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Therapeutic Equivalence In Biosimilar Challenges And Solutions

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Abstract

Biologic therapies have completely transformed modern medicine by providing targeted treatment options for chronic, inflammatory, and oncological diseases. However, biosimilars-biological medications designed to closely mimic reference biologics in terms of safety, effectiveness, and quality have emerged because of the high cost and complexity of producing biologics. Because manufacturing of biologics is complicated and requires extensive analytical, pharmacokinetic, and clinical tests to prove therapeutic equivalency, biosimilars are not perfect replicas like generic medications. In addition to the difficulties of immunogenicity, a lack of long-term studies, patent hurdles, and prescriber-patient distrust, this review examines the regulatory frameworks, clinical trial evidence, and real-world data that support the use of biosimilars. Case studies of biosimilars such as etanercept and infliximab confirm comparable efficacy, safety, and immunogenicity with originators. Current solutions, such as advanced analytical tools, pharmacovigilance, education, and regulatory harmonization, are vital to increasing acceptance and global accessibility. Ultimately, establishing therapeutic equivalence is critical for building trust, guaranteeing patient safety and facilitating sustainable healthcare delivery through biosimilars.

Key Words: *Biologics, Biosimilar, Regulatory bodies, Generics*

Introduction

Biologics are a category of medications developed from living cells and have become essential in contemporary healthcare. In contrast to conventional chemical drugs, biologics function through distinct pharmacological pathways and possess advanced biophysical characteristics, which contribute to their high effectiveness in managing numerous chronic and complex conditions .(Obiezu et al., 2024) Biologic drugs are highly complex, making it impossible to replicate them precisely. Instead, Biosimilar are developed to closely resemble the original biologic, although they are not exact copies (Patel et al., 2015). Biological medicine has a much larger and more complex structure compared to small-molecular drugs. They are generally categorized into three main groups (1) those closely related to natural bodily substances and often used in replacement therapies, (2) monoclonal antibodies (mAbs) that target soluble molecule or cell surface markers to disrupt signaling pathways and associated biological functions and (3) engineered protein that act as receptors mimics, receptors blockers, or fusion proteins. These

biologics are manufactured in various forms, including hormones (such as insulin and growth hormones for hormones deficiencies), monoclonal antibodies (for treating autoimmune disorders and cancers), blood derived product (for condition like hemophilia), immunomodulatory (interferon beta for multiple sclerosis), enzyme (used to dissolve blood clot) and vaccines aimed at preventing numerous infectious diseases (Mascarenhas-Melo et al., 2024). Biologic therapies have transformed the management of patients with severe inflammatory autoimmune disorders and, more recently, advanced cases of osteoporosis.

Biologic therapies are medicine developed from living cell and play an important role in prevention, diagnosis and treatment of numerous conditions including cancers and immune mediated diseases this category includes agents such as monoclonal antibodies and interleukins, which act on specific biological targets and are often classified as biologic agents. (Adami et al., 2019). one of the major distinction between biologic and small molecule drug is the method of production. While small molecule drug is manufactured through chemical synthesis, biologics are generated using living cells or biological system. These therapies have greatly improved the management of many diseases including anemia, autoimmune disorders, inflammatory conditions, diabetes and cancer. (Crespi-Lofton & Skelton, 2017). Gene therapies another form of biologic treatment have shown remarkable promise for genetic diseases such as spinal muscular atrophy and inherited retinal disorders. They work by addressing and correcting the underlying genetic defects that cause the condition, offering the potential for long lasting or even permanent therauptic benefits.(Abdullah Saeed Alghamdi et al., 10-12-2024). It is important to note that biosimilar are not equivalent to conventional generic drugs. For generic medications, demonstrating pharmaceutical equivalence (same active ingredient) and bioequivalence (same pharmacokinetic behavior) is usually sufficient to establish therauptic equivalence and extensive clinical trials are generally unnecessary. In contrast, biosimilar cannot be exact copies of their reference biologics and therefore required more rigorous testing to confirm similarity in terms of safety, efficacy and quality (Schellekens, 2009).

