different from the originators with a DNA vector encoding the target molecule. However, replicating the amino acid sequence alone is insufficient. Higher-order structures and post-translational modifications (PTMs) that govern biological activity are heavily shaped by the cellular environment and process conditions, meaning sequence accuracy does not guarantee functional equivalence. Quality-by-Design (QbD) has become the standard framework for navigating this complexity, requiring developers to understand how variations in process parameters, raw materials, and equipment influence critical quality attributes and to use that knowledge to engineer similarity systematically. Full structural characterization spanning primary through higher-order architecture, PTM profiles, and biological activity is mandatory, with the reference product serving as the constant benchmark. Monoclonal antibody biosimilars with antibody-dependent cellular cytotoxicity (ADCC) activity illustrate this challenge well: the glycan structures on the antibody's Fc region critically influence function and must be precisely controlled alongside multiple other interdependent quality attributes. Culture conditions, purification processes, and formulation strategies are all carefully optimized to ensure the biosimilar consistently matches the reference product across all clinically relevant attributes and remains stable throughout its intended shelf life. [12]

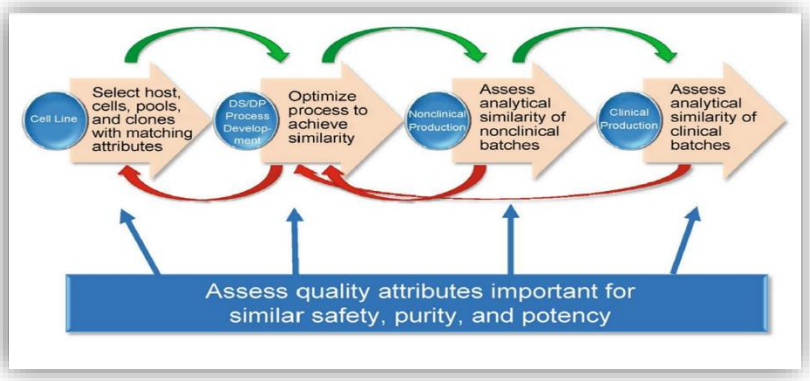


Figure 4. Iterative steps in the process development and analytical similarity assessment for a proposed biosimilar product. DP drug product, DS drug substance.

Biosimilar: - Concept and Development

A biosimilar is a biological medicine designed to be highly similar to an already approved biologic, known as the reference product. Like the original, it is produced using complex living systems and shares the same type of large, structurally intricate molecules that characterize biopharmaceuticals. A key feature of biologics and biosimilars is that the manufacturing process directly influences the final product. Since each biologic is made through a unique process, creating an exact copy is not possible. As a result, biosimilars are not identical but are developed to be very close in structure and function, with only minor acceptable differences arising from variations in production methods. Regulatory pathways ensure that biosimilars match their reference products in terms of quality, safety, and effectiveness. However, small differences may occasionally lead to slight variations in side effects, which is why continuous monitoring through pharmacovigilance is essential even after approval. [13]

Define vs. Principles of biosimilarity

The combined effects of global population ageing and societal modernization have precipitated a marked epidemiological shift, with non-communicable diseases encompassing malignancies, diabetes mellitus, chronic kidney disease, and chronic inflammatory disorders now representing the leading causes of mortality worldwide. This transition carries significant implications for long-term patient management, particularly given the progressive and interconnected nature of these conditions. Patients with advanced type 2 diabetes frequently require insulin analogues spanning a broad range of formulation profiles long-acting, short-acting, ultra-short-acting, and ultra-long-acting — tailored to individual glycaemic control needs. Disease progression may further necessitate erythropoiesis-stimulating agents such as erythropoietin to address renal failure-associated anaemia. Given the well-established links between diabetes and oncological disease, affected patients may additionally require biologics or biosimilars for cancer management or drug-induced neutropenia. Notably, the relationship is bidirectional — anticancer interventions such as hormone-based therapies or surgical pancreatectomy may themselves precipitate diabetes, resulting in therapeutically complex clinical scenarios requiring coordinated multidisciplinary management. [14, 42]

Higher Similar, not identical

Unlike small-molecule generics — which are chemically identical to their branded counterparts biosimilars are comparable but not structurally identical to their reference biologics. This distinction stems directly from the molecular complexity of biological products and the process-dependent nature of their manufacture. Both the EMA and FDA have established rigorous approval frameworks to address this. The EMA requires biosimilars to demonstrate high comparability to the reference product across molecular structure, biological activity, safety, efficacy, and immunogenicity. The FDA, under the Biologics Price Competition and Innovation Act (BPCIA), requires that biosimilars show no clinically meaningful differences in safety, purity, and potency. In both frameworks, minor physicochemical differences are acceptable but only when robust evidence confirms they have no impact on clinical performance. [15]

Stepwise Development Approach

The scientific foundation of biosimilar development rests on the principle of comparability originally developed to manage manufacturing changes in approved biologics, and later adapted as the conceptual backbone of biosimilarity assessment. In practice, developers follow a structured, stepwise approach built around the totality-of-evidence paradigm. The process begins with exhaustive analytical characterization, where the biosimilar's structural, functional, and quality attributes are rigorously compared against the reference product using state-of-the-art methods. From there, a targeted programme of non-clinical and clinical studies is conducted to confirm that any differences identified at the analytical level do not translate into clinically meaningful distinctions in safety, efficacy, or immunogenicity. [16]

