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Review Article

Exploring Global Regulatory Pathways for Biosimilars in Advanced Therapeutic Areas

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Abstract

Biosimilars are biologic drugs highly similar to an already approved reference biologic. They are transforming advanced therapeutic areas by increasing patient access to these drugs and lowering their costs. Guidelines for biosimilars have been established around the world but can be inconsistent and often reflect the inherent challenges associated with the adoption of biosimilars. For example, the first comprehensive biosimilar framework was established at the full European Medicines Agency (EMA) guidance level and was based on comparative quality, non-clinical, and clinical studies. The U.S. Food and Drug Administration (FDA) uses a stepwise manner with a strong emphasis on analytical testing followed by animal studies, as well as clinical trials, to confirm biosimilarity. SEBs are subject to post-market surveillance in Canada and local clinical trials and risk management plans in India. Japan stresses clinical comparability, and South Korea requires post-marketing surveillance. These regional differences impact prescribing behaviors and substitution policies, decelerating global biosimilar adoption. Advanced therapies, such as Cell and Gene Therapies (CGTs), add to the complexity of the regulatory landscape. For real improvement of biosimilar development, it is advisable to harmonize with international guidelines; to utilize real-world evidence, and to apply advances in technologies including machine learning and bioprocess optimization. By overcoming these regulatory and market barriers, ZENT is designed to improve patient care, lower healthcare costs, and change the dynamics of the constipated global pharmaceutical market.

Introduction

Biosimilars are an ever-increasing drug class that has been engineered to mimic and even replace biologics. Biologics are produced in living cells and are generally large, complex proteins that can have a wide range of applications. Biologics are used to treat inflammatory bowel diseases, cancers, and endocrine disorders within the field of gastroenterology alone. Biologics can be effective for many diseases, but access is often limited due to the high cost. Biosimilars have been developed as a way to lower treatment costs. Biosimilars must be virtually identical to their reference biologics in terms of efficacy, side effect risk profile, and immunogenicity [1].

The United States Food and Drug Administration (FDA) currently defines biosimilars as "a biological product that is highly similar to, and has no clinically meaningful differences from, an existing FDA-approved reference product." These drugs would still be made through living cells, but the synthesis pathway of the reference biologic is proprietary. Biosimilar origins, on the other hand, typically only study the final biologic and try to reverse-engineer a synthesis pathway that looks plausible [1].

The Affordable Care Act established a more streamlined licensing pathway for these drugs, but without having to demonstrate that the biosimilar drug is materially different from its reference product (i.e., will not have a greater effect or be less safe). The initial steps to approve biological as biosimilars were developed in Europe before the United States. The European Medicine Agency (EMEA)/ Committee for Medicinal Products for Human Use (CHMP) assesses the information compiled by pharmaceutical companies requesting marketing authorization of potential biosimilars [2].

Biosimilar drugs in the United States and Europe require structural analyses, functional assays, animal studies, and ultimately clinical studies. The biosimilar drug undergoes several comparative assessments to its reference biologic at each stage of the shortened approval process [3]. In contrast, a typical biological product goes through a conventional series of trials laboratory and animal testing to assess safety in humans followed by clinical trials.

In a European study of the acceptance of biosimilars, very few patients would be willing to switch to a biosimilar if they were already taking a biologic. The increasing rates of biosimilar treatment are predominantly attributable to the new patients who initiate a biosimilar. Major price decreases (often ≥ 50%) must be present in order for physicians to consider prescribing a biosimilar, even in a new patient population [4].

Biosimilars have gradually been gaining market shares. One of the filgrastim biosimilars, Zarxio, captured 15% of the filgrastim market in the United States in 2016, and Inflectra, one of the infliximab biosimilars, captured less than 10% of the infliximab market (United States biosimilar market). Biosimilars offer several potential benefits related to increased access to treatment and reduced cost of therapy in the field of gastroenterology. Biologics are commonly used for inflammatory bowel diseases and gastrointestinal cancers. In the gastroenterological endocrinological function, biosimilar insulin is also an area of active investigation as diabetes costs and the prevalence both continue to rise.

