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Regulating Biosimilars: A Comparative Study of The U.S. FDA and E.U. EMA Approaches

Biologics- complex medicines derived from living organisms- have revolutionized the treatment of chronic and life-threatening diseases, ranging from cancer to autoimmune disorders. However, their high cost has posed a significant burden on healthcare systems worldwide, prompting the emergence of biosimilars: highly similar, lower-cost alternatives to original biologic drugs. The introduction of biosimilars was a real game-changer from the public health perspective, decreasing the huge costs of biologic treatment and making them more accessible to patients of a lower socioeconomic status. As the global biosimilars market continues to expand, the regulatory frameworks that govern their approval, interchangeability, and market entry have become the subject of critical legal, economic, and public health debate.

Two of the most influential regulatory bodies in the world- the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have developed distinct pathways for the evaluation and authorization of biosimilars. The FDA's framework, formalized through the Biologics Price Competition and Innovation Act (BPCIA) of 2010, reflects a relatively recent and litigation-heavy approach, while the EMA, having approved the world's first biosimilar in 2006, offers a more established and scientifically flexible model. These differing strategies not only influence drug development and commercialization but also shape global access to affordable medicine.

This paper aims to provide a comparative analysis of the U.S. and E.U. regulatory systems for biosimilars, examining their legal structures, scientific standards, and market uptake mechanisms. In doing so, it explores the broader implications for innovation, competition, and healthcare equity. By analyzing the convergences and divergences between the FDA and EMA, this study seeks to identify regulatory best practices and offer policy recommendations for a more harmonized and effective global biosimilar landscape.

While Biosimilars cannot be exact copies of the biologic they are synthesizing, they mimic the active ingredient in the reference biologic. The need for Biosimilars derives from the often-high price-tags associated with biologics which can present a challenge in getting them to the patients who need them. Between research and development and clinical testing, studies have shown that the development of new biologics- including the cost of failures- can exceed $2 billion and can take 10 years or longer and that's on top of developing and deploying the state-of-the-art technology necessary for manufacturing.

Even with insurance, cost-sharing agreements for biologics can leave patients with a hefty bill or the inability to access the treatments at all. Drug companies, doctors, and governments want to expand access to the benefits of these treatments and that’s where biosimilars come in.

Drug companies can now charge lower prices for biosimilars because much of the upfront development phase has been completed. While biosimilars go through testing to ensure they are as safe and effective as the original biologics, it does not cost billions of dollars to create this new class of drugs.

According to the Association for Accessible Medicines, biosimilars have the potential to save the US healthcare system more than $133 billion by 2025 (*AccessibleMeds.org*). Reducing overall costs means more patients may be able to access these essential medicines and provide savings to the healthcare system, which can free up resources for other areas of patient care.

So why compare the FDA and EMA approaches to Biosimilar regulations?

The European Medicines Agency (EMA) and Food and Drug Administration (FDA) are the two most renowned agencies that govern drug approval procedures in the European Union and United States, respectively.

They are often viewed as counterparts, functioning in essentially the same way and differing mostly with respect to the covered region. While both countries agree on the definition of a Biosimilar- which is that the biological product is highly similar to the reference product and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product (*fda.gov*); the two agencies widespread efforts to standardize regulatory processes, such as adoption of ICH guidelines who's mission is to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed, registered and maintained in the most resource efficient manner (*ICH Official Web Site : ICH*) and joint international scientific meetings, many important differences still do exist, creating numerous challenges to the pharmaceutical industry.

Companies now need to prepare separate strategies, hire additional personnel and sometimes conduct additional studies to satisfy requirements of both agencies as both countries represent the two largest pharmaceutical markets in the world, together accounting for over 70% of global biologics and biosimilars sales (*iqvia.com*). This regulatory divergence is rooted in the historical timelines of biosimilar adoption by each agency.

The EMA introduced biosimilars guidelines many years ahead of the FDA, resulting in an early market growth and fierce competition between numerous biosimilar brands. The first biosimilar in the EU was licensed in 2006. In contrast, the first US biosimilar, Zarxio was approved nine years later in 2015.

The EMA's early approach to regulatory pathways comprised and still comprises of a centralized evaluation process where all biosimilars in the E.U. are evaluated through the EMA's centralized procedure, which results in a single marketing authorization valid across all E.U. member states. The E.U. also emphasizes scientific flexibility as the EMA requires a comprehensive comparability exercise but allows for case-by-case tailoring of clinical data requirements, especially as scientific understanding of biologics evolves.

The foundation of the biosimilar framework in the E.U. lies in Directive 2001/83/EC and Regulation No. 726/2004, which define biosimilars and empower the EMA to oversee their authorization. While the EMA also approves biosimilars as interchangeable which refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect (*ema.europa.eu*) it does not make formal interchangeability determinations at the EU level. Instead, individual member states decide on substitution policies, resulting in variable national practices. This lack of an E.U. wide "interchangeability designation" is important as it leads to faster penetration of biosimilars across the European markets.