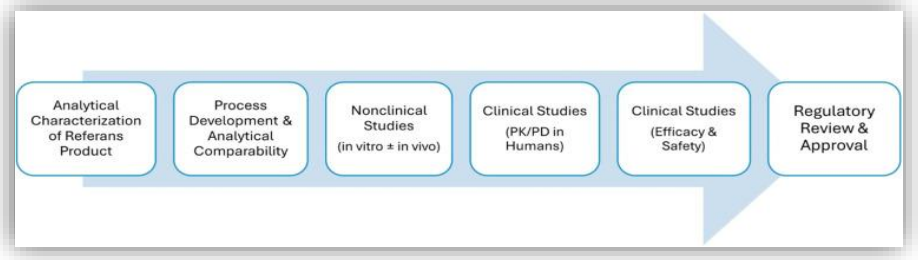


Figure 5. Stepwise development pathway for biosimilars

Analytical Characterization

Advances in analytical science now allow detailed characterization of not only the active biologic but also its excipients and impurities. When combined with existing knowledge of the reference product, this makes thorough characterization the foundation of biosimilar development. A central step is the physicochemical comparison between the biosimilar and the reference product, ensuring that all attributes remain within statistically defined limits based on variability observed across multiple reference batches. These studies also provide insight into the manufacturing process, expression system, and product stability. [17,18] Comprehensive analytical evaluation supports comparison of structural and functional features such as biological activity, target binding, immunochemical properties, impurity profiles, and overall product stability. Regulatory bodies like the FDA stress that, along with identifying critical quality attributes, the sensitivity and limitations of analytical methods and statistical tools must be carefully considered. To strengthen

reliability, the FDA recommends using orthogonal methods—multiple techniques based on different principles and including samples from U.S. and European reference batches, pharmacopoeia standards, and test batches. [18, 19] Filgrastim, a non-pegylated recombinant G-CSF marketed as Neupogen by Amgen, is widely used to manage chemotherapy-induced neutropenia by reducing infection risk and supporting neutrophil recovery. Its biosimilar, Zarxio by Sandoz, was approved via the 351(k) pathway based on comparative studies involving several batches from both the biosimilar and reference products across different regions. [20,21]

Table3. The most important CQAs selected for Zarxio

Criticality and attributes	Clinical Relevance	Analytical tests
Very High		
Primary amino acid structure	Efficacy, safety, and immunogenicity	Peptide mapping and tandem mass spectroscopy
Potency	Efficacy and safety	Bioassay
Target binding	Efficacy and safety	Surface plasmon resonance
High		
High order structure	Efficacy and Immunogenicity	Circular dichroism spectroscopy
High molecular weight aggregates	Immunogenicity	Size-exclusion Chromatography
Oxidised variants	Efficacy	Reverse phase chromatography
Sub visible particles	Immunogenicity	Light obstruction

Non-Clinical Studies

Preclinical disease models provide valuable dose-response insights when both the biosimilar and reference product show cross-reactivity in a relevant animal species. Evaluating doses within the steep region of the dose-response curve maximizes sensitivity for detecting meaningful differences in biological activity. This is especially relevant in oncology biosimilar development, where the lack of well-defined PD biomarkers makes equivalence assessment difficult. Humanized tumor-bearing models allow direct head-to-head dose comparisons and can support extrapolation of biosimilarity across untested indications. Preclinical programs should cover comparative PK/PD, toxicology, and immunogenicity profiling but only where a pharmacologically relevant species is available. As analytical and in vitro evidence accumulates, the need for animal testing diminishes, and minimizing animal use in line with the 3Rs framework should be actively pursued. A targeted repeat-dose toxicology study potentially restricted to a single high dose and one sex is often sufficient to confirm comparable toxicity profiles. Cell-based bioactivity assays are an increasingly preferred alternative to animal studies, offering strong mechanistic sensitivity and potentially reducing the broader evidence burden when adequately validated. Animal immunogenicity data, where included, should be interpreted cautiously useful for detecting qualitative differences in immunogenic potential, but not a reliable predictor of human outcomes. [21, 22]

Clinical Studies

The primary goal of a biosimilar's clinical development programme is to conclusively demonstrate no clinically meaningful differences in safety, efficacy, and immunogenicity compared to the reference product. The scope of required clinical evidence is not fixed it is calibrated

proportionally to the similarity already established through preceding analytical and preclinical work, reflecting a risk-based, stepwise approach. For monoclonal antibodies and other complex biologics such as fusion proteins, comparative clinical trials are likely to remain mandatory. The frequent absence of well-validated PD biomarkers means clinical efficacy studies cannot easily be replaced by surrogate measures, and are needed both to confirm therapeutic equivalence and to adequately characterize safety risks. [23, 24] Clinical development typically begins with a rigorously designed pharmacokinetic (PK) similarity study, with comparative human PK and/or PD assessments forming the essential foundation of the biosimilarity evidence package.[25, 26]

Extrapolation of Indications

Achieving these goals requires a coordinated multidisciplinary effort, supported by strong institutional frameworks that promote treatment adherence, continuous monitoring, and post-marketing surveillance. As more biologics lose patent protection, biosimilar availability is set to expand extending access to broader patient populations, including those in low- and middle-income countries where non-communicable diseases are rising rapidly. To fully realize this potential, nations must build robust regulatory infrastructures covering the entire biologic lifecycle from manufacturing standards and supply chain integrity to substitution policies, expanded indications, and post-approval safety monitoring. [27] At the clinical level, a significant knowledge gap persists among practicing physicians regarding the breadth and versatility of biologic therapies. Clinicians must proactively engage with evolving treatment paradigms, understand cross-indication biologic use, carefully weigh risks against benefits, and rigorously evaluate patient outcomes. Beyond direct patient care, physicians also have a responsibility to advocate engaging health authorities, insurers, and manufacturers to champion equitable access to safe, effective, and high-quality therapies, with biologics playing a central role in that effort.[28]

Global Regulatory Guidelines

World Health Organization (WHO)