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Objectives

The main objectives of biosimilars are to:

1. **Show what is biosimilarity:** It is achieved by developing biosimilars to be consistent with a reference medicine regarding structure, biological activity, efficacy, safety, and immunogenicity profile [5].
2. **Decreased the necessity of clinical trials:** Reduced Number of clinical trials because the safety and efficacy of the reference medicine can be used in biosimilars [6].
3. **Lower-cost medicines:** In this time of escalating drug prices, it's crucial not just for the pharmaceutical industry, but more importantly, for patients to get access to lower-cost medicines out to the most number of people who need access. Biosimilars help these advanced, lifesaving medicines become more affordable, potentially improving the lives of individuals across the globe [7,8].

Biosimilar Clinical and Commercial Potential

a) **Clinical potential:** The clinical potential of biosimilar products is tremendous as they may help improve access to low-cost medicines for serious diseases. The market value of biologics in MEA is increasing, yet biosimilar uptake is a concern. Doing so will require stricter local guidelines, compilation of real-world data, and local clinical trials. Decisions on engaging stakeholders, increasing HCP awareness, optimizing pricing, and biotech partnerships will ease acceptance of the dominant systems while creating a technological transfer and procurement with an open market that promotes competition for patients and healthcare systems [9].

b) **Commercial Opportunity:** The biosimilars market is expected to be a multi-billion-dollar field, offering huge growth opportunities for biopharma organizations. Early engagement with the national regulatory authorities is imperative, recognizing that the biosimilar regulatory process is at varying levels of maturity in individual countries.

   a. In 2005, EMA summarized guidelines on biosimilarity for clinical, non-clinical, and quality. It keeps updating its guidelines from real-world experiences [10].

   b. In 2012, as per guidelines and principles issued by FDA on biosimilars emphasized a more flexible outcome for animal/clinical testing, taking in a totality of evidence approach based on comparative analytical characterization. Stepwise Approach: The FDA

Fingerprint-like analysis (analytical testing)

In-vitro functional testing

In-vivo animal studies

PK, PD, efficacy, safety (clinical studies)

The FDA guidance suggests that the development program of a biosimilar would assess so many reference products, and the biosimilar used in clinical trials must be comparable to the commercial product in order to obviate late-stage bridging studies [11].

Regulatory Pathways for Biosimilars

1. **United States (U.S.) - FDA Biosimilar Pathway:** The U.S. Food and Drug Administration (FDA) provides the regulatory framework to approve biosimilars within the Biologics Price Competition and Innovation Act (BPCI Act) of 2009. The 351(k) Pathway under the PHS Act serves as the primary approval pathway for biosimilars, which requires that the biosimilar must show no clinically meaningful differences between the proposed biosimilar and the FDA-approved reference product concerning safety, purity, and potency [10]. The FDA mandates a series of studies: analytical studies that demonstrate similarity, animal studies (if needed), and clinical studies focused on immunogenicity, Pharmacokinetics (PK), Pharmacodynamics (PD), and safety. More data are needed to receive the interchangeability designation for a biosimilar. Important guidelines from the FDA include the "Scientific Considerations in Demonstrating Biosimilarity" AND "Guidance (FDA, 2015) on Interchangeability" [11].
2. **European Union (EU) - EMA Biologic Pathway:** The European Medicines Agency (EMA) has one of the earliest regulatory frameworks in place for biosimilars based on Directive 2001/83/EC and Regulation (EC) No 726/2004. In this case, followed stepwise, the EMA expects studies to establish biosimilarity, including quality, non-clinical- and clinical-studies [12]. EU guidelines for the approval of these products focus on showing the biosimilarity to an EU-authorized reference product and stipulate that clinical studies should be performed, as appropriate, to evaluate immunogenicity and PK/PD [11]. At the European level, the EMA permits indication extrapolation with adequate scientific rationale. Key guidelines are: "Guideline on Similar Biological Medicinal Products" and "Guideline on Immunogenicity Assessment" (EMA, 2021) [13].
3. **Canada - Health Canada Biosimilar Pathway:** Canada regulates biosimilars *via* the Biologics and Genetic Therapies Directorate (BGTD). In Canada, this term is known as Subsequent Entry Biologics (SEBs). The regulatory guidelines necessitate extensive comparability studies, across quality, nonclinical, and clinical domains. Licensing also requires immunogenicity and safety data and strong post-market surveillance [14]. Interchangeability is not automatically granted, although indication extrapolation is acceptable. The main guideline for biosimilars is the (Information and Submission Requirements for Subsequent Entry Biologics) (Health Canada, 2010) [15].
4. **New Delhi - CDSCO Biosimilar Pathway:** In India, the Central Drugs Standard Control Organization (CDSCO) regulates biosimilars by the Drugs & Cosmetics Act of 1940 and updated Biosimilar Guidelines of 2022, created joint with the Department of Biotechnology (DBT) [16]. The guidelines demand comparative quality, animal, and clinical studies. Indication extrapolation is permitted, and post-marketing Pharmacovigilance (PMS) is required. Approval also needs pre-clinical and clinical comparability data, and bridging studies for a reference product if it is approved not in India. Safety is ensured by the vigilance of regulatory authorities in the form of post-marketing risk management plans (CDSCO, 2022) [17].