Methodology

This review is native in nature does not involve original laboratory work or clinical trials. Relevant literature published from 2020 to 2025 was identified by searching PubMed and google scholar using terms such as biosimilar, therauptic equivalence, real world evidence and awareness of patient.

To broaden the scope of review, additional insights were drawn from industry reports, legal analysis and document release by regulatory authority. Together these sources helped build a comprehensive understanding of the evolution landscape of biosimilar.

Understanding The Biosimilar

A biosimilar is a type of biological product that gains approval by demonstrating, through comprehensive evidence, that it closely resembles an already approved originator biologic in structure, function, quality, and clinical performance. It is developed to ensure that there are no significant clinical differences from the reference product in terms of safety, purity, or potency (Declerck et al., 2017).

Regulatory Approval Of Biosimilar

In the United States, biologics are typically regulated under the Public Health Service Act (PHSA). While traditional chemical drugs fall under the Federal Food, Drug, and Cosmetic Act

(FDCA). Under the PHSA, original biologic products gain approval via a biologic license Application (BLA), also referred to as the 351a pathway. which involves extensive preclinical and clinical studies to establish their safety, efficacy, and quality. In 1984, the Hatch-Waxman Act modified the FDCA to introduce the 505(i) and 505(b) pathways, streamlined routes that permit approval of generic drugs through an Abbreviated New Drug Application (ANDA). However, the PHSA originally did not outline a formal regulatory pathway for the approval of biosimilars.

In February 2012, the FDA released three draft guidance documents outlining the regulatory framework for biosimilars.

- Scientific consideration in demonstrating bio-similarity to the reference product.
- Quality consideration in Demonstrating bio-similarity to a reference protein product.
- Biosimilars: Questions and Answers on the implementation of the biologic price Competition and Innovation Act 2009 (Ventola, 2013)

Comparison Of Biosimilar With Biologics: How It Differs From Generic

Potential variation between a biosimilar and its reference product may arise from post-translational modification such as glycosylation, oxidation, deamidation, and protein aggregation, which can result from differences in host cell and expression system. Every stage of bioprocess, from production through purification and formulation for long-term stability, must be evaluated to determine possible effect on pharmacokinetics, efficacy, and safety. Continuous monitoring of bio-similarity is therefore an integral part of the manufacturing process. A biosimilar is a biological medicine in which an identical protein sequence is produced using new production cell lines and redeveloped manufacturing methods. It must demonstrate a high degree of similarity to the approved biologics RP in terms of analytical properties, biological activity, purity, and pharmacokinetics/ pharmacodynamics properties. .(Schreiber et al., 2020)

Therapeutic Equivalence

Analytical similarity: In vitro bioassays, peptide mapping, glycan profiling, and aggregation studies have all demonstrated that there are no appreciable differences between reference biologics and biosimilars (Kabir et al., 2019)

Pharmacokinetics (PK): For the CT-P13 SC autoinjector (AI) versus CT-P13 SC prefilled syringes (PFS) groups, the geometric mean ratios (90% confidence interval) of AUC_{0}–inf (area under the concentration-time curve from zero to infinity) and C_{max} (maximum serum concentration) were 94.15% (85.02–104.26%) and 92.48% (84.66–101.01%), respectively. As the 90% confidence intervals fell within the accepted bioequivalence range of 80–125%, the two administration routes showed comparable pharmacokinetic profiles. Regarding immunogenicity, 70 (97.22%) patients in the CT-P13 SC AI group and 73 (98.65%) in the CT-P13 SC PFS group tested positive for anti-drug antibodies (ADAs) at the study's conclusion, with both groups also testing positive for neutralizing antibodies. No significant differences in safety outcomes were observed between the groups, confirming that both formulations were pharmacokinetically and immunogenically equivalent (Park et al., 2024).

Study conducted across multiple therapeutic fields such as rheumatoid arthritis, inflammatory bowel disease and cancer. Shows that biosimilar performe just as safely and effectively as the original biologic product. These finding support the conclusion that moving patients from a reference biologic to biosimilar is generally safe does not lead to any meaningful rise in immunogenicity. (Aljahili et al., 2025)

Extrapolation of indications (WHO): According to the 2022 WHO guidelines, it may be feasible to extrapolate results to additional RBP indications if the comparable effectiveness and safety of the SBP and RBP have been demonstrated for a specific therapeutic use.

