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REVIEW ARTICLE

Increasing adoption of quality-assured biosimilars to address access challenges in low- and middle-income countries

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Non-communicable diseases (NCDs) disproportionately affect people living in low- and middle-income countries (LMICs) compared to high-income countries (HICs). Given the particularly limited healthcare resources in LMICs, increasing the adoption of biosimilar products can be a viable solution to expand access to medicines. Biosimilars can allow patients to be treated with more affordable biologic products compared to their originator biologics. As most of the literature around biosimilars focuses on HICs, this review article offers insights into the benefits of biosimilars for better access to biologics in LMICs, focusing on data from selected emerging markets. Insights were mainly gathered via conducting interviews in LMICs on exploring challenges towards access to biosimilars and were supplemented with a literature search. This review article highlights the burden of non-communicable diseases (NCDs) in LMICs, trends in the regulatory space for biosimilars, benefits of biosimilars, and challenges in accessing biosimilars in emerging markets. The challenges include weaker regulatory frameworks, dependence on importation, low awareness of biosimilars, and the need for effective policies encouraging access to and use of biosimilars. This review article suggests recommendations to increase access to and adoption of quality-assured biosimilars in LMICs, including strengthening regulatory and pharmacovigilance systems, providing guidance on prescribing biosimilars and education on biosimilars, strengthening national policies to increase adoption of biosimilars, encouraging local manufacturing, and encouraging stakeholders' initiatives promoting access to biosimilars. Acknowledging that affordability remains a main factor for stakeholders' purchasing decisions, this paper offers additional criteria beyond price that may help stakeholders in LMICs select quality-assured biosimilars.

Keywords: Affordability, biosimilars, low- and middle-income countries (LMICs), market access, non-communicable diseases, regulatory framework

Introduction

The burden of non-communicable diseases (NCDs) is increasing rapidly across the globe. NCDs cause nearly 75% of all deaths worldwide, and 85% of the people who die yearly due to NCDs are from low- and middle-income countries (LMIC) [1]. The risk of dying prematurely from NCDs in LMICs is almost twice as high as in high-income countries (HICs) [2]. The healthcare budgets are more limited, and the regulatory systems, although evolving, are less developed in LMICs compared to those of HICs, which translates to poor access to life-saving medicines. The disparity in access to essential medicines for NCDs is a plausible contributing factor to a higher number of premature deaths from NCDs in LMICs compared to HICs [3]. Biosimilars can help increase patients' access and affordability to lifesaving biologic medicines by promoting pricing competition with the originator biologics/reference products (RPs). As most of the literature around biosimilars focuses on HICs, this review article offers insights into the challenges faced for biosimilar uptake and offers recommendations for faster and better access to biosimilars in emerging markets and, more broadly, LMICs. Focusing on data from selected emerging markets (Brazil, Colombia, Malaysia, Mexico, Nigeria, Turkey, and Taiwan), we explored trends in the regulatory framework of biosimilars, potential and actual benefits of biosimilars, and challenges in accessing quality-assured biosimilars. Finally, recommendations to enhance access and use of quality-assured biosimilars in LMICs and a list of potential criteria to help stakeholders in LMICs select these quality-assured biosimilars are also provided.

Methodology

Interviews

Three interviews were conducted with ex-government officials/individuals who had worked with governments in Nigeria, Colombia, and Taiwan to explore the challenges related to access to biosimilars and ways to facilitate the adoption of quality biosimilars.

Recruitment: Participant eligibility was restricted to former government officials/people affiliated with governments and familiar with the reimbursement of biosimilars in Nigeria, Colombia, and Taiwan.

Interview guide: the interview guide included open-ended questions so that the participants could be relatively free to share insights based on their experience (Box 1).

Interviews: Three interviews were conducted, one in each of the following countries: Nigeria, Colombia, and Taiwan, by Clarivate between February and August 2023, after obtaining consent to collect insights.

Analysis: Content analysis was performed on the transcripts of the interviews to extrapolate insights, and the interviews were summarized to be included in the review.

