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ARTICLE COMMENTARY

Bridging the gap: The future of biosimilars regulations

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ABSTRACT

Biosimilar vaccines and immunotherapeutic are innovative approaches in medical research. This commentary addresses the current disparities in regulations of biosimilar vaccines and immunotherapeutic products across different nations. It also navigates the benefits of global regulatory alignment and challenges that may be encountered. The current discrepancies in regulations across different countries, which pose significant challenges for the development and approval of biosimilar vaccines and immunotherapeutic products. These disparities often lead to delayed market access, increased development costs, and hindered innovation. The commentary stresses that such obstacles could be mitigated through harmonized regulations, resulting in faster approvals, reduced healthcare costs, and improved patient outcomes. Moreover, the commentary explores the specific complexities associated with biosimilar vaccines and immunotherapeutic, such as the intricate evaluation of biosimilarity due to their molecular composition and immunogenic properties. In conclusion, the editorial advocates for collaborative efforts to overcome the challenges in achieving global regulatory harmonization for biosimilars. This includes establishing uniform standards, fostering international cooperation among regulatory agencies, and promoting educational initiatives for healthcare providers and regulators. The ultimate goal is to ensure that patients worldwide have timely access to safe, effective, and affordable biosimilar treatments.

Keywords
Biosimilars; Vaccines; Immunotherapeutics; Biopharmaceutics; Guidelines; Regulations

Introduction

Biopharmaceuticals encompass a broad range of medications, including proteins and non-proteins, produced through various technologies. These include not only monoclonal antibodies generated via hybridoma technology but also other crucial treatments like erythropoietin, insulin, and growth hormones created using recombinant DNA methods. Vaccines and immunomodulators are also examples of biopharmaceuticals. Additionally, certain biopharmaceuticals, such as the hemoderivative Factor VIII and heparin, are derived from biological sources without employing recombinant techniques.[1] As many biopharmaceuticals' patents have expired, a class of substitute medications known as biosimilars has emerged.[1] According to NHS England, a biosimilar is "a biological medicine which has been shown not to have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy."[2] Biosimilar medicines offer an appealing approach for closing healthcare equity gaps among populations without access to expensive biologic treatments. Biosimilars in the United States have been demonstrated to reduce spending on biologic medicines by billions, underscoring their role in creating more equitable health outcomes.[3] Owing to their numerous advantages, biosimilar adoption rates vary considerably; adoption rates are highest in Europe as opposed to the United States, due to knowledge gaps among healthcare professionals contributing to decreased usage rates. Therefore, efforts aimed at expanding biosimilar access would significantly benefit low-income individuals, older adults, rural populations, and indigenous peoples, among others – offering essential treatments at significantly less expense.[3]

Approval of biosimilars relies on demonstrating their high similarity to an originator through comprehensive analytical, non-clinical, and clinical testing, without significant differences in safety, purity, and potency.

[4]The initial biosimilar guideline received approval from EMA in 2006,[5] while the US FDA issued the Biologics Price Competition and Innovation Act (BPCI Act) in 2009.[6]

The WHO has offered guidance to 194 countries, encompassing the regulatory approval of biosimilars; however, concerns persist regarding its scientific validity.[7,8] Numerous guidelines have also been established in several countries around the world, which requires extensive testing for efficacy and animal toxicology.[9] Moreover, although the WHO's most recent biosimilar guidelines and recommendations reflect the perspectives of international regulatory bodies, they are insufficient to create a strong scientific foundation.[7] Concerns about the growing expense of healthcare, the rising cost of research and development, and the need to quickly make new, safe treatments available to patients have prompted the need to rationalize and harmonize these regulations.[10] In contrast to the development costs of biosimilars, which range between USD 100 million and USD 300 million, the cost of developing a reference biologic drug has been significantly higher. A recent report by Deloitte highlighted that the average cost for developing a new drug, including reference biologics, has reached about $2.3 billion.[11]

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Sarfaraz K Niazi and colleagues proposed guidance for streamlining biosimilar approval processes without compromising standards.[10] They reported that despite their potential, regulatory pathways have been hindered by costly and complex requirements, including extensive animal and efficacy studies. While agencies like the EMA, MHRA, and FDA have simplified some requirements, others insist on strict adherence to these comprehensive guidelines, slowing indigenous biosimilar development.[10]

To build upon the foundational insights provided by Sarfaraz K. Niazi and colleagues on the need for streamlined biosimilar approval processes, this commentary extends the discussion by highlighting the specific challenges and potential solutions within the current global regulatory frameworks. We explore the diverse regulatory approaches adopted by key agencies such as the WHO, EMA, and FDA, and their impact on the speed and cost of biosimilar development. Our analysis also emphasizes the critical need for international cooperation and educational initiatives to achieve a harmonized regulatory environment. This commentary aims to shed light on the current disparities in biosimilar regulations across different countries and the need for a more harmonized approach. It will also explore the benefits of global regulatory alignment, such as increased accessibility, improved patient outcomes, and stimulation of innovation in the biopharmaceutical industry.

