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COMMENTARY

Recommendations for Interchangeability in a Growing Biosimilar Market in Latin America

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ABSTRACT

Background: Biosimilars offer significant advantages for improving access to biologic treatments in Latin America. However, their uptake has been slow due to misconceptions, regulatory uncertainties, and inadequate pharmacovigilance.

Objective: To address these issues, Americas Health Foundation convened a multidisciplinary panel of regional experts in biosimilar use and interchangeability from Latin America. The panel assessed the current landscape and recommended steps to enhance access.

Results: Key recommendations include strengthening biosimilar regulations, ensuring transparent enforcement, implementing robust pharmacovigilance, and promoting collaboration among stakeholders to educate about the safety, efficacy, and economic advantages of biosimilars and their interchangeability.

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Conclusions: By embracing biosimilars and interchangeability, Latin American countries can expand patient access, foster competition, diversify treatment sources, and enhance the sustainability of their healthcare systems. However, achieving these goals requires addressing knowledge gaps and biases among healthcare providers, patients, regulators, and government agencies. This can be accomplished through clear communication and the use of real-world evidence.

PLAIN LANGUAGE SUMMARY

Biosimilars offer an opportunity to expand access to crucial biologic treatments in Latin America by providing lower-cost alternatives when patents expire. However, adopting biosimilars has been slow due to misconceptions and regulatory uncertainties. To address this, experts recommend considering approved biosimilars as interchangeable with reference products, allowing for switching without compromising safety or efficacy, with the limitation of switching only once per year. To improve access, well-defined regulations, enforcement, and transparency from regulatory agencies are necessary, along with education for healthcare providers, patients, and other stakeholders to address knowledge gaps and negative perceptions. Improved pharmacovigilance systems and collaboration between stakeholders can help communicate the benefits of biosimilars and interchangeability. By embracing biosimilars, Latin American countries can expand patient access, foster market competition, diversify treatment options, and improve the sustainability of healthcare systems.

Keywords: Biosimilar pharmaceuticals; Cost–benefit analysis; Health inequities; Latin America; Patient advocacy; Pharmacovigilance

Key Summary Points

Biosimilars offer significant advantages for improving access to biologic treatments in Latin America, but their uptake has been slow due to misconceptions, regulatory uncertainties, and inadequate pharmacovigilance.

The panel recommends that Latin American regulatory agencies adopt a default position that considers biosimilars approved by the European Medicines Agency or following World Health Organization guidelines as interchangeable, with a recommendation to limit switching between a biosimilar and its reference product, or between biosimilars of the same reference product, to no more than once per year.

Effective communication and education are crucial to improving knowledge, perception, and utilization of biosimilars among Latin American healthcare professionals, patients, regulators, and government agencies.

Strengthening biosimilar regulations, ensuring transparent enforcement, implementing robust pharmacovigilance, and promoting collaboration among stakeholders are key recommendations to enhance access to biosimilars in Latin America.

By embracing biosimilars and interchangeability, Latin American countries can expand patient access, foster competition, diversify treatment sources, and enhance the sustainability of their healthcare systems.

INTRODUCTION

Biosimilars are biologics that are highly similar to approved reference biologics, known as reference products, with no significant differences in efficacy, safety, and quality [1]. Biologics have significantly improved treatment in several fields, including oncology, rheumatology, endocrinology, dermatology, and gastroenterology. However, the increasing reliance on these targeted therapies has led to higher

healthcare costs, and challenges the sustainability of healthcare systems. Biosimilars serve as a recognized global strategy to expand patient access to treatments, promote market competition, and provide equivalent efficacy and safety to their reference product at a reduced cost [2]. This is particularly relevant in resource-constrained healthcare settings, like Latin America (LA), given its diverse healthcare challenges and health disparities.