As biosimilars referred to by WHO as Similar Biotherapeutic Products (SBPs) began entering development pipelines and gaining approval worldwide, WHO recognized the need for a standardized regulatory framework. This led to the adoption of the "Guidelines on Evaluation of Similar Biotherapeutic Products" at the 60th WHO Expert Committee on Biological Standardization meeting in 2009. The guidelines establish universal principles for licensing SBPs that are comparable to already-approved reference products, focusing primarily on well-characterized recombinant DNA-derived therapeutic proteins with established quality, safety, and efficacy profiles. [29]

United States (FDA)

In the US, the approval pathway for biosimilars depends on the legislation under which the original biologic was authorized either the Food, Drug, and Cosmetic Act (FD&C Act) or the Public Health Service Act (PHS Act). [30] The landmark Biologics Price Competition and Innovation (BPCI) Act, passed in March 2010, amended the PHS Act to create an abbreviated approval pathway for biologics that are highly similar to or interchangeable with an FDA-approved reference product, codified under Section 351(k). Early-generation biologics originally approved under the FD&C Act such as insulin and somatropin may

instead seek biosimilar approval via a Section 505(b)(2) New Drug Application. [31, 32]

Interchangeability and Substitution

Interchangeability refers to replacing one biologic with another expected to deliver equivalent clinical outcomes. The EU takes a straightforward position EMA approval inherently confers interchangeability, allowing biosimilars to replace their originator or another biosimilar with the same reference product. Switching (physician-directed) and substitution (pharmacy-level, without prescriber involvement) are both recognized practices, regulated at the individual member state level. [33,34] The US takes a stricter approach, requiring multiple switch studies before granting a formal interchangeability designation that permits pharmacy-level substitution though prescribers can always override this by specifying the product by name. [35, 36]

Clinical implications

A biosimilar's clinical programme is fundamentally comparative — designed to confirm equivalence rather than independently establish safety and efficacy from scratch. Its scope is directly shaped by the strength of preclinical comparability data; robust analytical and functional evidence can substantially reduce the clinical burden. The FDA acknowledges that formal efficacy trials may be unnecessary when preclinical data have adequately resolved outstanding uncertainties. However, human safety and immunogenicity studies cannot be bypassed these endpoints are inherently unpredictable from preclinical data alone and require adequately powered studies with sufficient follow-up and sensitive assays. [37]

Country-specific differences

The multiple-switch PK studies currently required for US interchangeability designation appear scientifically redundant in light of existing evidence, and a reassessment of this separate designation is warranted. More broadly, misconceptions about biosimilar safety, efficacy, and substitutability remain a significant barrier to clinical uptake — regardless of interchangeability status. [37]

Quality, Safety, and Immunogenicity

The evaluation of biosimilar efficacy and safety has been conducted through rigorously designed randomized, double-blind clinical trials, with therapeutic indications selected on the basis of their capacity to yield a reliable and quantifiable estimate of treatment effect informed by prior clinical experience with the originator product. To ensure the most meaningful and discriminating comparison, the primary efficacy endpoints chosen for these trials were those considered most sensitive to detecting any potential differences between the biosimilar and its reference product. Across all biosimilar monoclonal antibodies (mAbs) and etanercept-based products evaluated, the predefined equivalence criteria for efficacy were successfully met, providing robust evidence in support of their comparability to the respective originators. [38] Comparative immunogenicity studies constitute a mandatory component of the biosimilar development program. In accordance with regulatory requirements, such studies have been systematically conducted and subsequently documented within the European Public Assessment Reports (EPARs) for all relevant biosimilar products, ensuring transparency and scientific rigor throughout the approval process. [39,40]

Analytical Comparability

Comparability assessment is widely accepted as a reliable and sensitive scientific approach for evaluating changes in biologic products, whether due to manufacturing modifications or the development of biosimilars by different manufacturers. Its evolution has been supported by clearer regulatory guidelines, risk-based evaluation strategies, advances in analytical technologies, and improved understanding of post-translational modifications. [41] The main goal of comparability assessment is to confirm that two biologic versions show no meaningful differences in safety or efficacy. It is essential when manufacturing processes change or when biosimilars are developed, ensuring consistent clinical performance. [42, 43]

Immunogenicity Causes

Immunogenicity testing is a crucial part of biosimilar development, as increased anti-drug antibody (ADA) responses compared to the reference product may indicate underlying quality differences. The immune response to therapeutic proteins is influenced by multiple factors, including structural variations, impurities, formulation, administration route, and patient-related characteristics. However, in biosimilars, patient population and route of administration remain the same as the reference product, narrowing the focus to product-related factors such as molecular structure, impurity levels, and formulation. Key contributors to immunogenicity include differences in glycosylation patterns, oxidative changes, and protein aggregation, all of which can alter how the immune system recognizes the drug. [44]

Clinical Consequences

Immunogenicity can lead to varied clinical outcomes, ranging from mild to severe. For example, infliximab has been associated with infusion reactions and delayed adverse effects due to ADA formation. A more serious case involved recombinant erythropoietin, which caused pure red cell aplasia, a life-threatening condition. In contrast, some biologics like rituximab show minimal clinical impact despite detectable ADA levels. These differences highlight the product-specific nature of immunogenicity. Therefore, strict regulatory guidelines require thorough immunogenicity evaluation to ensure the safety and efficacy of biosimilars. [45]