Current regulatory landscape

Biosimilar development involves a rigorous process that includes analytical, functional, and nonclinical evaluations, as well as clinical trials.[12] Key issues in this development include selecting the appropriate reference medicine, which must demonstrate similarity in quality, safety, and efficacy through a stepwise approach. Functional analytical studies play a critical role in this process, assessing the structural and functional attributes of biosimilars compared to their reference products. These studies aim to validate the biosimilar's comparability rather than independently establishing efficacy and safety. Despite the growth in knowledge about biosimilars, discrepancies remain regarding aspects like immunogenicity, interchangeability, and nomenclature. Maximizing the benefits of biosimilars requires collaboration between regulators and developers to ensure quality, safety, and efficacy standards are maintained[12]

The WHO has made great efforts to harmonize the regulatory framework and nomenclature surrounding biosimilars on a global scale since the publication of its guidelines for the regulatory evaluation of biosimilars in 2009.[13,14] Many authorities have based their guidelines on existing guidelines produced by other agencies mainly by WHO, but also by EU and USFDA. The extent of overlap of the guidelines varies.[14] Significant advancement has been made in the adoption of regulatory guidelines since 2010.[15] In 2005, EMA released a general framework guideline for biosimilars, which introduced the fundamental concepts of biosimilarity, which form the foundation for most other guidelines. Following technological advancements and application review experience, an updated draft guideline was released in 2013 and approved by the Committee for Medicinal Products for Human Use (CHMP) in October, 2014.[16] In addition, EMA created additional guidelines for comparability exercises that took quality, non-clinical, and clinical aspects into account, as well as a special guideline for immunogenicity assessment. With the experience gained from the approval of biosimilars over time, the EMA's regulatory process is strong, and the guidelines are updated and revised on a regular basis.[17] Furthermore, since the issuance of the WHO guidelines for regulatory evaluation of biosimilars in 2009, WHO has made substantial efforts to harmonize the terminology and regulatory framework for biosimilars worldwide. Over the past decade, these guidelines have played a pivotal role in establishing the regulatory framework for biosimilars in various countries and fostering greater regulatory convergence at the global level. As a result, the terminology used for biosimilars has become more consistent, and biosimilars are now approved in all participating countries.[14]

Harmonization of biosimilar regulatory standards is vital in providing accessible, safe, effective, and high-quality biosimilar products worldwide. These endeavors involve several strategies, including the establishment of comprehensive guidelines by regulatory entities like the FDA and EMA.[14,18] However, differences among these guidelines demonstrate the complexity of classifying biosimilar drugs and verifying their long-term equivalence with their original source product in terms of efficacy and safety. Initiatives such as information sharing, international regulatory approvals, and the development of pharmacovigilance systems are essential. Furthermore, the evolving nature of biosimilars necessitates clearer guidance. The World Health Organization's role in setting international standards serves to reinforce a collective drive toward harmonization. The ICH's proposal for an integrated regulatory guideline seeks to make biological drugs more readily accessible and safe, reflected in legislation such as the 2009 Biologics Price Competition and Innovation Act in the US, which expedited biosimilar approval pathways.[6] Europe has taken strides toward the harmonization of biologicals through the approval of numerous biosimilars for various biological products; this marked progress toward global regulatory alignment as it reinforced education's key role in building trust among healthcare systems and patients alike.

However, disparities in these guidelines do exist, such as the inconsistency in nomenclature and terminology used for biosimilars and their assessment. For example, in 2019, the term "biosimilars" was used in the guidelines of Canada, EU, China, Egypt, Iran, Jordan, Malaysia, Singapore, Thailand, USA, and Zambia, while "biosimilar products" was used in Ghana, Indonesia, and Korea, "similar biologics" was used in India, "similar biological medicinal products" in Ukraine, "follow on biologics" in Japan, and "bioanalogue" in Russia.[14] The term "comparability" is often used instead of "similarity," for the comparison of a biosimilar candidate's structural or biological characteristics with those of its reference product.[6] A regulatory concept known as "extrapolation" where regulatory guidelines may allow the use of a biosimilar in additional indications without the need for independent clinical trials if it shows similarities to an approved reference biologic in one of those indications. Discrepancies in the criteria and processes

concerning extrapolation could make it more difficult for biosimilar to be approved for new indications, which could delay their timely introduction into the market. Another example on discrepancy that in order to serve as a reference product, the WHO recommends that the product be selected must have been on the market for a "suitable period" and have demonstrated its quality, safety, and efficacy. However, there is no defined period of time,[6] calling for more clarification and harmonization with this regard.