5. **Japan - PMDA biosimilar pathway:** In Japan, the regulation of biosimilars falls under the PMDA under the Pharmaceutical Affairs Law. The approval process mandates comparability studies for quality, safety, and efficacy. PMDA issued the guidelines in 2020 that enable the extrapolation of indications but not interchangeable automatically [18]. Generics approval of a drug requires comparability studies of adequate quality, nonclinical studies (if necessary), and pivotal studies examining PK/PD and safety. The first publication of "Guidelines for the Quality, Safety and Efficacy of Biosimilars" was published in 2009 (PMDA, 2009) [19].

6. **World Health Organization (WHO) - WHO Global Biosimilar Guidelines:** The World Health Organization (WHO) serves as an international reference point for outdated biosimilars assessments through the Expert Committee on Biological Standardization (ECBS). Comparability exercises are emphasized by the WHO and extrapolation of indications based on scientific rationale is supported. Prepared by the WHO in 2010, the "WHO Guidelines on the Evaluation of Similar Biotherapeutic Products" continues to serve as a foundational document for global harmonization initiatives around biosimilar regulation (WHO, 2010) [20].

7. **Australia - TGA Biosimilar Pathway:** The Therapeutic Goods Administration (TGA) regulates biosimilars in Australia under the Therapeutic Goods Act of 1989. The process follows stepwise through analytical studies, non-clinical studies, and clinical trials [18,20]. The TGA supports indicate extrapolation, but differences exist at the state level regarding interchangeability policy. Long-term biosimilar safety can only be established through post-marketing surveillance. TGA Biosimilar Guidelines were revised in 2021 and are consistent with current regulatory practices (TGA, 2021) [21].

8. **Brazil - Biosimilar Pathway:** In Brazil, the Agência Nacional de Vigilância Sanitária (ANVISA) governs biosimilars in an RDC 55/2010 framework [12]. There are two routes to approval for biosimilars under ANVISA: the Comparability Pathway, which necessitates a complete dossier containing comparative data, and the Individual Development Pathway, which requires complete non-clinical and clinical data [22]. The approval process consists of analytical studies, non-clinical studies, clinical trials, and risk management and pharmacovigilance plans to ensure safety in the post-market (ANVISA, 2010) [23].

9. **South Korea - MFDS Biosimilar Pathway:** In South Korea, biosimilars are governed under the Ministry of Food and Drug Safety (MFDS) through the MFDS Biosimilar Guidelines which were initially released in 2009 and amended in 2020 [22]. Comparability exercises are at the core of the regulatory framework, and indication extrapolation can take place as per scientific justification. Surveillance post-marketing is needed to maintain the safety of biosimilars. They can only be approved after quality comparability studies, non-clinical and clinical trials, and a risk management plan (MFDS, 2020) [24].