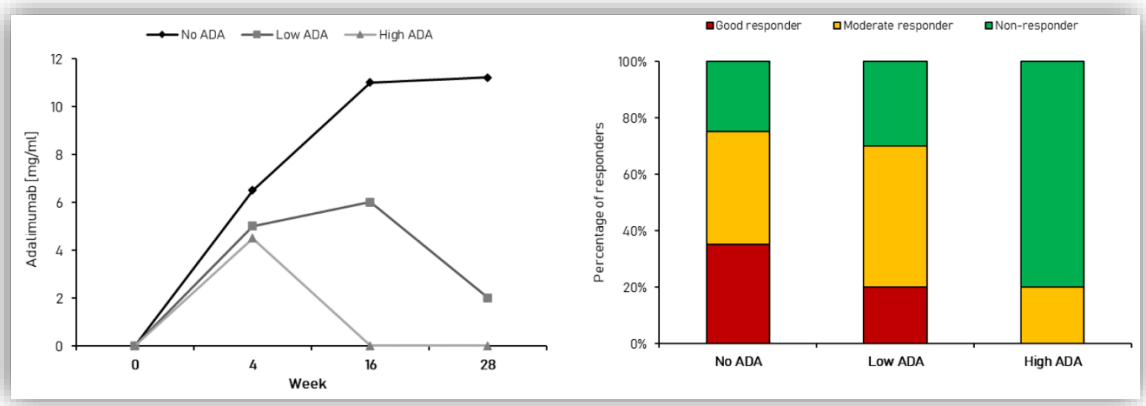


Figure 6. Immunogenicity

Mitigation Strategies

Literature identifies several practical strategies to support successful biosimilar switching, focusing

on effective communication, education, and organized clinical practices. These include clear and positive communication, empathetic interaction, shared decision-making, and patient reassurance techniques. [46] A key challenge in biosimilar adoption is the nocebo effect, where negative expectations about biosimilars can lead to perceived reduced efficacy, increased reporting of side effects, or treatment discontinuation—despite no actual difference from the original biologic. These responses are driven mainly by lack of awareness and confidence. [47] To address this, a coordinated approach combining communication, education, and patient involvement is essential. Such strategies help minimize the nocebo effect, ensure smoother transitions, and promote wider acceptance of biosimilars in clinical practice. [48]

Pharmacovigilance

Biologics and biosimilars are complex products derived from living systems, making them more prone to risks such as immunogenicity and batch variability. These risks may not be fully detected during clinical trials due to limited patient exposure, highlighting the need for strong pharmacovigilance systems. Post-marketing surveillance plays a vital role in monitoring long-term safety and identifying rare or unexpected adverse events in real-world settings. [49 ,50] Pharmacovigilance involves not only reporting adverse drug reactions (ADRs) but also tracking drug interactions, medication errors, and therapeutic failures. Regulatory bodies like the EMA, FDA, and India's PvPI have established guidelines to ensure effective safety monitoring. Marketing authorization holders must maintain robust systems for ADR collection, ensure timely reporting, and collaborate with partners through safety agreements. Accurate documentation, including brand name and batch number, is essential to detect product-specific safety issues. [51,52]

Post-Marketing Surveillance and Traceability

Effective safety monitoring is often challenged by incomplete recording of product details, especially batch numbers, which limits traceability. Studies show that while brand names are often reported, batch numbers are frequently missing. Improving data recording systems in clinical settings is therefore critical to enhance traceability, ensure patient safety, and strengthen pharmacovigilance practices. [53, 54]

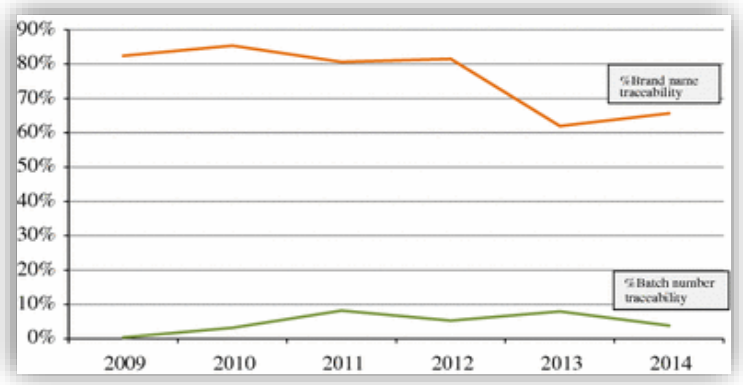


Figure 7. Brand name and batch number reporting over time

Clinical Applications of Biosimilars

Biologics are advanced therapeutic proteins produced using living cells, designed to either mimic natural biological functions or block

disease-causing pathways. Their high specificity and complex structure enable targeted treatment across multiple medical fields, including cancer, autoimmune disorders, and hormonal diseases. Biosimilars extend these benefits by providing more affordable alternatives, improving patient access without compromising efficacy or safety. [55,56]

Oncology

In cancer treatment, biologics and biosimilars play a key role in targeted therapy, improving survival and disease management. With the global cancer burden rising, these therapies are increasingly important in addressing major cancers such as breast, lung, and colorectal cancer, offering more precise and effective treatment options. [57,58]

Gastroenterology

In inflammatory bowel diseases like Crohn's disease and ulcerative colitis, biosimilars of anti-TNF agents (e.g., infliximab) have significantly improved patient outcomes. They have demonstrated comparable efficacy and safety, while also reducing treatment costs and expanding access to long-term therapy. [59,60]

Rheumatology

In conditions like rheumatoid arthritis, biosimilars of biologic DMARDs help manage inflammation and prevent disease progression. By reducing costs, they make advanced therapies more accessible, especially for patients who do not respond adequately to conventional treatments. Overall, biosimilars are transforming clinical practice by maintaining therapeutic effectiveness while enhancing affordability and accessibility across major disease areas. [61, 62]