The EMA evaluates biosimilars against the same standards of pharmaceutical quality, safety, and efficacy as all biological medicines. This process involves comprehensive comparability studies to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference medicine in terms of safety, quality, and efficacy. Similarly, the FDA also ensures that biosimilars are safe and effective treatment options for various conditions, emphasizing the importance of increasing access to lifesaving medications at potentially lower costs. The regulatory pathways for drug approval, including biosimilars, differ significantly between the EMA and the FDA. The FDA's process is centralized, requiring submission of an Investigational New Drug (IND) application that includes preclinical data, manufacturing information, and clinical trial plans. The FDA takes 30 days to review the IND before proceeding[19]. On the other hand, the EMA operates a centralized process for certain medicines, including biosimilars, which are often used for biotechnology products, medications for HIV/AIDS, cancer, and other significant diseases. This process results in a recommendation for approval across all EU member states, with the European Commission making the final decision.[19]

The US FDA has requires additional evidence for interchangeability to approve a biosimilar. For instance, the US FDA approved Wezlana (ustekinumab-auub) as a biosimilar to and interchangeable with Stelara (ustekinumab) for multiple inflammatory diseases.[20] The FDA emphasizes comparability across parameters. On the other hand, biosimilar development and access are facilitated by the EMA, which reviews biosimilars based on classification-based guidelines and has authorized their interchangeability with reference medications. Additionally, pharmaceutical companies or research organizations might have to generate more data or perform needless tests, which would waste resources and delay time to market. For example, the biosimilar product usually undergoes animal testing after it satisfies the analytical similarity requirements. Even though it is known that the unique mechanism of action of biological products primarily involves receptor binding, it is impossible since most animal species lack these receptors.[6] The regulatory frameworks that vary by region with regard to exclusivity periods, assessment fees, and interchangeability criteria have a substantial impact on the adoption of biosimilars, their market penetration, and the potential for cost savings in healthcare.[21] Developers seeking FDA interchangeability designation for biosimilars must provide additional evidence proving they can switch their biosimilar with its reference product without impacting safety or effectiveness, often through switching studies where patients alternate between both treatments. Such studies incur greater development costs, as additional clinical trials must be conducted to demonstrate interchangeability beyond standard biosimilarity assessments; this process ensures adherence to stringent interchangeability criteria, potentially increasing costs and time investment for developers.

The regulatory bodies in the Middle East North Africa (MENA) region countries like Saudi Arabia, UAE, Jordan, Tunisia and Egypt have adopted guidelines resemble the EMA, FDA and WHO guidelines. However, they tend to be conservative in approaching and assessing biosimilar and adopt the concept of "reference" approval/country, making them some way behind Europe in terms of biosimilar approval.[22]

There is no consensus on the pathways adopted by the regulatory agencies in the MENA region for the biosimilars approval. In the Gulf region, the Saudi Food and Drug Authority regulatory framework follows FDA and EMA guidelines with specificities that accommodate for the local and regional Gulf Cooperation Council (GCC) requirements. In the UAE, biosimilar approval follows the EMA and WHO guidelines World for international markets and the UAE standards and guidance set by the GCC for local markets. The Jordanian FDA's not only follows the EMA guidelines for quality and comparability assessment, It also authorizes the approval of manufacturing sites as a prerequisite to product approval and filing, leading to vigilant and strict approval regulations. Nevertheless, more privilege goes to biosimilars that are manufactured and marketed in reference countries, such as UK, USA, Germany, France, Netherlands, Sweden, Australia, Austria and Japan. In Egypt, guidelines for biosimilar products approval adopts the EMA and FD safety and quality considerations, the WHO guidelines on the evaluation of similar biotherapeutic products.

In Saudi Arabia, different approval departments do not work together simultaneously. Instead, each new product is separately approved by each department, which make it a lengthy approval process and explain the few number of biosimilars approved in Saudi Arabia including Binocrit, Grastofil Omnitrope, Remsima, and Zarzio compared with 50 or more biosimilars approved by EMA.