10. **China - NMPA Biosimilar Pathway:** In China, biosimilars are governed by the NMPA Biosimilar Guidelines that were released by the National Medical Products Administration (NMPA) in 2019. The guidelines allow comparability studies of quality, safety, and efficacy, as well as post-marketing pharmacovigilance. Extrapolation of indication is generally permissible if scientifically justified. Between analytical studies, non-clinical studies, and clinical trials, the regulatory process is robust to protect against an unsafe or ineffective biosimilar (NMPA, 2019) [25,26].

Challenges

Global regulatory, scientific, and market challenges-arising from the unique regulatory frameworks and manufacturing processes for biosimilars, requirements for clinical trials, and acceptance in the market-pose multiple hurdles for biosimilars. This poses a significant challenge for manufacturers who want to launch biosimilars to meet this demand as it impedes their ability to reach markets and limit their presence and accessibility [18].

We know that one of the main obstacles for biosimilar approval is the lack of harmonization in regulatory pathways in different regions. By providing differing guidelines from regulatory bodies-like the FDA, EMA, WHO, and other national agencies-it becomes difficult for manufacturers to streamline their development processes [22]. Five companies are based in the European region where the biosimilar guidelines have already matured, whereas in most other regions (e.g. in India, China, Brazil) the guidance is still developing, and often brings uncertainty for the manufacturer [27]. Approvals timelines and requirements further complicate global regulatory strategies, with different timelines in different regions delaying product launches. Moreover, expectations for comparability studies, and exchangeability status, vary from one country to another, making it complex for manufacturers to achieve global standards [28].

Interchangeability and switching policies also differ around the world, presenting another regulatory challenge. Unlike in the United States - where interchangeable status necessitates more clinical data - this high hurdle has made it more difficult to achieve wide acceptance of biosimilars. Unlike countries in the European Union and Japan, where decisions about interchangeability and how biosimilars are prescribed and used in practice are left to local authorities, in the United States the FDA makes these decisions for the entire country [29].

And the manufacturing and quality concerns related to biosimilars are just as large. Biological products are more challenging to manufacture than small-molecule drugs because they are more complex. Biosimilars need to match the reference product's quality attributes exactly, which is difficult due to the inherent batch-to-batch variability [30]. Also, the manufacture of biosimilars is costly and time-intensive: it can cost $100 to $200 million to develop, and the approval process takes 8 to 10 years. Meeting quality standards has become more challenging, requiring specialized facilities and advanced analytical tools, increasing the complexity of manufacture even further [31]. Another important consideration is post-marketing quality control; manufacturers need to maintain production quality, even after approval. This is particularly challenging because biological products are sensitive and needs effective pharmacovigilance to address the adverse events and management of immunogenicity risks [32].

Clinical and scientific assessments for biosimilar approval involve

many extensive comparability studies to prove that the biosimilar has a similar structure and function when compared to the reference product [33]. These are complex, resource-heavy studies - especially in the case of rare diseases, where patient recruitment is particularly difficult. Immunogenicity is another important consideration in developing a biosimilar. Manufacturers are required to show that there are no clinically meaningful differences in safety, efficacy, and immunogenicity compared to the reference product. Immunogenicity is difficult to predict but poses risks that regulators now require rigorous testing to address [34]. Extrapolation of indications, which allows a biosimilar to be approved for all its reference product's indications without individual clinical trials for each indication, is not universally accepted. In some countries, additional clinical data is necessary for each indication, prolonging the approval timeline [35].