Additionally, the 8+2+1 rule established under the same directive outlines the period during which reference biologics enjoy protection from biosimilar competition with eight years of data exclusivity during which no biosimilar application or "aBLA" referencing the original biologic's clinical trial data can be submitted. After the 8-year data protection expires, two years of market exclusivity is granted, during which biosimilars may not be placed on the market plus a one year possible extension is granted if the reference product obtains approval for a new therapeutic indication within the first eight years that provides significant clinical benefit over existing therapies.

With over 15 years of experience, the EMA has continually issued multiple product-specific guidelines and maintains active collaboration with stakeholders, making the E.U. a global model in biosimilar regulation.

On the other side of things, while initially the level of similarity testing and the time required for the FDA to approve a new product, significantly exceeded those of the EMA, recent times provide change, as since then the time taken during registration processes in the U.S has been successfully streamlined and now the FDA approves many biosimilars several months before the European agency, overtaking EMA's position as a leader in this sector (*clinicalleader.com*). In some cases the approval is granted by the FDA without late-phase clinical studies. This has resulted in a rapid increase in biosimilar's uptake and a substantial decrease in healthcare costs.

The Biologics Price Competition and Innovation Act of 2009 ("BPCI Act") was passed as part of health reform "Affordable Care Act" that President Obama signed into law on March 23rd, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA licensed reference product. A biological product that is demonstrated to be "highly similar" to an FDA-licensed reference product may rely for licensure on, amongst other things, publicly available information regarding the FDA's previous determination that the reference product is safe, pure and potent. This licensure pathway permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act based on less than a full complement of product-specific preclinical and clinical data.

Applicants must demonstrate biosimilarity through a stepwise approach involving analytical, animal, and clinical studies. "Interchangeability"- a distinct and higher legal standard requires additional data showing the biosimilar can be substituted without clinical differences. While some drugs do get approved as biosimilars by the FDA they do not attain interchangeability status in the U.S., leading to distrust in the product.

Additionally, in contrast to the E.U's eight-year exclusivity deal, the reference biologic in the U.S. is granted 12 years of market exclusivity, and approved biosimilars receive a one-year exclusivity period if designated interchangeable.

In addition to these exclusivity provisions, U.S. regulation also addresses patent litigation through a unique mechanism. The BPCIA introduced the so-called "patent dance", a complex, voluntary exchange of patent information between the biosimilar applicant and the reference product sponsor which aims to resolve patent disputes before marketing the biosimilar. The patent dance involves two stages and multiple exchanges of information favouring larger, more financially stable biotech companies due to the significant brunt of legal costs.

The FDA is also solely responsible for approving biosimilars, issuing scientific guidance, and determining interchangeability status for all U.S. states.

While the EMA and FDA share similar views in regard to biosimilars and their relationship to reference drugs, biosimilar developers are still bound to use as a reference product a biological medicine originating from the given territory. Thus, the EMA application must be based on studies performed with the E.U.-sourced reference, while for the FDA application, it is necessary to use the U.S-sourced product. This territorial requirement limits the global harmonization of biosimilar development, leading to duplicative studies and increased development costs.

While both systems aim to ensure the safety, efficacy, and quality of biosimilars, their underlying legal philosophies diverge. The U.S. model emphasizes intellectual property protection, legal adjudication, and scientific conservatism, whereas the EU framework prioritizes public health access, centralized scientific oversight, and early market competition. These foundational differences have profound implications for the subsequent stages of biosimilar development and healthcare outcomes as although regulatory approval is a critical first step, biosimilars must also navigate the perplexing realities of market access to achieve widespread clinical use. These

regulatory philosophies extend beyond approval pathways and deeply influence the broader ecosystem in which biosimilars operate.

The United States and the European Union differ not only in regulatory design but also in how biosimilars are priced, reimbursed, substituted, and accepted by healthcare professionals and patients. These structural and cultural factors profoundly shape the uptake and financial sustainability of biosimilar markets.

Within the U.S, pricing and reimbursement policies are often fragmented and market-driven, heavily relying on public players like Medicaid and Medicare and private players like Pharmacy Benefit Managers or PBM's. Medicare Part B covers many biologics and reimburses providers based on average sales price plus a fixed margin, which can disincentivize the use of lower cost biosimilars. PBMs, acting as intermediaries for private insurers, wield considerable power in formulary decisions and rebate negotiations i.e. confidential agreements made usually between pharmaceutical manufacturers and payers such as insurance companies, PBMs, or government health programs where the manufacturer offers discounts or rebates off the list price of a drug in exchange for increased market access. This lowered net price of the drug is not always passed to the patient.