A clinical test model is used to find any potential differences between the Reference Bio Therapeutic Product (RBP) and the Similar Bio therapeutic Product (SBP), with a focus on the same mechanism of action and receptor(s). If the mechanism is different, more data and strong scientific justification are required. Additionally, the safety profiles and immunogenicity of the SBP must be sufficiently explained, and the extrapolated indications shouldn't cause any additional safety concerns.

Suppose the efficacy trial shows acceptable safety and effectiveness. In that case, the company must provide relevant clinical data and a thorough scientific justification that addresses the risk-benefit profile for expanding to new applications (Wadhwa et al., 2022)

Case Studies Of Approved Biosimilar

Table 1.

Case	Objective	Method	Result	Conclusion
Case 1: Original Etanercept vs. Bio-Etanercept	To evaluate the effects of original etanercept (O-etanercept) and biosimilar bio-etanercept in treating RA patients.	Phase III randomized trial; patients with moderate to severe RA assigned to O-etanercept or bio-etanercept; primary endpoint: ACR20 at 24 weeks.	156 patients assessed: no significant differences in ACR20 response between groups. Antibodies developed in 4 (bio-etanercept) vs. 5 (O-etanercept).	Bio-etanercept was equivalent to the original etanercept (Pekhenko et al., 2024).
Case 2: GP2015 vs. Etanercept	Comparing the efficacy and safety of GP2015 (biosimilar) vs. etanercept in moderate-to-severe RA patients unresponsive to DMARDs.	Phase III double-blind RCT; 376 patients; 50 mg GP2015 or ETN weekly × 24 weeks + methotrexate (10–25 mg). Responding to week 48.	DAS28-CRP change at week 24: −0.07 (95% CI −0.26 to 0.12), within equivalence margin. Similar TEAE rates (ETN 49.5%, GP2015 43.5%). No NAbs in GP2015 group; few in ETN group.	GP2015 demonstrated equivalent efficacy, safety, and immunogenicity to ETN (Matucci-Cerinic et al., 2018)
Case 3: PF-SZ-IFX vs. Infliximab	To assess long-term safety, efficacy, and immunogenicity of infliximab biosimilar PF-SZ-IFX in RA patients, including switchers from IFX-EU.	Phase III double-blind active-controlled trial; 650 patients randomized to PF-SZ-IFX or IFX-EU; switch at week 30 or 54; all received PF-SZ-IFX until week 78.	Week 78 ACR20 response: 75.9% (biosimilar), 77.8% (week 30 switch), 68.3% (week 54 switch). TEAEs: 28.9%–30.2% across groups. ADA and NAb rates are consistent.	PF-SZ-IFX maintained safety, efficacy, and immunogenicity up to week 78 with no significant differences across groups (Cohen et al., 2020)

TEAEs: Treatment-emergent adverse events. ETN = Etanercept. GP2015 and bio-etanercept are biosimilars of etanercept. NAb: neutralizing antibody. RCT: randomized controlled trial, RA: Rheumatoid Arthritis.

Challenges In Establishing Therapeutic Equivalence

Scientific and technical challenges: Bas et al. (2025) highlight that even modest variations in glycosylation patterns (e.g., sialylation or fucosylation) can modify pharmacokinetics and impact receptor binding affinity, clearance rates, and effector activities such as antibody-dependent cell cytotoxicity (ADCC). (Bas, 2025)

Clinical study limitations: Few studies have examined multiple or "back and forth" switching between originators and biosimilars, or between biosimilars; the majority have focused on a single move from an original to a biosimilar. Notably, the follow-up periods for these studies ranged from 4 to 21 months, with a median of just 133 individuals (range: 36–309) (Allocati et al., 2022) further limiting the generalizability of their findings

Prescriber and patient concerns: According to results from a recent poll conducted in the US in 2022, 10% of rheumatologists reported feeling uneasy about writing prescriptions for biosimilars. Furthermore, just 35% of respondents in this research were willing to go from a biologic reference product to a biosimilar, and 38% voiced worries about the effectiveness of biosimilars. (Giavatto et al., 2024)