The uptake of biosimilars in LA has been slow, although low- and middle-income countries should benefit the most from a robust biosimilar market [3, 4]. This can be attributed to limited understanding and acceptance of biosimilars among healthcare stakeholders, inconsistent regulatory environments across countries, and inadequate pharmacovigilance practices [2].

This paper aims to provide clear information about the status of biosimilars and the interpretation of interchangeability in LA. It outlines the challenges that have hindered their adoption and proposes solutions to address them, intending to increase the appropriate use of biosimilars to improve access to critical medical treatments in the region. It is important to note that intended copies are non-innovator biologics that, unlike biosimilars, lack sufficient evidence to demonstrate biosimilarity; these products may have clinically significant differences from the reference product [5]. This review will not cover intended copies; the information provided is irrelevant to these products. Definitions of the terms "automatic substitution," "switching," and "interchangeability" can be found in Fig. 1. Understanding these definitions is crucial for the clarity of the concepts discussed.

METHODS

Americas Health Foundation (AHF) assembled a multidisciplinary panel of six biosimilar use and interchangeability experts from Brazil, Chile, Colombia, Ecuador, and Mexico.

They met virtually on February 6 and 7, 2024, to develop guidelines for biosimilarity interchangeability in LA. AHF used PubMed, MEDLINE, and EMBASE to identify scientists, clinicians, and policymakers from LA. All the experts who participated in the meeting are listed as authors of this manuscript.

Search strategy: AHF researched biosimilar interchangeability in PubMed, MEDLINE, and EMBASE. "Interchangeability," "regulatory

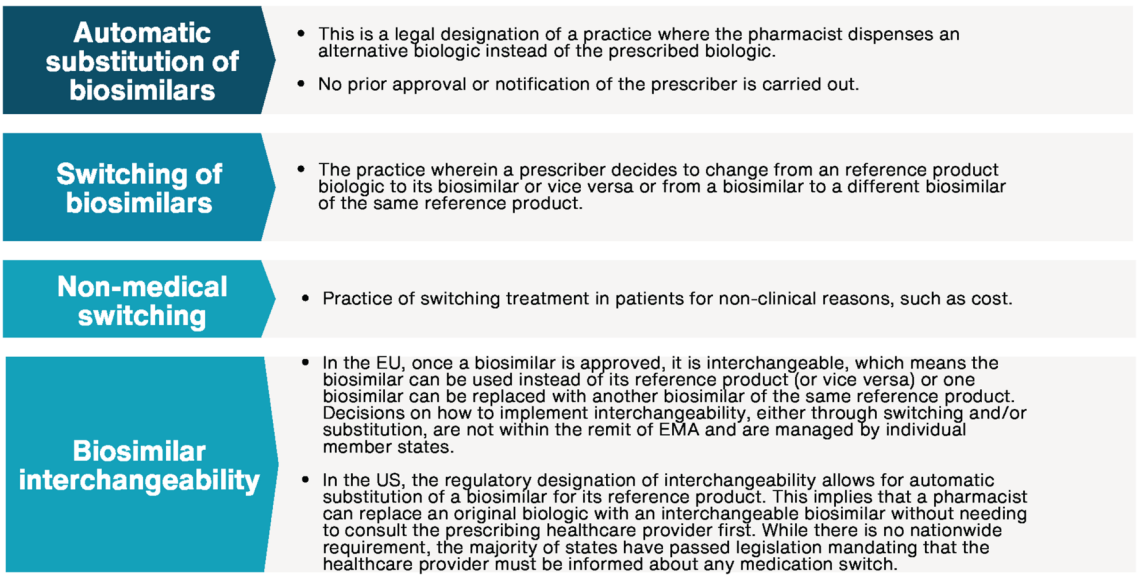

Fig. 1 Definitions related to biosimilar interchangeability. *EU* European Union, *EMA* European Medicines Agency, *US* United States

pathways," "pharmacovigilance," and "cost savings" in combination with "Latin America" and "biosimilars" were searched with dates ranging from 01/01/2018 to 12/01/2023. The articles identified were in English, Portuguese, and Spanish. AHF prioritized articles from LA.