More obvious varied approach and lack of agreement exists between countries of MENA regarding biosimilar interchangeability and switching. In Saudi Arabia, biosimilarity alone is not enough for switching and only biosimilars approved by EMA are considered interchangeable. Additionally, a clinical trial that involves switching represents a pre-request to cross-switching approval. Furthermore, switching is approved by the local authority, prescriber and the patient. However, the scenarios differ in Tunisia and Egypt, where patient choice traditionally plays no role in the decision to switch biosimilars. In Tunisia, a specialized committee rigorously evaluates each case of interchangeability, making decisions based on clinical evidence without direct patient input. In Egypt, the Ministry of Health dictates interchangeability decisions, similarly bypassing direct patient involvement.

To address these concerns and enhance patient-centered care, it is crucial to implement strategies that clearly inform patients about potential switches to biosimilars. Such strategies should include comprehensive educational programs that explain the rationale, benefits, and potential risks associated

with switching. Patients should receive this information well in advance of any change, allowing ample time for discussion and to address any concerns. Furthermore, it is essential to establish a clear policy that permits patients to revert to the original biologic if they experience adverse effects or a nocebo response after switching to a biosimilar.

In contrast, other countries often employ more inclusive strategies, such as opt-in or opt-out systems, allowing patients more autonomy in their treatment choices. For instance, in several European countries, patients can opt out of switching to a biosimilar if they express a preference for continuing with their current biologic treatment, provided this decision is supported by their healthcare provider. Such policies empower patients and respect individual preferences, thereby enhancing adherence and satisfaction with treatment.

Inconsistencies in regulatory pathways could contribute to diminish confidence regarding biosimilar efficacy, reliability and quality, and lead to a delay in biosimilar development. This necessitates open discussion across national borders and different stakeholders as a key to achieve global agreement on regulatory approval issues in the MENA region, particularly in terms of biosimilar switching and interchangeability.

Benefits of global regulatory alignment on biosimilars

Aligning technical requirements between different countries expedites drug approval processes both globally and in specific nations. This alignment facilitates a uniform regulatory review mechanism, eliminating the need for individual tests and applications with each regulatory body. Thus, this system not only reduces the time necessary to introduce pharmaceutical products onto global markets but also facilitates their introduction in individual countries more quickly. By eliminating redundant efforts spent meeting various national standards, manufacturers can focus on one comprehensive submission strategy to expedite access for patients worldwide while conserving significant financial and operational resources.[23]

Besides, more rapid approval and commercialization of novel medications is made possible by harmonized regulations, which help patients benefit from early access to medications by having more timely treatment options, and hence, better health outcomes.[23] Moreover, harmonized regulations encourage competition in the market, and as businesses compete to provide better, more affordable solutions, this often sparks innovation, benefiting patients and industry.[23]

Challenges in achieving harmonization

The agreements reached between the EMA and the FDA on reference medicines for biosimilars represent major steps toward the harmonization of global biosimilar regulatory standards, reflecting mutual recognition of each agency's regulatory rigor while streamlining development by reducing redundant clinical trials. These partnerships are critical in expediting faster, more affordable biosimilar access around the globe and creating opportunities for international regulatory collaboration. Still, these positive advances highlight the challenges associated with aligning regulatory frameworks within an expanding biosimilar landscape and varying scientific assessment methods. Among the remaining challenges are variations between agencies when it comes to biosimilar interchangeability policies, which could create confusion for healthcare providers and patients alike. Addressing these challenges involves ongoing dialogue and collaborative efforts aimed at standardizing interchangeability criteria, increasing transparency to build public trust, and sharing post-marketing data; all this while emphasizing the necessity of taking an international approach to increase biosimilar market growth and patient access globally.

In addition to the above challenges, lack of global consensus on regulatory guidelines is one of the main issues hindering harmonization in biosimilar guidelines. Despite efforts by the World Health Organization (WHO) to help member states implement evaluation principles for biosimilars, discrepancies remain in regulatory practices among different countries. These include insufficient reference products, lack of resources, problems with biosimilar quality, and difficulties with interchangeability and naming of biosimilars.[24]

Healthcare providers and regulators may have differing degrees of knowledge and awareness about biosimilars. Every nation has its own set of regulations, which are occasionally not updated in accordance with international standards, which represents an obstacle to regulatory harmonization.[25] In addition, guidelines harmonization could be hampered by the disparities in approval procedures, evaluation standards, and regulatory frameworks, which makes it difficult to establish uniform global regulations for biosimilars. Furthermore, lack of collaboration between regulatory agencies may also play a role in hindering the harmonization of biosimilars guidelines. This lack of cooperation could hinder the pharmaceutical industry's capacity to offer reasonably priced biologic substitutes by delaying the approval and market access of biosimilars. Moreover, a nation's capacity to invest in and access biosimilars is influenced by its economic standing. When healthcare's financial components diverge, it becomes more difficult to harmonize regulations, which makes it difficult to decide on fair pricing, reimbursement policies, and biosimilars' overall market strategies.