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Box 1: The interview questionnaire

- Could you provide a brief overview of your current or previous job role relating to access to biosimilars? What country do you work in? Which bodies do you typically work with? Are you involved in reimbursement decisions or tendering for biosimilars?
- What would help to wean the decision-makers from biologics over to quality biosimilars approved in regulated and other markets? What perceptions and apprehensions stand in the way of faster and better adoption of biosimilars?
- When you/your team decide to purchase and/or reimburse a biosimilar, what are your criteria for choosing it? How do you shortlist a biosimilar?
- To what extent are biosimilars' quality and price considered when deciding to reimburse and purchase biosimilars?
- What are the quality criteria for biosimilar selection that you currently follow for purchasing and reimbursement decisions? Additionally, are there specific guidelines you follow, such as those from the government or other bodies/stakeholders.
- According to you, which should be the ideal criteria for governments to select quality biosimilars? We are interested in understanding how selection criteria for quality biosimilars may be enhanced (For instance, characteristics of the manufacturer such as manufacturing capabilities and capacity, R & D capabilities, high number of approvals in different countries, inspection history, or things such as product's adverse events. Please do suggest any others).
- According to you, what are your country's main challenges and barriers to access biosimilars?
- According to you, what actions could the government take to increase patient access to quality biosimilars in your country?
- What could other stakeholders do to contribute to increasing patient access to biosimilars? (stakeholders can include the biopharmaceutical industry, regulators, payors, healthcare providers (HCPs), and patients).

Literature search

A literature search was conducted to gather insights, focusing on the following emerging markets: Brazil, Colombia, Malaysia, Mexico, Nigeria, Turkey, and Taiwan. These countries, except Taiwan, are middle-income countries (MICs) with varying income levels, ranging from lower- to upper-middle-income countries. Taiwan was included in this search, given its successful move from LMIC to HIC; insights from Taiwan may be relevant for emerging markets that might evolve into HICs in the future. Various sources were analysed, including articles, peer-reviewed papers, and reports. Biocon Biologics Limited (BBL) established the research method and contracted Clarivate to help conduct the interviews and the literature search and draft the review article. BBL reviewed and co-developed the review article.

The burden of NCDs in LMICs and growing interest in biosimilars

NCDs are responsible for the deaths of 41 million people annually, corresponding to 74% of all deaths globally. Every year, 17 million people below the age of 70 die from NCDs. Of these premature deaths, 86% occur in LMICs. Notably, cancer and diabetes are among the most common NCDs, together with cardiovascular and chronic respiratory diseases [1].

NCDs disproportionately affect people in LMICs, where more than three-quarters of all deaths (31.4 million) occur due to NCDs. According to the World Health Organization (WHO), NCDs are a barrier to achieving the United Nations (UN) 2030 Agenda for Sustainable Development, which, among other objectives, aims to reduce premature mortality (between the ages of 30 and 70) caused by NCDs by one third by 2030 [1].

As outlined in Table 1, there is a vast disparity in health spending per capita across countries in the world, with LMICs spending considerably less compared to HICs, see Figure 1. This can contribute to overall poorer health outcomes in LMICs, making access to affordable biosimilars, particularly important.

Table 1: Health spending per capita across selected countries 2019 (US$) [4]

Country	Health spending per capita (US$)
Mali, Sudan	<50
India, Nigeria	50–99
Iraq, Morocco	100–299
Colombia, Malaysia, Turkey	300–499
Brazil, Mexico, Taiwan	500–999
Poland, Saudi Arabia	1,000–1,900
Germany, USA	>2,000

Biosimilars are increasingly recognized as viable treatment options

The Model List of Essential Medicines of WHO, 2023 requires the inclusion of critical medicines, such as monoclonal antibodies and insulins, 'to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford' [5]. However, the burden of the cost of anticancer medicines often falls on the patients as an out-of-pocket expense in LMICs and low-income countries (LICs). For instance, the patient bears the cost of 58% of essential cancer medications in LICs, compared to 32% in low-middle-income countries and just 1.8% in upper-middle-income countries [6]. Additionally, some costly treatment options may not even be integrated into national formularies; for example, a recent study published in 2023 reports that by 2019, only 19% of countries had incorporated trastuzumab, a drug required by WHO Model Lists of Essential Medicines 2015, into their formularies [6].

Biologics are large, complex molecules from a living organism or its products. Due to their complexity, it is possible to only develop similar but not identical molecules, 'biosimilars', of the originator RP [7]. Biosimilars differ from generics, which can contain medicinal ingredients identical to their RPs. Although

the definition of a biosimilar slightly varies across countries, WHO defines it as 'a biologic product that is shown to be highly similar in terms of its quality, safety, and efficacy to an already licensed reference product' [8].