Economics and Healthcare Impact

Cost Savings and Market Competition

Biologic therapies, despite their high development costs, have become essential in treating many serious and chronic diseases due to their targeted action and strong clinical outcomes. Their global demand is reflected in the success of several blockbuster biologics generating billions in revenue. However, as patents for these products expire, biosimilars are entering the market, creating opportunities for more affordable treatment options. Regulatory agencies are supporting this shift by enabling faster approval pathways, encouraging competition, and ultimately reducing healthcare costs while improving patient access. [63,64]

Market Competition

India has established itself as a key player in the global biosimilar market, with over 20 companies actively involved in development and more than 70 approved biosimilar products. The country's biotechnology sector is rapidly expanding, supported by strong growth and increasing global recognition. With its large-scale manufacturing capacity and cost-efficient production, India is well-positioned to drive future growth in the biosimilar industry. Overall, biosimilars not only reduce treatment costs but also strengthen market competition, making advanced therapies more accessible worldwide. [65,66]

Challenges and Limitations

The development and use of biologics and biosimilars face several challenges that limit their full potential, particularly in areas such as manufacturing, acceptance, legal frameworks, and global access.

Manufacturing Complexity

Biologic production is highly complex because it relies on living cells, unlike simpler chemical drugs. The process involves advanced bioreactor

systems, careful purification, and strict quality control to maintain product consistency. It is time-consuming, often taking many months, and requires significant financial investment, making it one of the most demanding areas in pharmaceutical manufacturing. [67,68]

Physician and Patient Acceptance

Adoption of biosimilars is also influenced by patient and physician preferences. Factors such as dosing frequency, convenience, and place of administration play important roles. While many prefer less frequent dosing and home-based treatment for convenience, some patients still favor clinical settings for safety reassurance. Acceptance tends to improve with prior experience and better awareness.[69,70]

Legal and Patent Challenges

Biologics are protected by complex patent systems that cover not only the drug itself but also its manufacturing process and formulation. Even after primary patents expire, multiple secondary patents can delay biosimilar entry, requiring companies to navigate complicated legal pathways. [71, 72]

Global Inequality in Access

High costs of biologics limit access, especially in low- and middle-income regions. Biosimilars offer a practical solution to improve affordability, but wider adoption depends on increased awareness, supportive policies, and collaboration among healthcare stakeholders to ensure equitable access to treatment. [73]

Table 4. Biologics, Biosimilar, Biobetters differences

Biologics	• Novel therapeutics • Patentable • Reference price • 15 years to develop • $ 1200MM cost
Biosimilar	• Competitive therapeutics • Non patentable • Reduced price • 8-10 years to develop • $ 100-200 MM cost
Biobetter	• Improved efficacy/ safety • Patentable • Premium price • 10 years to develop • $ 500 MM cost

Future Perspectives

The future of biologics and biosimilars is highly promising, driven by innovation in drug delivery, technology, and global healthcare strategies.

Emerging Drug Delivery and Market Growth

Next-generation delivery systems, such as oral and inhalation-based biologics, are gaining strong momentum. Rapid growth in these areas reflects increasing confidence in more patient-friendly and efficient treatment options that could transform how biologics are administered. [74, 75]

Biobetters

Biobetters represent an advanced evolution beyond biosimilars. While biosimilars focus on similarity, biobetters are improved versions of existing biologics with enhanced efficacy, safety, or dosing convenience. They benefit from lower development risk, shorter timelines, and better market opportunities, making them an attractive strategy for pharmaceutical companies. [76, 77]

Advanced Analytics and AI

The integration of advanced analytics and artificial intelligence is revolutionizing biopharmaceutical manufacturing. Technologies such as machine learning enable better process control, prediction of outcomes, reduced variability, and improved product quality, ultimately enhancing efficiency and reducing costs. [78,79]

Global Regulatory Harmonization

Harmonizing biosimilar regulations across countries remains a key goal. Differences in clinical requirements, labeling, and testing create challenges for developers. Greater international collaboration can streamline approvals, reduce duplication of studies, and improve global access to biosimilars. [80,81]

Sustainability of Healthcare Systems

Biosimilars play a crucial role in making healthcare more sustainable by reducing treatment costs and expanding access to biologic therapies. The savings generated can be reinvested into innovative treatments and healthcare improvements, supporting long-term system efficiency and patient care. Overall, continued innovation, regulatory alignment, and technological advancement will drive the future growth and acceptance of biologics and biosimilars worldwide. [82]

CONCLUSION

Biologic therapies have marked a major advancement in modern medicine, offering targeted and effective treatments for diseases that were once difficult to manage. This review highlights the complexity of biologics, their development challenges, evolving regulatory pathways, and expanding clinical applications. Unlike conventional drugs, biologics require rigorous evaluation due to their structural complexity, and biosimilars are approved based on demonstrated similarity rather than exact replication. Regulatory systems worldwide have made significant progress in establishing clear pathways for biosimilar approval, although differences in policies and practices still exist. Clinically, growing evidence supports the safety and efficacy of biosimilars, though concerns such as immunogenicity and switching practices continue to require attention. From an economic perspective, biosimilars play a crucial role in reducing treatment costs and improving patient access, especially in resource-limited settings. Moving forward, advancements in analytical technologies, stronger pharmacovigilance, and global regulatory harmonization will be key. Overall, continued collaboration and innovation will help maximize the potential of biologics and biosimilars in improving global healthcare outcomes.