Based on the literature search, AHF formulated specific questions (Supplementary Material Table S1) to address barriers restricting LA's access to biosimilars. Each panel member was assigned a question and provided a written response based on the literature review and personal expertise. The panel reviewed and edited each response during the two-day conference, engaging in numerous rounds of discussion until unanimous agreement. An AHF staff member moderated the debate. The panel based their recommendations on the evidence gathered and expert opinion. All authors reviewed and approved the final manuscript.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Biosimilar Regulatory Landscape

Global Overview

The first regulatory pathway for biosimilars was established in Europe in 2005, and the first biosimilar was approved in 2006. In the United States (US), a biosimilar pathway was created in 2010, and the first biosimilar was approved in 2015 [6]. Biosimilar regulations and guidelines have also been implemented in LA [3, 7, 8] and many other countries worldwide [9]. There are substantial variations in biosimilar uptake among countries and regions. As of 2021, biosimilars represented 10% of the total biologics pool in Europe [10], with 7% achieved in the last five years. However, biosimilar uptake in the US and LA has been slower. This suggests that not all regions have fully realized their potential [10].

Latin American Overview

LA is a complex emerging market due to vast diversity in drug regulation, healthcare systems, and political regimes despite some cultural and linguistic similarities. However, in recent years, significant advances in biosimilar regulation pathways have been made in most LA countries, which have increased biosimilar uptake [3, 11]. Most countries have adopted regulations based on World Health Organization (WHO) guidelines, which are based on European Medicines Agency (EMA) regulations. This approach aims to provide "globally acceptable principles for the licensing of biological products"[7, 12, 13]. However, lack of awareness and understanding, non-adherence to regulatory pathways, distinct market opportunities, issues related to biosimilars' traceability, and pharmacovigilance deficiencies still hinder the uptake of biosimilars in the region.

Biosimilar Interchangeability

The European Union and the United States

Interchangeability in biosimilars refers to swapping one medicine for another that is expected to have the same clinical effect. If a biosimilar is interchangeable, it can be used in place of its reference product or vice versa, and one biosimilar can be substituted for another of the same reference product [14]. In 2022, the EMA and the Heads of Medicines Agencies (HMA) established a clear position on interchangeability, stating that all European Union (EU)-approved biosimilars are interchangeable. This statement aimed to eliminate uncertainty among stakeholders [14, 15]. EU experts, with over 15 years of clinical experience in evaluating and monitoring the post-marketing safety of various biosimilars, have developed a deep understanding of these medicines. They believe approved biosimilars have demonstrated comparable efficacy, safety, and immunogenicity to reference products [16]. Interchanging between biologics from different manufacturers has become commonplace. Therefore, a biosimilar approved in the EU requires no additional systematic studies to support its interchangeability [16].

In contrast, the Food and Drug Administration (FDA) has a unique approach that requires clinical interchangeability studies to assess

immunogenicity as a secondary endpoint. This position is unprecedented among regulatory bodies worldwide [17]. The FDA's guidance on interchangeability highlights immunogenicity as a potential concern when switching between a reference product and its biosimilar multiple times [17, 18]. Therefore, "switching studies assess whether one product will affect the immune response to the other, once the switch occurs, and whether this will result in differences in immunogenicity or pharmacokinetic profiles" [17]. These concerns arise from prior experience switching between biologics and non-biosimilars; hence, they do not apply to biosimilar interchangeability [8, 19, 20]. The American Society of Clinical Oncology released a statement on interchangeability, stating that a biosimilar is clinically equivalent to its reference product. The FDA's regulatory term, 'interchangeability,' has created confusion regarding the lack of clinically meaningful differences between a biosimilar and its reference product; this further complicates clinician and patient education and access, as it creates a distinction between a biosimilar and an interchangeable biosimilar for regulatory purposes [21].