Challenges in the market and commercial aspects play a key role in the adoption and success of biosimilars. Proving success is the hesitancy of healthcare providers and patients to regard biosimilars as effective and safe as their original counterparts, which can delay market acceptance. This skepticism is commonly driven by unfamiliarity with biosimilar regulation and their therapeutic equivalence. Biosimilar prices are also affected by the reimbursable availability of granted prices at different prices and the global range. Although biosimilars are anticipated to be cheaper than reference biologics, prices can still be unaffordable in LMICs, leading to restricted access to patients. Another major hurdle is patent litigation, with biosimilar manufacturers often having to wrestle with the opposition of the producers of the reference product in the courts [32]. After this long initial patent duration, additional patents are often generated in what is called the patent thicket, where different patents can capture different aspects of the biologic, creating additional barriers to market entry to the point where even a small delay can result in a significantly weakened market for the biosimilars [36].

Interchangeability and switching policies are a key challenge in the US (and other markets), where data are needed to establish that patients can switch between a biosimilar and its reference product and can do so without negative consequences. Automatic substitution of biosimilars has not been introduced in Europe, and switching responsibilities are assigned to healthcare providers, which creates differences in biosimilar uptake on a regional basis [37].

Finally, post-marketing and pharmacovigilance requirements represent an ongoing burden for biosimilar manufacturers. As biosimilars are approved, regulatory agencies rely on ongoing post-marketing surveillance data to verify safety and efficacy in real-world contexts. These pharmacovigilance systems are resource-intensive, and their maintenance can particularly burden smaller manufacturers, increasing the overall complexity and cost of biosimilar production as well as commercialization [38].

The global biosimilar approval landscape involves regulatory inconsistencies, manufacturing complexities, scientific requirements, and market acceptance challenges. The solution lies in unifying policies, bringing efficiency to the manufacturing process, improving studies, and increasing market recognition and acceptance for biosimilars [39].

Interchangeability Policies

There is one area in which they are treated differently:

1) In the US, once a company applies for interchangeability, it requires additional clinical data and is important for automatic substitution at pharmacies.

2) As for the EU, it has different policies from member state to member state, and automatic substitution is generally not allowed.

Do (3) India, Japan, China, and Brazil have no Automatic Interchangeability Policies? [50]

Case Studies

The approval of biosimilars, including Zarxio, Truxima, Hyrimoz, Ontruzant, and Erelzi, has vastly benefited public health, perception, and overall access to healthcare. Patent litigation, acceptance by physicians, and interchangeability remain critical hurdles. Effective regulatory strategies, high-quality clinical evidence, and post-marketing monitoring are essential for ensuring the safe use of biosimilars and maintaining the confidence of the healthcare community.

Regulatory challenges

1) Patent litigation is a significant roadblock to timely entry into the market.

2) More data on interchangeability will need to be prepared by the biosimilar developer to ensure they penetrate the depth of the market [51-53].

Clinical challenges

1) Biosimilars are initially viewed with skepticism, particularly in oncology and autoimmune disorders.

2) This skepticism can be tackled through physician education and post-marketing surveillance (RWE) [54,55].

Market impact

1) Biosimilars have helped lower healthcare costs significantly.

2) The availability of biosimilars fosters competition and lowers prices [56,57].

Post-Marketing surveillance

1) Long-term safety and immunogenicity require ongoing pharmacovigilance, including submission of periodic safety update reports (PSURs).

2) In gaining trust for biosimilar therapies, real-world data is taking a more prominent place [58].

Advanced Therapies

Cell therapies, gene therapies

Innovative Cell and Gene Therapies (CGTs) have recently started offering new therapeutic options for patients with previously untreatable conditions and hold the potential to disrupt the treatment paradigm for genetic disorders, cancers, and other chronic conditions by delaying disease progression or providing cures [7]. Yet they are also responsible for considerable challenges owing to their high costs, with the potential to dramatically drive-up spending and stretch payers' budgets [59].

The FDA regulates the approval of CGTs and also oversees the approval of biosimilars. A prediction of the regulatory landscape for potential CGT biosimilars must take into consideration both the current regulatory landscape for originator CGTs as well as for biosimilar products and how the two regulatory domains are likely to intersect [8]. Indeed, the development of follow-on CGT products is

Table 1: FDA approval of biosimilars.