Moreover, patient trust in biosimilars is heavily influenced by branding, prescriber endorsement, and insurance coverage- all of which can be inconsistent in the U.S. leading to hesitancy amongst prescribers who may fear liability leading to low market penetration.

By contrast, in the European Union, pricing and reimbursement decisions are typically made at the national level through Health Technology Assessment agencies. These bodies evaluate the cost-effectiveness, clinical benefit, and budget impact of new therapies, including biosimilars. Many E.U. countries employ reference pricing systems, where the biosimilar is benchmarked against the cost of the originator product. The availability of state-funded healthcare and centralized negotiation often results in aggressive price competition, with biosimilars entering the market at

discounts of 20-40%, and sometimes over 50%. Additionally, greater regulatory transparency, early access to post-market data, and proactive outreach by health authorities have helped normalize biosimilars as standard-of-care alternatives leading to higher market penetration.

A good case study to highlight the differences between biosimilar markets in the E.U. vs. the U.S. is the market penetration differences of biosimilars of the drug Remicade.

Used to treat Crohn's disease, the reference product Remicade developed by Janssen Biotech has faced competition from multiple biosimilars, most notably Inflectra and Remsima both approved in the E.U. and the U.S. While the biosimilars enjoyed rapid market integration within the E.U. through centralised approval from the EMA resulting in quick geographic reach, incentivising substitution policies and prescriber confidence leading to speedy adoption things looked different in the U.S. as Inflectra approved under the BPCIA faced interchangeability hurdles as it failed to acquire the additional legal tier, payer complexity as insurers were slow to include biosimilars on formularies, favouring the originator due to rebate lock-ins despite Inflectra being 20% cheaper, and physician hesitancy. All these factors led to biosimilars capturing over 90% of the Remicade market in the EU and only 20% of the market in the U.S.

The Remicade study encapsulates the focus of each country's framework.

The U.S. framework leans more heavily toward protecting innovation. The 12-year exclusivity period, coupled with the legally distinct "interchangeability" designation, reinforces strong intellectual property rights and gives originator companies prolonged market control. The BPCIA's provisions while aimed at fostering a biosimilar pathway, often favour established firms with the legal and financial capacity to navigate the complex "patent dance" and engage in extensive litigation. From an innovation standpoint, this environment incentivizes high-risk R&D and rewards biological pioneers with time to recoup their investment.

However, this innovation orientation comes at the cost of delayed biosimilar access and limited competition. Uptake has been slow and inconsistent across the States, largely due to fragmented

insurance markets, prescriber hesitation, and the dominance of rebate-driven pricing strategies by Pharmacy Benefit Managers. For patients, this has translated into higher prices and restricted access, particularly for the uninsured or underinsured.

In contrast, the E.U. framework, while still protective of originator interests, places stronger emphasis on timely market access and cost containment. The 8+2+1 exclusivity structure, lack of a formal interchangeability designation, and widespread use of health technology assessments allow biosimilars to enter the market earlier and more aggressively. Centralized procurement systems and national substitution policies combined with public healthcare systems promote competition and drive significant savings for national health budgets.

The future of biosimilars rests not only on scientific progress, but also on the regulatory decisions that shape their development and accessibility. As demonstrated through the comparative analysis of the FDA and EMA frameworks, both innovation and access can be promoted but only through strategic regulatory choices and active industry participation. To support a sustainable biosimilar ecosystem, several key areas of reform and collaboration should be prioritized by both regulators and industry stakeholders.

An area where reform is needed is the legal and procedural framework surrounding interchangeability. In the United States, the FDA's formal designation creates a barrier to pharmacy-level substitution that does not exist in the European Union. While the intent is to protect patient safety, the rigidity of the interchangeability standard may discourage biosimilar use. Aligning more closely with the E.U. model where interchangeability is left to prescribers, and national policy could help garner greater confidence among physicians and reduce market entry hurdles.

Moreover, even when biosimilars are approved, their uptake remains uneven, particularly in the U.S. due to a combination of economic disincentives and limited trust among prescribers and

patients. Both regulators and industry must invest in educational outreach that clearly communicates the science behind biosimilarity and the rigorous nature of regulatory reviews.

In conclusion, biosimilars present a unique opportunity to reshape access to biologic therapies once the domain of high-cost, monopolised drugs into a more competitive and equitable field. However, realising this potential requires far more than scientific equivalence. Regulators must adopt flexible, science-driven approval policies, work collaboratively across borders, and actively promote trust and uptake. Industry actors must similarly commit to transparency, responsible pricing, and strategic partnerships that extend the reach of biosimilar therapies. Together, these reforms can ensure that the promise of biosimilars is not only achieved, but sustained for patients, payers, and innovators alike.

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