Latin American Perspective

Regulators in most LA countries have not provided clear guidance on interchangeability. As a result, it is often considered a clinical decision rather than an evidence-based characteristic of biosimilars and their reference products. This poses a problem because clinicians must make case-by-case decisions, which they are not necessarily trained to make, and may not fully consider the available evidence for biosimilars.

Regarding the biosimilar market, Brazil closed 2023 as the second largest public market for biosimilars, following the EU [22, 23]. The biosimilar regulatory framework in Brazil is under review by the National Health Surveillance Agency (ANVISA) [22, 24, 25]. In the meantime, a 2018 technical note states that the decision on interchangeability is left to the physician and patient. ANVISA acknowledges the need to address the issue of interchangeability, but believes that the field is still too immature to change the current status based on the issue's complexity, absence of global consensus, and differing opinions from the FDA and EMA [25, 26].

Chile and the Dominican Republic only allow interchangeability with the explicit authorization of the prescribing physician [27]. In other LA countries, the matter of interchangeability is not explicitly addressed in regulatory frameworks.

Current Evidence on Interchangeability

The risks associated with switching between a reference product and its biosimilar are very low, based on available real-world evidence [28–32]. There is no clinically significant difference between a biosimilar and its reference product [33], so switching between them or between different biosimilars of the same reference product is not expected to negatively impact pharmacokinetics, immunogenicity, safety, or efficacy [6].

Systematic reviews support the view that biosimilars do not pose a higher risk of immunogenicity compared to batch variations of reference products. Therefore, it is reasonable to consider biosimilars as interchangeable, barring conclusive evidence to the contrary [34].

Concordant with current evidence, this panel endorses the EMA's position on biosimilar interchangeability in LA. According to the EMA, a biosimilar is considered interchangeable if it meets one of the following two requirements:

1. Biosimilar is EMA- or HMA-approved.
2. If the biosimilar is not EMA- or HMA-approved, there is sufficient evidence of biosimilarity following WHO guidelines.

Of note, data on multiple switches over short periods are not yet available, and frequent switches are not conducive to an effective pharmacovigilance system. Therefore, it is necessary to regulate the frequency of switching. This panel proposes that switching from a reference product to a biosimilar or a different biosimilar of the same reference product in LA should not occur more than once a year, based on current evidence and global best practices (Fig. 2).

Benefits of Biosimilars for Latin America

Economic Benefits and Increased Access

Innovation has brought enormous benefits to population health but has also challenged its sustainability. These innovative products often come with high costs, creating an imbalance between the demand and supply of healthcare systems. Conversely, biosimilars cost less than their reference products, resulting in substantial savings for healthcare systems [3, 4, 7, 35, 36]. Therefore, considering that financing [37] is a key pillar of healthcare sustainability, biosimilars present an opportunity for efficient resource allocation. Cost savings from biosimilars can be particularly beneficial for resource-constrained healthcare systems in LA, where access to expensive biologics is often limited. Patients can also benefit economically from biosimilars, as reduced out-of-pocket expenses make essential treatments more affordable and accessible [38]. Clear support for biosimilar interchangeability could enhance access and efficiency, especially if a clinical management model leads the process.

Financial toxicity is a significant issue in LA healthcare systems when providing true access to reference products. This leads to disparities in cancer survival rates, with a 40% gap between high- and low-income countries, mainly due to inequitable access to care and medicines [39]. In LA, cancer is the leading cause of premature death, with projections indicating a surge of over 64% in new cancer cases in the region's most populous nations [38]. Breast, colorectal, and lung cancers have the highest costs globally, primarily because of the emergence of new treatment technologies. The high cost of new cancer drugs, with over 90% of those approved in the US priced above US$20,000 for 12 weeks of treatment, exacerbates the financial strain and widens the access gap between private and public healthcare [40]. Autoimmune diseases also pose a significant burden in LA. Although their impact and projection are not as substantial as for cancer, the costs of therapies have been increasing significantly. The estimated prevalence of rheumatoid arthritis (RA) in LA countries ranges from 0.15% (Colombia) to 2.8% (Mexico). The annual direct cost in Mexico was estimated at US$3599 per person, while, for patients with severe RA in Brazil, these costs were approximately US10,000 [41]. Given the scenario above, access to biosimilars can be part of the approach to address this issue.