Biosimilars offer lower-cost alternatives to their reference products (RPs), promote competition, and can contribute to reducing the prices of RPs. Biosimilars can thus facilitate increased patient access to biologics, contributing to improved patient outcomes and sustainable use of healthcare system resources.

As patents of RPs expire, biosimilars are being approved in various countries. As of June 2021, biosimilars of nine RPs were approved in Taiwan [9]. By July 2020, 30 biosimilars of 13 RPs, 13 biosimilars of four RPs, 96 biosimilars of 20 RPs, 22 biosimilars of 13 RPs, 12 biosimilars of eight RPs, and eight biosimilars of six RPs were approved in Brazil, Ghana, India, Iran, Jordan, Ukraine, respectively [10, 11]. In 2022, biosimilars of at least nine RPs, and four RPs were approved, respectively, in Mexico and Colombia [10, 12, 13]. By October 2023, biosimilars of 16 RPs were approved in Malaysia [14]. The growing number of biologics under development suggests opportunities for increased biosimilar development and use in the future. However, in the LMICs, the quality of the biosimilar or similar biotherapeutic product can be of concern as some of these products were either approved prior to the adoption of regulations or guidelines for biosimilar evaluation or may not have been approved following a strict comparative regulatory process as recommended by the WHO guidelines [11]. Table 2 shows the adoption of biosimilar regulations in selected countries of interest.

How are regulatory frameworks for biosimilars evolving?

Emerging and evolving regulatory frameworks

EMA was the first regulatory authority to establish a framework for approving biosimilars, issuing guidelines in 2005 [15]. Since then, various regulatory authorities, including the US Food and Drug Administration (FDA), have developed frameworks and guidelines for approving biosimilars.

Regulatory pathways are different for biologic originators (the RP) and biosimilar drugs, with the latter subject to 'abbreviated clinical development pathways'. Biosimilar development is, in fact, more streamlined and linked to lower costs compared to the development of RPs. Nevertheless, these differences do not imply a difference in the efficacy and safety of biosimilars [16]. Generally, for a biosimilar to be approved, no demonstratable clinically meaningful difference in quality, safety, or efficacy should exist when compared to the RP [17]. Developing a biosimilar involves a stepwise, head-to-head comparison exercise, which starts with analytical assessments of structural and functional attributes of the biosimilar compared with the RP, followed by non-clinical and clinical assessments. The clinical assessments usually involve a pharmacodynamics (PD)/pharmacokinetics (PK) comparison followed by at least one comparative safety and efficacy trial. This comparison exercise aims to establish a high similarity between the biosimilar and its RP [17]. In the last decade, no relevant differences between biosimilars and their respective originators/RPs have been identified via the safety monitoring system in the European Union. None of the approved biosimilars has been withdrawn due to safety or efficacy concerns, thus providing reassurance and validation concerning the biosimilar approval pathway in highly regulated regions [17].

Regulatory frameworks for biosimilars differ among countries. However, WHO is making continuous efforts to increase global regulatory convergence. Ever since the WHO guidelines for the regulatory evaluation of biosimilars were issued in 2009, WHO has worked towards harmonizing the terminology and the regulatory framework for biosimilars globally [11, 18, 19]. WHO describes the progress made and the regulatory landscape changes for biosimilars in 21 countries through a survey carried out in 2019–2020 [18, 19]. The following salient points were surmised: (1) WHO guidelines have contributed towards setting the regulatory framework for biosimilars in the countries surveyed and have increased regulatory convergence at the global level; (2) Has made the terminology used for biosimilars more consistent than in the past; (3) Has worked towards biosimilars being approved in all participating countries. Despite this effort, the survey revealed some challenges that still remain: unavailable/insufficient RPs in the the countries surveyed, lack of resources, problems with the quality of some biosimilars, and difficulties with the practice of interchangeability and naming of the biosimilars [19]. The survey also put forth opportunities/solutions for regulatory authorities to manage the challenges faced, namely: (1) exchange of information on products with other regulatory authorities and accepting foreign licensed and sourced reference products, hence avoiding conducting unnecessary (duplicate) bridging studies; (2) use of a 'reliance' concept and/or joint review for the assessment and approval of biosimilars; (3) review and reassessment of the products already approved before the establishment of a regulatory framework for biosimilar approval; and (4) setting appropriate regulatory oversight for good pharmacovigilance, which is essential for the identification of problems with products and establishing the safety and efficacy of interchangeability of biosimilars [19].