REFERENCES

1. Prof. Paul J Declerck. PhD. Biologics and Biosimilar: A Review of the Science and its implications. Generics and Biosimilars Initiative Journal 2012; vol. 1; Issue 1
2. Liang BA, Mackey TK. Tipping point: Biosimilars, emerging markets, and public ‐ private engagement to promote global health. J Commerc Biotechnol 2012;18:65 ‐ 74. [Google Scholar]

3. I.M.S. Institute for Healthcare Informatics. Delivering on the potential of biosimilar medicines. The role of functioning competitive markets. Available at www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/IMS_Institute_Biosimilar_Brief_March_2016.pdf. Accessed June 5, 2017.
4. Crommelin DJ, Storm G, Verrijk R, de Leede L, Jiskoot W, Hennink WE. Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. Int J Pharm. 2003;266:3-16.
5. -Sekhon BS, Saluja V. Biosimilars: an overview. Biosimilars. 2011;1:1-11
6. Kinch MS. An overview of FDA-approved biologics medicines. Drug Discov Today 2015;20:393–8. 10.1016/j.drudis.2014.09.003 [DOI] [PubMed] [Google Scholar]
7. Roger SD. Biosimilars: how similar or dissimilar are they? Nephrology 2006; 11:341–6. 10.1111/j.1440-1797.2006.00594.x [DOI] [PubMed] [Google Scholar]
8. Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and anti-erythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 2002;346:469–75. 10.1056/NEJMoa011931 [DOI] [PubMed] [Google Scholar]
9. Palak Patel. The science of cell line development for biologics: Improving stability and yield.Patheon: Pharma service;2025
10. -Jayakrishnan A, Wan Rosli WR, Tahir ARM, Razak FSA, Kee PE, Ng HS, Chew Y-L, Lee S-K, Ramasamy M, Tan CS, Liew KB. Evolving Paradigms of Recombinant Protein Production in Pharmaceutical Industry: A Rigorous Review. Sci. 2024; 6(1): 9.
11. Liu M, Judd N, Nogal N. Considerations for a successful tech transfer of a biologics upstream process. EPR. 2024; 5: .
12. - Born T, Fung V, editors. Analytical and functional assessments when developing biosimilar candidates. Paris: European League Against Rheumatism (EULAR); 2014.
13. Thorpe R, Wadhwa M. Intended use of reference products & WHO International Standards/Reference Reagents in the development of similar biological products (biosimilars). Biologicals. 2011;39:262–5. doi: 10.1016/j.biologicals.2011.06.005. [DOI] [PubMed] [Google Scholar]
14. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and Cancer: a consensus report. Diabetes Care 2010;33:1674–85.
15. N. Nupur, S. Joshi, D. Gulliarme, A.S. Rathore. Analytical similarity assessment of biosimilars: global regulatory landscape, recent studies and major advancements in orthogonal platforms,Front. Bioeng. Biotechnol., 10 (2022), Article 832059, 10.3389/fbioe.2022.832059
16. H. Rahalkar, H.C. Cetintas, S. Salek. Quality, non-clinical and clinical considerations for biosimilar monoclonal antibody development: EU, WHO, USA, Canada, and BRICS-TM Regulatory guidelines, Front. Pharmacol., 9 (2018), p. 1079, 10.3389/fphar.2018.01079
17. Sullivan PM, DiGrazia LM. Analytic characterization of biosimilars. Am J Health Syst Pharm. 2017 Apr; 74(8):568 579.
18. Tan Q, Guo Q, Fang C, Wang C, Li B, et al. Characterization and comparison of commercially available TNF receptor 2-Fc fusion protein products. MAbs. 2012 Nov-Dec; 4(6):761-774.
19. Storz U. Of patents and patent disputes: The TNFα patent files. Part1: Humira. Hum Antibodies. 2017; 25(1-2):1 16.

20. Kuhlmann M, Covic A. The protein science of biosimilars. Nephrol Dial Transplant. 2006 Oct; Suppl 5:v4-8.
21. Jacobs I, Petersel D, Shane LG, Ng CK, Kirchhoff C, et al. Monoclonal Antibody and Fusion Protein Biosimilars Across Therapeutic Areas: A Systematic Review of Published Evidence. BioDrugs. 2016Dec; 30(6):489-523.
22. Walker MR, Makropoulos DA, Achuthanandam R, Van Arsdell S, Bugelski PJ. Development of a human whole blood assay for prediction of cytokine release similar to anti-CD28 superagonists using multiplex cytokine and hierarchical cluster analysis. Int Immunopharmacol. 2011;11(11):1697–705.
23. US Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. Rockville, MD. 2015.
24. -European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. London, UK. 2013
25. US Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. Rockville, MD. 2015.
26. Nick C. How can the biosimilar concept be applied to monoclonals? Regul Rapp. 2011;8(1):11–4.
27. -Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2095–128.
28. Godman B. Health authority perspective on biosimilars. Generics and Biosimilars Initiative Journal 2013;2:10–11.
29. WHO. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) WHO; Geneva, Switzerland: 2009. [Google Scholar]
30. FDA. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. FDA; Silver Spring, USA: 2012. [Google Scholar]
31. FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. FDA; Silver Spring, USA: 2012. [Google Scholar]
32. FDA. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. FDA; Silver Spring, USA: 2012. [Google Scholar]
33. -Interchangeability of Biosimilars: A European Perspective. Pekka Kurki, Leon van Aerts, Elena Wolff-Holz, Thijs Giezen, Venke Skibeli, Martina Weise. BioDrugs 2017 Apr;31(2):83 91
34. Regulatory Information and Guidance on Biosimilars and Their Use Across Europe: A Call for Strengthened One Voice messaging. Liese Barbier, Allary Mbuaki, Steven Simoens, Paul Declerck, Arnold G. Vulto, and Isabelle Huys. Frontiers in Medicine 2022, Vol 9, 820755
35. Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective. Pekka Kurki, Sean Barry, Ingrid Bourges, Panagiota Tsantili, Elena Wolff-Holz. Drugs 2021 Nov;81(16):1881-1896
36. The safety of switching between therapeutic proteins. Ebbers H, Muenzberg M, Schellekens H. Expert Opinion Biol Ther. 2012;12:1473-85
37. -Cohen HP, McCabe D. The importance of countering biosimilar disparagement and misinformation. BioDrugs. 2020;34:407–14.