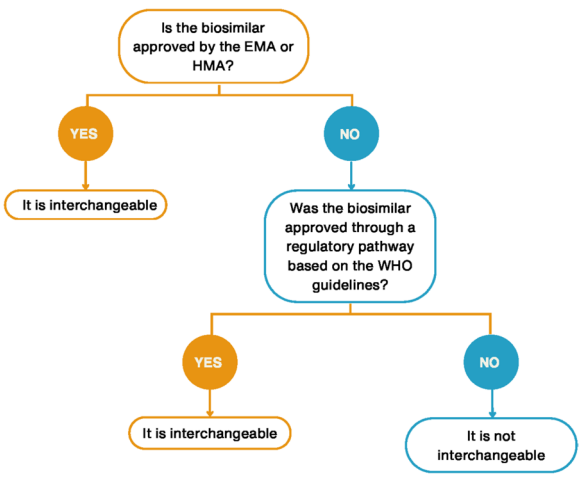

Fig. 2 Recommendations for biosimilar interchangeability in Latin America. *EMA* European Medicines Agency, *HMA* Heads Medicines Agency, *WHO* World Health Organization

Market Competition

Biosimilars, and their interchangeability promote competition in the pharmaceutical market, leading to lower prices and improving affordability for patients and healthcare systems [42]. This competition incentivizes therapeutic innovation, driving improvements in treatment options [43]. Ultimately, patients benefit from this dynamic with increased access to necessary therapies.

Multiple Treatment Sources

Biosimilar interchangeability allows the market to have multiple sources of the same biologic [44]. This expansion improves patient access to essential treatments for various diseases, including cancer, autoimmune disorders, and chronic inflammatory conditions [45]. With a wider range of treatment options available, patients and healthcare providers can

customize therapies to individual patient needs, preferences, and tolerances, ultimately improving treatment outcomes and quality of life. In addition, biosimilar interchangeability can help address medication shortages and supply chain disruptions [46]. Access to certain medications in LA can be unpredictable due to distribution challenges and regulatory constraints [47]. Biosimilars have the potential to provide a reliable substitute for reference biologics, thus mitigating the risk of treatment interruptions for patients.

Challenges to the uptake of biosimilar and interchangeability in Latin America.

1. Negative perception of biosimilars and lack of education

To achieve widespread acceptance of biosimilars, it is necessary to address misconceptions among healthcare providers, patients, regulators, and government agencies. A survey of LA rheumatologists revealed significant knowledge gaps regarding their understanding of biosimilars [48]. Furthermore, recent studies have shown inconsistent knowledge of biosimilars, notably on their interchangeability [3, 4, 6] among stakeholders [3, 4, 6]. This is despite strong evidence that interchangeability does not significantly impact clinical efficacy and safety [18, 43, 49]. Additionally, the nocebo effect, where adverse effects result from negative expectations rather than the treatment itself, often hinders patient acceptance. The effect is significant, affecting approximately 12.8% of patients transitioning from a reference product to a biosimilar [9].

In LA, there is a lack of educational efforts by regulatory agencies. Information about biosimilars is mainly provided by scientific societies, the pharmaceutical industry, and patient organizations.

2. Regulatory uncertainties

Mistrust stemming from regulatory uncertainties has also contributed to the lack of acceptance of biosimilars in LA. While regulation is essential, it does not guarantee a sustained biosimilar market. Even in countries with regulatory frameworks for biosimilars, these are not always enforced, leading to intended copies being approved or biosimilars being evaluated through generics pathways [50]. Thus, unequivocal enforcement of biosimilar regulatory pathways must ensure adequate evaluations and reduce uncertainty.