Region	Manufacturer	Originator Product	Biosimilar	Approval Year	Article Reference	Supporting References
United States	Sandoz	Neupogen (Filgrastim)	Zarxio	2015	FDA Approval of Zarxio	FDA Guidance on Biosimilars
European Union	Samsung Bioepis	Herceptin (Trastuzumab)	Ontruzant	2019	EMA Approval of Ontruzant	EMA Biosimilar Guidelines
Canada	Celltrion	Remicade (Infliximab)	Inflectra	2017	Health Canada Approval of Inflectra	Health Canada SEB Guidelines
India	Biocon	Lantus (Insulin Glargine)	Semglee	2021	India Approval of Semglee	CDSCO Biosimilar Guidelines
Japan	Chugai Pharmaceutical	Avastin (Bevacizumab)	Abevmy	2020	PMDA Approval of Abevmy	Japan Biosimilar Guidelines
Australia	Pfizer	Humira (Adalimumab)	Hyrimoz	2018	TGA Approval of Hyrimoz	Australia TGA Biosimilar Guidelines
South Korea	Celltrion	Remicade (Infliximab)	Remsima	2016	MFDS Approval of Remsima	South Korea MFDS Guidelines
China	Shanghai Henlius	Rituxan (Rituximab)	Hanlikon	2022	NMPA Approval of Hanlikon	China NMPA Guidelines
WHO	Various	Multiple Biotherapeutics	WHO-listed Biosimilars	Various	WHO Reports	WHO Guidelines on SBPs

Table 2: Biosimilar Regulatory Pathways.

Region	Regulatory Agency	Legal Framework	Key Guidelines	Approval Process	Key References
United States (US)	U.S. Food and Drug Administration (FDA)	Biologics Price Competition and Innovation Act (BPCI Act), 2009	351(k) Pathway under the Public Health Service (PHS) Act; Demonstrate biosimilarity to a reference product	Analytical studies to demonstrate similarity; Animal studies (if required); Clinical studies for immunogenicity, PK/PD, and safety	FDA Guidance on Scientific Considerations in Demonstrating Biosimilarity; FDA Guidance on Interchangeability
European Union (EU)	European Medicines Agency (EMA)	Directive 2001/83/EC and Regulation (EC) No 726/2004	Most mature biosimilar framework; Requires comparative studies	Demonstrate biosimilarity to a reference product authorized in the EU; Focus on comparative studies for quality, safety, and efficacy	EMA Guideline on Similar Biological Medicinal Products; Guideline on Immunogenicity
Canada	Health Canada	Biologics and Genetic Therapies Directorate (BGTD)	Termed Subsequent Entry Biologics (SEBs); Requires comprehensive comparability	Comparative quality, non-clinical, and clinical data; Immunogenicity and safety data; post-market surveillance	Health Canada Guidance for Sponsors: Information and Submission Requirements for SEBs (2010)
India	Central Drugs Standard Control Organization (CDSCO)	Drugs & Cosmetics Act, 1940 and Biosimilar Guidelines (2016, updated 2022)	Biosimilar Guidelines (2022) developed jointly by CDSCO and DBT; Requires comparative quality studies	Pre-clinical and clinical comparability data; post-marketing risk management plan; Bridging studies required if reference product is approved outside India	CDSCO Biosimilar Guidelines (2022)
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	Pharmaceutical Affairs Law	Comparability studies required in quality, safety, and efficacy; Extrapolation of indications	Quality comparability studies; non-clinical studies (if required); Clinical trials for PK/PD and safety	Guidelines for the Quality, Safety, and Efficacy of Biosimilars (2009)
World Health Organization (WHO)	WHO Expert Committee on Biological Standardization (ECBS)	N/A	Provides a global reference framework for biosimilar evaluation	Comparability exercises; Clinical and non-clinical studies; Support for extrapolation of indications	WHO Guidelines on the Evaluation of Similar Biotherapeutic Products (SBPs) (2010)
Australia	Therapeutic Goods Administration (TGA)	Therapeutic Goods Act, 1989	Requires stepwise comparability exercises; Supports indication extrapolation	Analytical studies; non-clinical and clinical studies; post-marketing surveillance	TGA Biosimilar Guidelines (2013, updated 2021)
Brazil	Agência Nacional de Vigilância Sanitária (ANVISA)	RDC 55/2010	Two pathways for approval: Comparability Pathway and Individual Development Pathway	Analytical studies; non-clinical and clinical studies; Risk management and pharmacovigilance	ANVISA RDC 55/2010
South Korea	Ministry of Food and Drug Safety (MFDS)	MFDS Biosimilar Guidelines (2009, updated 2020)	Emphasizes comparability exercises; Allows extrapolation of indications	Quality comparability studies; non-clinical and clinical trials; Risk management plan	MFDS Biosimilar Guidelines (2009, updated 2020)
China	National Medical Products Administration (NMPA)	NMPA Biosimilar Guidelines (2019)	Requires comparability studies for quality, safety, and efficacy; Allows indication extrapolation	Comparability studies for quality, safety, and efficacy; Indication extrapolation; post-marketing pharmacovigilance	NMPA Biosimilar Guidelines (2019)