38. European Medicines Agency. Find medicines. Available at: https://www.ema.europa.eu/en/medicines. Accessed 6 Apr 2021
39. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/ BMWP/42832/2005 Rev1. Available at: https://www.ema.europa.eu/en/similar-biological-medicinal-products. Accessed 24 Apr 2021
40. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process: Q5E. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guide line.pdf. Accessed 21 Jan 2021.
41. Jefferis R. Biologics: structural heterogeneity and immunogenicity. Br Jo Hosp Medi. 2017 doi: 10.12968/hmed.2017.78.8.443. [DOI] [PubMed] [Google Scholar]
42. Vlasak J, Ionescu R. Heterogeneity of monoclonal antibodies revealed by charge-sensitive methods. Curr Pharm Biotechnol. 2008;9:468–481. doi: 10.2174/138920108786786402. [DOI] [PubMed] [Google Scholar]
43. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process: Q5E. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guide line.pdf. Accessed 21 Jan 2021.
44. Parikh, Chinar R., et al. "Impact of immunogenicity on clinical efficacy and toxicity profile of biologic agents used for treatment of inflammatory arthritis in children compared to adults". Therapeutic Advances in Musculoskeletal Disease 2021;13: 1759720X211002685
45. Han PD, Cohen RD. "Managing immunogenic responses to infliximab: treatment implications for patients with Crohn's disease". Drugs. 2004;64(16): 1767-77. doi: 10.2165/00003495-200464160-00004.
46. Car, E., Vandenplas, Y., Lacosta, T. B., Simoens, S., Huys, I., Vulto, A. G., & Barbier, L. (2024). Mitigating the Nocebo Effect in Biosimilar Use and Switching: A Systematic Review. Pharmaceutical Medicine, 38(6), 429–455. https://doi.org/10.1007/s40290-024-00541-y
47. EMA. (2022). Biosimilars in the EU – Information guide for healthcare professionals. European Medicines Agency. Retrieved from
48. World Health Organization (WHO). (2022). Guidelines on evaluation of biosimilars. WHO Technical Report Series, No. 1028.
49. Vora, M. B., Trivedi, H. R., Shah, B. K., & Tripathi, C. B. (2017). Adverse drug reaction reporting in biosimilar drugs: Role of pharmacovigilance. Indian Journal of Pharmacology, 49(6), 410–416.
50. Indian Pharmacopoeia Commission. Pharmacovigilance Guidance Document for Marketing Authorization Holders of Pharmaceutical Products. 2018 [Google Scholar]
51. -Felix T, Jordan JB, Akers C, Patel B, Drago D. Current state of biologic pharmacovigilance in the European Union: Improvements are needed. Expert Opin Drug Saf. 2019;18:231–40. doi:

10.1080/14740338.2019.1577818. [DOI] [PubMed] [Google Scholar]
52. Seidl A, Hainzl O, Richter M, Fischer R, Böhm S, Deutel B, et al. Tungsten-induced denaturation and aggregation of epoetin alfa during primary packaging as a cause of immunogenicity. Pharm Res. 2012;29:1454–67. doi: 10.1007/s11095-011-0621-4. [DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
53. European Commission. What you need to know about biosimilar medicinal products. 18 December 2014. http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/e.... Accessed 23 Oct 2015.
54. Sharma B. Immunogenicity of therapeutic proteins. Part 3: impact of manufacturing changes. Biotechnol Adv. 2007;25:325–331. doi: 10.1016/j.biotechadv.2007.01.007. - DOI - PubMed
55. Chirino AJ, Mire-Sluis A. Characterizing biological products and assessing comparability following manufacturing changes. Nat Biotechnol. 2004;22:1383–1391. doi: 10.1038/nbt1030. - DOI - PubMed
56. Schiestl M, Stangler T, Torella C, Čepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011;29:310–312. doi: 10.1038/nbt.1839. - DOI – PubMed
57. Calvez T, Chambost H, Claeyssens-Donadel S, et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. Blood. 2014;124:3398–3408. doi: 10.1182/blood-2014-07-586347. - DOI - PubMed
58. Socinski MA, Curigliano G, Jacobs I, Gumbiner B, MacDonald J, Thomas D. Clinical considerations for the development of biosimilars in oncology. MAbs. 2015;7:286–293. doi: 10.1080/19420862.2015.1008346. [DOI] [PMC free article] [PubMed] [Google Scholar]
59. -Mellstedt, H. Clinical considerations for biosimilar antibodies. EJC Suppl. 2013,11, 1–11. [CrossRef] [PubMed]
60. World Health Organisation. Cancer. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer (accessed on 20 September 2022).
61. Dörner T et al. The role of biosimilars in the treatment of rheumatic diseases. Ann Rheum Dis. 2013;72(3):322-8.
62. Danese S et al. Biosimilars in IBD: From theory to practice. Nat Rev Gastroenterol Hepatol. 2017;14(1):22-31.
63. Gecse KB et al. Efficacy and safety of the biosimilar infliximab CT-P13 treatment in inflammatory bowel diseases: A prospective, multicentre, nationwide cohort. J Crohns Colitis. 2016;10(2): 133-40.
64. Jahnsen J et al. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: A Norwegian observational study. Expert Rev Gastroenterol Hepatol. 2015;9(Suppl 1):45-52.
65. H. Kim The future of biosimilars: maximizing benefits across immune-mediated inflammatory diseases Drugs(2020)
66. C. Gasteiger A bio-what? Medical companions' perceptions towards biosimilars and information needs in rheumatology Rheumatol Int (2021)
67. Mullard A. Hearing shines spotlight on biosimilar controversies. Nat Rev Drug Discov 2010;9:905–6. 10.1038/nrd3325 [DOI] [PubMed] [Google Scholar]
68. Arshad, K. (2023). an Overview of Biosimilar Market in India, Its Business Environment and Exports. Journal of the Asiatic Society of Mumbai, 97(5), 36–47.