Lack of transparency is also an obstacle to biosimilar acceptance in LA, as it undermines public confidence in biosimilars and creates unnecessary resistance to interchangeability. Regulatory agencies provide limited information about the authorization of commercialization granted to products. Unlike the FDA and EMA, most LA authorities do not provide detailed information about biosimilarity and the approval process.

Insufficient Biosimilar Traceability and Pharmacovigilance

Effective pharmacovigilance programs and comprehensive risk minimization plans are necessary for monitoring biosimilars. Biosimilars require the same level of surveillance as reference products due to potential minor structural or constituent-related changes. This is even more critical than with generics because of the strict temperature regulation, specialized delivery systems, and the risk of post-translational changes. Regulatory authorities should strive to maintain the risk–benefit balance of biosimilars compared to the reference product and to ensure that adequate quality standards are met [11].

LA countries lag behind Europe and the US in establishing effective pharmacovigilance systems for biosimilars. Insufficient resources often restrict the implementation of these systems, leading to under-reporting of adverse events. Moreover, routine monitoring to assess the impact of biosimilar use on patients is lacking [7, 48]. One of the most challenging aspects to address in the short term is the lack of highly qualified personnel with postgraduate training to develop suitable pharmacovigilance systems [48].

Additionally, traceability is essential for distinguishing between a biosimilar and its reference product or another biosimilar. This can be achieved through various strategies, such as naming, registered numbers, and batch numbers. Regardless of the approach, traceability

is vital for reporting adverse events that may occur with both reference and biosimilar products [51].

Recommendations

Understand interchangeability: This panel recommends that LA regulatory agencies adopt a default position that considers biosimilars approved by the EMA or regulations following WHO guidelines as interchangeable. However, conclusive evidence to the contrary should be considered [34]. The designation of interchangeability can be supported by current analytical, functional, and clinical data, and real-world evidence [34, 52]. Nonetheless, the frequency of switching between a biosimilar and its reference product or between biosimilars of the same reference product should not occur more than once a year [53].

Education: There is a vast opportunity to improve knowledge, perception, and utilization of biosimilars at all levels. Effective communication and education are crucial in maximizing the benefits of biosimilar interchangeability in resource-constrained healthcare settings. Healthcare professionals and patient organizations play a vital role in educating patients about biosimilars, including their safety, efficacy, and cost-effectiveness compared to reference biologics [54]. By providing clear and accurate information, healthcare professionals empower patients to make informed decisions about their treatment options and dispel misconceptions or concerns[55–57] (Fig. 3).

Strengthen biosimilar regulations: We recommend each country establish a specific regulatory pathway for biosimilars that differs from reference products and is independent of the generics' pathway. These pathways should be based on WHO guidelines or the processes already implemented by the EMA [7]. Interchangeability must be addressed within the regulatory framework. Unequivocal biosimilar traceability must be ensured, regardless of the strategy employed.

Enforcement of regulations: Once a suitable biosimilar regulation is implemented, it must be enforced. Economic or political arguments are