The new WHO guidelines for biosimilar evaluation published in 2022 include the current data requirements and considerations for licensing biosimilars [20]. The framework for biosimilars in LMICs is continuously evolving, and, like HICs, many LMICs have established abbreviated clinical development pathways for biosimilars' evaluation, often following the frameworks of WHO and EMA. Despite this step towards facilitating access to biosimilars, comparability pathways for biosimilars are not always implemented effectively in LMICs, due to ambiguity in the regulatory oversight [21].

Many LMICs also rely on WHO's list of prequalified products to guide their selection of medicines. The WHO Prequalification of Medicines Programme (PQP) is a service to assess medicines' quality, safety, and efficacy, helping to ensure that procurement agencies supply medicines that meet acceptable standards [22]. This programme has resulted in improved access to two oncology drugs trastuzumab, since 2019, and rituximab, since 2020 in many LMICs [22].

The importance of streamlining development requirements

Although the development cost of biosimilars is lower compared to their RPs, it is still high in absolute terms and much

Table 2: Adoption of biosimilar regulations in selected countries of interest (Brazil, Colombia, Malaysia, Mexico, Nigeria, Turkey, and Taiwan)

Country	Regulatory Body	Year of Institution	Comments	Reference Link
Brazil	ANVISA (*Agência Nacional de Vigilância Sanitária*)	2010	In Brazil, the legal framework that approves the marketing of biologic products and biosimilars is the Resolution 55 (16 December 2010). Note: Insulin, EPO and G-CSF biosimilars were available prior to 2010.	https://www.gabionline.net/biosimilars/general/biosimilars-approved-in-brazil
Colombia	INVIMA (*Instituto Nacional de Vigilancia de Medicamentos y Alimentos*)	2014	In Colombia, a draft guideline was issued entitled *License for manufacturing facilities of biologic products*.	https://www.gabionline.net/biosimilars/general/biosimilars-approved-in-colombia
Malaysia	NPRA (National Pharmaceutical Regulatory Agency)	2008	Malaysia follows a stringent regulatory pathway for the approval of biosimilars. Country's first biosimilar, somatropin, was approved in 2010. In Malaysia, final guidance was issued on 30 July 2008 by the Ministry of Health Malaysia, entitled 'Guidance Document for registration of Biosimilars in Malaysia'.	https://www.gabionline.net/biosimilars/research/Biosimilars-regulation-clinical-trials-approval-and-adverse-events-in-Malaysia
Mexico	COFEPRIS (*Comisión Federal para la Protección contra Riesgos Sanitarios*)	2009	In Mexico, biologic products with expired patents are known as biocomparables. It should be noted that 'biocomparables' approved in Mexico may not have been authorized if they had been subjected to the strict regulatory processes required for approval of biosimilars in the EU*. In Mexico, guidelines were issued in 2009 entitled '*Ley general de medicamentos biotecnológicos*'.	https://www.gabionline.net/biosimilars/general/biocomparables-approved-in-mexico
Nigeria	NAFDAC (National Agency for Food and Drug Administration and Control)	2012	It should be noted that 'biosimilars' approved in Nigeria may not have been authorized following as strict a regulatory process as is required for approval of biosimilars in the EU.	https://www.gabionline.net/guidelines/Nigerian-guidelines-for-biosimilars
Turkey	MoH (Turkish Medicines and Medical Devices Agency of the Ministry of Health)	2008/2021	In Turkey, a final guideline was issued in August 2008 by the General Directorate of Pharmaceuticals and Pharmacy, entitled 'Instruction Manual on Biosimilar Medical Products'. To obtain approval of a 'biosimilar product', an applicant must submit an 'abridged' application to the MoH that demonstrates that there are no significant differences in terms of the quality, safety or efficacy between the biosimilar product and a biologic reference product. The 2008 version largely referred to the European Medicines Agency (EMA) guidelines; however, the new guidelines (2021) do not offer the detailed product-specific guidelines on biosimilars that EMA has published.	https://www.productlifegroup.com/news-turkey-issues-new-detailed-biosimilar-guidance-support-registrations/
Taiwan	TFDA (Taiwan Food and Drug Administration)	2008	In Taiwan, a final guideline was issued on 21 November 2008 by the Department of Health, entitled 'Review Criteria for Registration and Market Approval of Pharmaceuticals-Registration and Market Approval of Biologic Products'. TFDA published two additional guidelines subsequently: (1) Points to Consider for Review and Approval of Biosimilar Products (2010), and (2) Guideline for Review and Approval of Biosimilar Monoclonal Antibodies (2013).	https://www.amgenbiosimilares.com.co/pdfs/pages-from-amgen-biosimiliars-booklet_e-version-final.pdf

