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BIOSIMILARS AND INTERCHANGEABLE BIOLOGICS: GLOBAL REGULATORY HARMONIZATION AND CLINICAL UPTAKE FROM 2022 ONWARD

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ABSTRACT

Biosimilars are biological products that are highly similar to an approved reference biologic, with no clinically meaningful differences in safety, purity, or potency. They offer the potential to reduce healthcare costs and expand patient access to biologic therapies. Regulatory frameworks for biosimilars have evolved significantly, with the European Medicines Agency and US Food and Drug Administration leading the way. A key development is the designation of interchangeability, which in the US allows a biosimilar to be substituted for the reference product without prescriber intervention, subject to state laws. Since 2022, multiple interchangeable biosimilars have been approved, including for adalimumab and insulin glargine. This review critically examines global regulatory harmonization efforts, clinical uptake, and real-world evidence for biosimilars from 2022 onward. Differences remain between regulatory requirements for interchangeability and substitution, and clinical acceptance varies by region and therapeutic area. Real-world studies have generally shown comparable effectiveness and safety for biosimilars, but concerns persist regarding immunogenicity, extrapolation, and nocebo effects. Future directions include harmonized interchangeability standards, increased physician and patient education, and expansion into emerging markets. Overall, biosimilars are a critical component of sustainable healthcare, but their full potential requires continued regulatory alignment and robust post-marketing surveillance.

Keywords: Biosimilars; Interchangeability; Regulatory Harmonization; Biologics; Real-World Evidence; Substitution

1 INTRODUCTION

Biologics have revolutionized the treatment of cancer, autoimmune diseases, and metabolic disorders, but their high cost limits access. Biosimilars offer a competitive alternative, potentially reducing prices and increasing utilization. A biosimilar must demonstrate analytical, functional, and clinical similarity to a reference product, but it is not identical due to inherent variability in biological manufacturing. Regulatory pathways for biosimilars were established in the European Union in 2005 and in the United States in 2010. Since then, over 100 biosimilars have been approved in major markets.

A major recent development is the US interchangeability designation, which allows substitution at the pharmacy level without prescriber involvement. The first interchangeable biosimilar was approved in 2021, and several more have followed, including interchangeable adalimumab, ranibizumab, and insulin products. This review focuses on developments from 2022 onward, emphasizing regulatory harmonization and clinical uptake.

2 REGULATORY FRAMEWORKS AND GLOBAL HARMONIZATION

The EMA and FDA have similar overarching principles for biosimilar approval: comprehensive comparability exercises including analytical, nonclinical, and clinical studies. However, interchangeability is a US-specific designation requiring additional switching studies demonstrating that alternating between biosimilar and reference product does not increase risk or reduce efficacy. Other regions, including Canada, Australia, and many low- and middle-income countries, rely on the WHO guidelines and may accept reference products from other jurisdictions.

Global harmonization efforts include the International Council for Harmonisation and the WHO prequalification program, but significant differences remain. The EU does not have a formal interchangeability designation but allows member states to decide substitution policies. In many countries, automatic substitution is not permitted, and prescribers must specify brand. Efforts to harmonize interchangeability data requirements are ongoing, with the FDA revisiting the need for switching studies.

3 CLINICAL UPTAKE AND REAL-WORLD EVIDENCE

Uptake of biosimilars varies widely by country and therapeutic area. In Europe, high uptake has been achieved in oncology supportive care (filgrastim, epoetin) and some monoclonal antibodies (rituximab, trastuzumab), driven by tendering and physician acceptance. In the US, uptake has been slower due to patent litigation, rebate systems, and prescriber reluctance, but recent interchangeable approvals and payer policies are increasing use. Adalimumab biosimilars entered the US market in 2023 with multiple interchangeable products, leading to significant price reductions.

Real-world studies have consistently shown comparable effectiveness and safety for biosimilars across indications, with no increase in immunogenicity-related events. Nocebo effects—negative patient expectations causing perceived loss of efficacy or new side effects—have been documented but can be mitigated through education. Switching studies have supported interchangeability, though some physicians remain cautious.

4 CHALLENGES AND BARRIERS

Barriers to biosimilar uptake include lack of prescriber and patient confidence, insufficient financial incentives, legal and regulatory complexities, and misinformation. In some markets, originator companies use exclusion contracts or rebate schemes to limit biosimilar penetration. Regulatory uncertainty around interchangeability and extrapolation to unstudied indications also slows adoption. In low- and middle-income countries, access to reference products for comparability and limited manufacturing capacity are major hurdles.

5 FUTURE PERSPECTIVES

Future directions include harmonized interchangeability standards, reduced switching study requirements, and reliance on real-world evidence for post-marketing safety. The WHO and regional harmonization initiatives can accelerate access in emerging markets. Education for healthcare professionals and patients is critical. Emerging biosimilars for complex molecules, including monoclonal antibodies, fusion proteins, and insulins, will expand the market. As patents expire, more originator biologics will face biosimilar competition.

6 CONCLUSION

Biosimilars and interchangeable biologics are essential for sustainable healthcare, but their impact depends on regulatory alignment and clinical acceptance. Since 2022, progress has been made in interchangeability designations and real-world evidence generation. Continued collaboration among regulators, industry, and healthcare providers will be necessary to realize the full benefits of biosimilars worldwide.

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