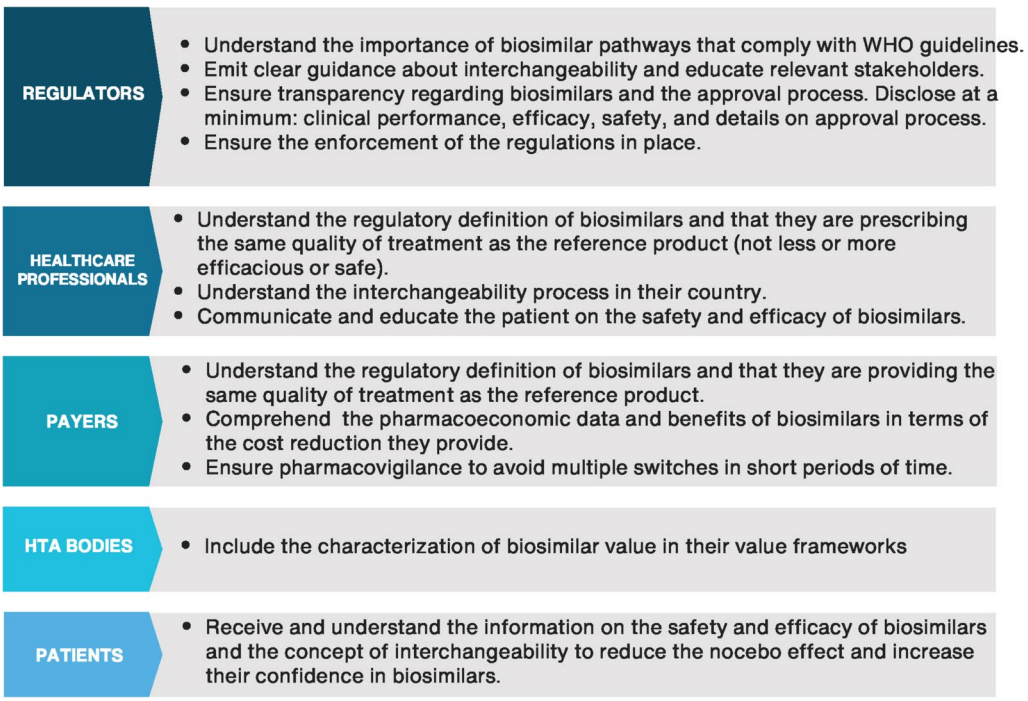

Fig. 3 Necessary education on biosimilars according to stakeholders. *HTA* health technology assessment

invalid for making exceptions to evaluate and/or purchase products outside the designated pathways.

Regulatory Transparency: Relevant information on biosimilar development and evaluation must be publicly available. The European Public Assessment Reports from the EMA proved a suitable model. When regulatory authorities lack transparency, it creates uncertainty and undermines stakeholder confidence in biosimilars.

Pharmacovigilance: Each country's regulatory agencies must establish robust pharmacovigilance systems for monitoring biosimilars and their reference products. Postgraduate programs in pharmacovigilance should be implemented and included in health-related curricula. The programs implemented in Spain provide an adequate example to follow.

Stakeholder collaboration: Effective communication of the benefits of biosimilar interchangeability relies on collaboration. Payers, policymakers, patient advocacy organizations, and pharmaceutical industry representatives should work together to develop coordinated strategies and messaging campaigns [58]. By aligning their efforts and sharing best practices, stakeholders can amplify their impact and reach a broader audience with consistent and accurate messaging about biosimilars' access and economic advantages [59, 60].

CONCLUSIONS

Biosimilars offer great promise for improving patient access to effective treatments in LA. Embracing biosimilars can significantly contribute to the sustainability of healthcare systems, ensuring that life-saving therapies are accessible to a larger population. Interchangeability allows maximum benefits, provided stakeholders understand and accept the process. Through cost savings, increased competition, and diverse treatment sources, biosimilars address many of the challenges of accessing biologics. Effectively communicating these benefits to stakeholders requires clear and transparent messaging, collaboration, and reliance on real-world evidence.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Gilberto Castañeda-Hernández reports receiving an honorarium from the American Health Foundation, payments to his institution from CONAHCYT, consulting fees from Laboratorios Sophia, payments from Pfizer, Sandoz, and Amgen, and non-payment leadership role in Biored CAC. Manuel Antonio Espinoza reports receiving an honorarium from AHF, grants or contracts to his department from World Bank, research grants from ANID FONIS SA19101882220002, ANID FONDAP152220002, consulting fees from Interamerican Bank of Development, World Bank, and Center for Global Development, payment or honoraria from Merck, MSD, Grunenthal, Novartis, Abbvie, Boehringer

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