Biosimilar drugs resemble original biologic medication but come at lower costs; their pricing, however, varies significantly across nations due to a complex interplay among healthcare systems, legal frameworks, and economic considerations. Understanding these subtleties is integral for increasing global acceptance and use of biosimilars.

Healthcare systems worldwide face unique difficulties when integrating biosimilars, including procurement practices, healthcare budgets, incentive structures for manufacturers, and reimbursement policies. At the micro-level, challenges include stakeholders' recognition and feasibility of biosimilars. The meso-level faces issues like organizational culture and expertise, while the macro-level grapples with regulatory and economic factors. These complexities can significantly impact the integration and acceptance of biosimilars in healthcare system.[26] Health Technology Assessment (HTA) agencies play a vital role in informing policymakers regarding the adoption and use of biosimilars by providing vital economic impact analysis as well as clinical use guidance and regulatory assistance relating to their clinical application and regulatory aspects.[27] Such assessments

also assist healthcare systems in navigating these complexities more smoothly by offering systematic analyses of benefits vs. challenges related to biosimilar integration into healthcare systems. For example, different HTA agencies, such as CADTH in Canada, NICE in the UK, and PBAC in Australia, may criticize or report variably on the methodological aspects of biosimilars, affecting their integration into healthcare systems. This variability can hinder consistent decision-making regarding biosimilar procurement and use.[28]

Operational considerations are critical to the successful introduction of biosimilars into healthcare systems. These include assuring biosimilars are safe and efficacious compared to their reference biologic counterparts, providing healthcare providers and patients with education about them, managing logistical aspects like storage and handling while differentiating in electronic health records as necessary. Acquiring both provider and patient trust in biosimilars is central to their acceptance and use.[29] However, operational challenges, including handling regulatory changes and providing support services equivalent to reference products, must also be carefully taken into account. This involves considering insurance contracts, clinical training for staff members, nursing support services as well as optimizing distribution models so as not to interfere with hospital workflow.

Legal and intellectual property issues pertaining to patent protection often become obstacles in the adoption of biosimilars by patients and clinicians alike, preventing their widespread usage within healthcare environments and restricting any cost savings or access improvements they could potentially offer. These challenges could delay biosimilar introduction into markets as well as limit their potential cost-cutting benefits or accessibility improvements.

Furthermore, capacity-building initiatives, including training programs, technical assistance, and knowledge transfer efforts, are an integral component of developing biosimilar markets in countries without established markets. Such measures support regulatory capabilities as well as increase understanding of the economic, clinical, and operational implications of biosimilars.

Strategies for harmonization

Strategies for achieving harmonization in biosimilar labeling include establishing uniform naming standards to prevent misunderstandings, fostering international collaboration among regulatory agencies worldwide to align guidelines, and setting up standardized regulatory standards for biosimilar approval. This should be overseen by an independent, nonprofit international council dedicated to harmonization, with the aim of increasing the affordability of these medications.[6] Additionally, engaging patient advocacy groups, healthcare professionals, and industry stakeholders in these efforts is crucial for ensuring comprehensive and inclusive biosimilar policy development.

Since knowledge regarding reference biologics and biosimilars is highly important in the development of biosimilars, educational initiatives to healthcare providers and regulators are deemed necessary. In this regard, the FDA provides extensive multimedia educational materials for healthcare providers and regulators on biosimilars.[30] These materials include fact sheets, infographics, and videos in multiple languages aimed at demystifying biosimilars and their interchangeability with reference biologics. The goal is to enhance understanding among healthcare professionals and to ensure they can effectively communicate these concepts to their patients. However, while educational initiatives are critical for improving understanding among healthcare professionals, it is clear that education alone is not the sole barrier to wider biosimilar adoption.[31] A comprehensive strategy that includes improving the approval process, regulatory clarity, and competitive practices is essential to fully realize the benefits of biosimilars in terms of access and affordability.

Conclusion

Harmonizing biosimilar regulations is critical for improving efficient market access, reducing healthcare costs, and enhancing patient outcomes worldwide. Addressing the challenges to achieve global regulatory alignment necessitates collaborative efforts, educational initiatives, and the development of unified standards.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contributions

ASJ, SRH, and AZA have contributed equally to the study design development, data extraction, manuscript drafting and reviewing

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