69. Nagarajan, B., Anandbabu, T., Lakshmi, K., Neethirajan, G., Dabburu, K., Prasanna, P. M., Grace, D. C., Prabha, K. S., & Vasudevan, E. (2026). Navigating the complexity of biologics and biosimilar: structural, clinical, and regulatory insights. Journal of Applied Biology & Biotechnology. https://doi.org/10.7324/JABB.2026.274436
70. Gelhorn, H., Wu, S. S., Collacott, H., Webb, E., Bond, M., Sanchez, S. Z., Lindsley, A., Ambrose, C., Franzese, C., & Damask, C. (2025). PATIENT AND PHYSICIAN PREFERENCES FOR ATTRIBUTES OF BIOLOGIC TREATMENTS FOR CHRONIC RHINOSINUSITIS WITH NASAL POLYPS. Annals of Allergy, Asthma & Immunology, 135(5), S102–S103. https://doi.org/10.1016/j.anai.2025.08.303
71. European Medicines Agency. (n.d.). Biosimilar medicines overview. Retrieved from https://www.ema.europa.eu/en/human-regulatory-overview/biosimilar-medicines-overview
72. MedPak. (n.d.). Biosimilar vs. Generic Drugs. Retrieved from https://medpak.com/biosimilar-vs-generic-drugs/
73. Piggin, M. M. (2022). Addressing Inequality of Access to Biologics: What Is Your Role? A Patient (Advocate)'s Perspective on Biosimilars. HemaSphere, 6(4), e702. https://doi.org/10.1097/HS9.0000000000000702
74. Market Data Forecast. Global Oral Biologics Market Size, Share, Trends & Growth Forecast Report by Drug Class, Disease Indication, Distribution Channel, and Region (North America, Europe, Asia-Pacific, Latin America, Middle East and Africa), Industry Analysis from 2025 to 2033. Market Research Report. April 2025.
75. The Business Research Company. Inhalation CDMO Global Market Report 2025—by Product (Dry Powder Inhaler (DPIs), Metered Dose Inhaler (MDIs), Nebulizer, Soft Mist Inhaler), by Disease Indication (Asthma, Chronic Obstructive Pulmonary Disease (COPD), Pulmonary Arterial Hypertension, Acut. Market Research Report. January 2025.
76. Sharma A, Reddy P, Kuppermann BD, Bandello F, Loewenstein A. Biosimilars in ophthalmology: is there a big change on the horizon? Clin Ophthalmol. 2018;12:2137–43. doi: 10.2147/OPTH.S180393. [DOI] [PMC free article] [PubMed] [Google Scholar]
77. Kesik-Brodacka M. Progress in biopharmaceutical development: Progress in Biopharmaceutical Development. BiotechnolApplBiochem. 2018;65:306–22. doi: 10.1002/bab.1617. [DOI] [PMC free article] [PubMed] [Google Scholar]
78. LoRusso PM, Weiss D, Guardino E, Girish S, Sliwkowski MX. Trastuzumab Emtansine: A Unique Antibody-Drug Conjugate in Development for Human Epidermal Growth Factor Receptor 2-Positive Cancer. Clin Cancer Res. 2011;17:6437–47. doi: 10.1158/1078-0432.CCR-11-0762. [DOI] [PubMed] [Google Scholar]
79. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med. 2012;367:1783–91. doi: 10.1056/NEJMoa1209124. [DOI] [PMC free article] [PubMed] [Google Scholar]
80. Iyanda, C., & Yang, K. (2023). Advanced Analytics and Predictive Maintenance in Pharmaceutical Manufacturing. IARJSET, 10(11). https://doi.org/10.17148/IARJSET.2023.101102

81. Kirchlechner, T. M., & Cohen, H. P. (2025). Global Harmonization of Biosimilar Development by Overcoming Existing Differences in Regional Regulatory Requirements - Outcomes of a Descriptive Review. Therapeutic Innovation & Regulatory Science, 59(2), 245–255. https://doi.org/10.1007/s43441-024-00740-4
82. Kvien, T. K., Betteridge, N., Brückmann, I., Bodenmüller, W., Bryn, G., Danese, S., Gonçalves, J., Maravic, Z., Thorne, C., Wingate, L., & Cornes, P. (2025). Beyond Cost: Observations on Clinical and Patient Benefits of Biosimilars in Real-World Settings. BioDrugs, 39(4), 537–553. https://doi.org/10.1007/s40259-025-00727-z
83. Zhang, E., Xie, L., Qin, P., Lu, L., Xu, Y., Gao, W., et al. (2020). Quality by Design-Based Assessment for Analytical Similarity of Adalimumab Biosimilar HLX03 to Humira. AAPS J. 22, 1–14. doi:10.1208/s12248-020-00454-z
84. US Food & Drug Administration. Guidance for industry. Considerations in demonstrating interchangeability with a reference product. 2019
85. European Medicines Agency. Guideline on Immunogenicity assessment of therapeutic proteins EMEA/CHMP/ BMWP/14327/2006 Rev 1. Available at: https://www.ema.europa.eu/en/similar-biological-medicinal-products. Accessed 24 Apr 2021.
86. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J. Clin. 2021, 71, 209–249. [CrossRef] [PubMed]

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