Table 3: Global Biosimilar Approval Challenges [40-42].

Category	Challenges	Impact
Regulatory	Inconsistent regulatory frameworks globally	Delays in global approval and commercialization
Manufacturing	Complex and costly manufacturing processes	Higher development costs and longer timelines
Clinical	Rigorous comparability and immunogenicity studies	Resource-intensive clinical trials
Market Acceptance	Lack of awareness and skepticism among healthcare providers	Slow biosimilar uptake
Pricing and Reimbursement	Varying pricing policies and reimbursement strategies	Limited patient access in some regions
Interchangeability	Interchangeability requirements vary across regions	Complicates switching and substitution
Pharmacovigilance	Post-marketing surveillance requirements	Adds ongoing regulatory burden

Table 4: Key Regional Challenges.

Region	Key Challenges	References
United States	Interchangeability requirements; Complex patent litigation	40
European Union	No automatic substitution; Physician acceptance	41
Canada	Market acceptance and slow physician adoption	42
India	Evolving regulatory framework; Local clinical trial requirements	43
Japan	High regulatory standards; No automatic interchangeability	44
South Korea	Strict post-marketing surveillance	45
China	Complex regulatory pathway; High manufacturing costs	46
Brazil	Two-pathway approval system; Local clinical data requirements	47

conceptually hampered by the uncertainties that persist with respect to the regulatory environment for novel CGTs, so increasing regulatory clarity for novel CGT products will help inform how biosimilarity will be defined for these products [59].

CGTs are one of several classes of transformative therapies targeting disease progression and restoring or enhancing function, with a potential for durable or long-term efficacy, which may make them an optimal solution [60]. However, the regulatory system for CGTs, which use increasingly sophisticated technologies [61], is still only barely out of the cradle. CGT manufacturers encounter challenges throughout the development lifecycle in ensuring quality via manufacturing and testing, as well as efficiently establishing [62] safety, efficacy, and durability [63].

One noted that previous studies on biosimilars launched in both the European Union and the United States - for even less complex therapeutic protein products - have found reference product differences. Additional regulatory guidance, including information on flexibility opportunities, will enable sponsors to fully glean CGT reference products prior to biosimilar development that will inform standards for biosimilar characterization and development in this field. The nature of living cells, particularly cell therapies, is very complex, and this is very much the case here (in CAR T cell therapies). FDA has issued high-level guidance on preclinical research considerations and recommendations addressing CGTs [64]. Moreover, the agency also discussed in guidance the safety concerns and lack of clinical experience with CGTs that sponsors should evaluate when designing early-phase clinical trials of CGTs [65]. These guidance documents provide an initial framework to set quality standards for CGTs, yet much remains to be clarified for comprehensive characterization and clinical development.