Additionally, according to the poll, 65% of prescribers said that the current state of the economy did not support the switch to biosimilars. Additionally, a 2023 research study that was published in the Journal American Pharmacists Association polled 507 pharmacists to find out what they knew and thought about biosimilars. The study discovered that while pharmacists were aware of the biosimilars' safety and equivalency to their reference product, only 20% of them showed that they understood the idea of US Food and Drug Administration (FDA) interchangeability. Furthermore, half of the pharmacists polled said they felt either moderately or extremely comfortable answering patients' questions regarding biosimilars. The conclusions of this study can't be applied to other pharmacist professions, such as those that deal with health system specialty pharmacies, because the bulk of respondents (75%) were community pharmacists (Giavatto et al., 2024)

Legal and Patent-related Barriers: Patent claims against biosimilars are, on average, twelve times higher in the US than in the UK and nine times higher in the US than in Canada. Due to these high patent hurdles, biosimilars typically take four times longer to enter the U.S. market than they do in Canada and seven times longer to enter the U.K. market (Goode & Chao, 2022) This highlights how patent thickets and litigation tactics in the U.S. delay the introduction of biosimilars onto the market and hinder competition.

Current Solution And Future Innovations

Improved analytical technologies: Current regulatory standards permit biosimilar formulation innovation, such as changing excipients, switching to buffer-free systems, or raising protein content, but only within the parameters established by the comparability requirements. These requirements ensure that any modification made to a biosimilar do not create meaningful clinical difference from the original product. Regulatory authorities mainly rely on detail analytical and functional comparisons to assess biosimilarility. while clinical studies kept limited and used only when uncertainties remain. As a result, every new version must be supported by proof that it strengths, safety profile and purity remain consistent with reference product. This creates a balanced system manufactures can pursue improvements. But they must meet strict comparative standard to secure regulatory approval. (Bas, 2025)

Real-World Data And Post Marketing Surveillance

Indicates that biosimilar have safety patterns comparable to those of their original biologic products, as shown in major pharmacovigilance analysis using the Eudravigilance database.at the same time, reports of serious adverse outcomes including immune related reactions and certain cancers emphasize the ongoing importance of continuous safety monitoring. (Nikitina et al., 2023)

Education and awareness program: Finding from 2023 web based survey showed that a large portion participants were unfamiliar with biosimilar and concept of switching from original biologics. this study also noted that limited awareness was associated with the belief that autonomic substitutions in an appropriate policy changes. (Alanne et al., 2025) Likewise a south Korea survey reported that many patients neither favored not opposed biosimilar and lacked basic knowledge about them. This wide spread neutrality suggests that public understanding of biosimilar still need to be improved. Therefore, supported polices that strengths patients focused education are essential to enhance perception of biosimilar and encourage physician to prescribe them, ultimately increasing overall their use. (Choi et al., 2025)

Regulatory Integration: Bringing biosimilar regulations into closer alignment across can greatly improve both patient access and efficiency of product development. According to descriptive analysis standardizing biosimilar development criteria worldwide streamline the development process and creates boarder benefits for patients and society. (Kirchlechner & Cohen, 2025) In addition consistent and predictable approval pathways not only simplify regulatory steps but also strengthen trust greater regulatory alignment can help build confidence in biosimilar among patients and healthcare professional (Cazap et al., 2018)

Conclusion

Biosimilar offers a major opportunity to cut healthcare expenses and improve the viability of essentials biologic therapies. Evidence from analytical studies, clinical trials and post marketing and real world data consistently supports that these products deliver the same therauptic outcomes as their original biologics, making them reliable options in routine practice. Despite this, certain challenges remain particularly concerns about physicians and patient confidence, limited information's on safety of multiple switches and regulatory barrier that delayed their market entry.

Addressing these gaps requires a comprehensive approach that includes transparent regulatory path ways, stronger pharmacovigilance programs and targeted educational efforts and greater global alignment in biosimilar approved standards.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Considerations

This article is a review and does not involve original research on human or animal subjects; therefore, ethical approval was not applicable

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