Holds on CGT clinical trials are rampant, accounting for about 61 percent of all holds placed by FDA's Centre for Biologics Evaluation and Research (CBER) in 2022 [66], (though trending downward in absolute numbers, from a peak of 147 in 2018 to 70 in 2022). To illustrate, congressional leadership for the House Energy and Commerce Committee's Health Subcommittee raised the subject of clinical holds for CGTs in a letter directed to the CBER director and in a post-letter hearing [67]. The clinical hold issue emerges in the context of CGT research exploding to 1687 clinical trials based on figures from a recent industry report [68] Clinical trial holds are usually lifted but some companies decide against continuing trials [69]. To streamline the review of CGT, the FDA issued draft guidance encouraging sponsors to conduct a single 'umbrella' trial studying multiple iterations of CGT for one disease [70] and reorganized the Office of Tissues and Advanced Therapies into the Office of Therapeutics (OTP) to explicitly fast-track technology with CGT applicants.

Tissue engineering

Tissue engineering defines a combinatory approach between scaffolds, cells and/or biologically active molecules to repair, maintain, assist or replace damaged tissues and organs. A scaffold is used as a starting point of tissue engineering, which can contain various types of materials from naturally produced proteins to biocompatible synthetic polymers. Some tissue engineering therapies employ a pre-existing scaffold by removing the cells from a donor organ through a process referred to as decellularization, leaving behind only the original protein-based scaffold or Extracellular Matrix (ECM). Cells - and sometimes, other growth factors to help spur the cells to take root - are added, enabling a tissue or organ to develop and grow ex vivo. Biomaterials are any material purposefully designed to interact with a patient's living biological system for a medical purpose. These biomaterials are typically used for load-bearing applications as scaffolding for engineered tissues [71]. Tissue-engineered products

Table 5: [48,49].

Biosimilar	Reference Product	Indication	Region	Regulatory Pathway	Key Challenge	PMS Requirement
Zarxio	Neupogen	Neutropenia	US	FDA 351(k)	Patent litigation	Pharmacovigilance plan
Truxima	Rituxan	Oncology, RA	US	FDA 351(k)	Extrapolation to oncology	PSUR, RWE
Hyrimoz	Humira	Autoimmune diseases	US, EU	EMA Centralized, FDA 351(k)	Patent litigation	RMP, Immunogenicity monitoring
Ontruzant	Herceptin	Breast Cancer	US, EU	EMA Centralized, FDA 351(k)	Extrapolation of indications	PSUR, RWE
Erelzi	Enbrel	Autoimmune diseases	US, EU	EMA Centralized, FDA 351(k)	Patent litigation	Pharmacovigilance plan

fall under the category of biosimilar products - these are considered large, complex molecules synthesized through biotechnology. Some other examples of biosimilar products are [72-83]:

a) Recombinant proteins and hormones

b) Monoclonal antibodies (mAbs)

c) Cytokines

d) Growth factors

e) Gene therapy products

f) Vaccines

g) Cell-based products

h) Gene-silencing or gene-editing therapies

i) Stem cell therapies

Conclusion

Biosimilars can be cost-saving options for biologic treatments, however, varying regulations and interchangeability policies act as barriers to their global access. While EMA and FDA have both paths towards approval, they differ in their guidelines, blocking the way for the manufacturers. More clarity on the place of CGT in regulatory framework It is essential to deal with issues of manufacturing difficulties, physician skepticism, and admission to the market. Ensuring the safety, efficacy, and accessibility of biosimilars for patients worldwide will require harmonization of regulatory pathways, increased utilization of real-world data, and adoption of technological innovations. It is imperative for national authorities to partner with biopharma to boost biosimilar uptake moving forward. Addressing these challenges will help enable biosimilars to enhance health care and lower treatment costs across the globe - leading to a transformative shift in the pharmaceutical sector.

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