*COFEPRIS implemented modifications to the Official Mexican Standard (NOM) 177-SSA1-2013, in order to streamline the registrations of generic and biosimilar medicines [24]. It recognizes studies conducted in countries with criteria equal to or superior to those of Mexico, with health authorities accredited by WHO [24].

higher compared to generics, due to the complexity of biologic molecules. Waiving off regulatory requirements that might not be strictly essential can thus benefit biosimilar development costs and timelines [23]. According to the WHO guidelines, 'a comparative efficacy trial may not be necessary if sufficient evidence of biosimilarity can be inferred from other parts of the comparability exercise' [20]. Guidelines of the FDA, Health Canada, and EMA allow flexibility for phase III 'confirmatory' clinical safety and efficacy studies granted that specific essential requirements are met, such as the presence of PD biomarkers as

relevant markers or surrogates for efficacy [24]. Similarly, comparative clinical efficacy is not required in the UK, provided a solid scientific rationale exists for this [25].

Regulators in LMICs are also taking steps to streamline the approval process for biosimilars. In September 2023, Brazil's National Health Surveillance Agency (ANVISA) opened a consultation acknowledging the potential removal of certain studies or steps for biosimilar registration [26]. Similarly, for the registration of biosimilars, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) of Mexico announced the recognition of studies conducted in countries with criteria equal or superior to those of Mexico (with regulators recognized by WHO as reference regulatory authorities) [27]. With this measure, Mexico is also making progress in the implementation of a harmonization process through which local regulations are aligned with international standards or requirements [27].

The interchangeability debate

The requirement of interchangeability between an RP and its biosimilar or between two biosimilars highly varies among countries. Interchangeability remains an important yet challenging topic globally, and in LMICs, imprecise use of interchangeability remains an issue [28]. Table 3 provides the approach to the interchangeability status adopted by the countries that participated in the WHO survey [19].

In the concept of interchangeability, one product can be replaced with another by either switching, which is decided by a physician, or by automatic substitution at the pharmacy level. In the US, the biosimilar has to be denoted with an 'interchangeable product status' by FDA. Once denoted as an 'interchangeable biosimilar' it can be automatically substituted with the reference product at the pharmacy level. FDA determines a biologic product to be interchangeable with a reference product if: (1) the biologic product 'is biosimilar to the reference product' and 'can be expected to produce the same clinical result as the reference product in any given patient'; and (2) 'for a biologic product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch' [29]. In a recent development, FDA is considering eliminating interchangeability details from product labels as these are potentially confusing (according to the new draft guidance on biosimilar labelling) [30].

EMA defines interchangeability as 'the possibility of exchanging one medicine for another that is expected to have the same clinical effect'. This may imply changing an RP with a biosimilar (or the other way round) or a biosimilar with another. Such changes can happen via switching at the prescriber level [31]. There is no official position on interchangeability of a biosimilar at the EU level. Instead, several national regulatory authorities, including the Dutch Medicines Evaluation Board (MEB), the Finnish Medicines Agency (FIMEA), Healthcare Improvement Scotland, the Irish Health Products Regulatory Authority, and Paul-Ehrlich-Institute in Germany, have already taken national positions to endorse the interchangeability of biosimilars under the supervision of the prescriber [32, 33].

Table 3: Approach adopted towards interchangeability by the countries that participated in the WHO survey

Interchangeability (IC) Status	Countries
IC status given automatically upon approval of Biosimilar	Iran, Japan
IC status given depending on the clinical evidence provided by the biosimilar manufacturer	Brazil, Cuba, Ghana, Russia, Peru, Zambia
IC status based on the decision made by prescribers	Brazil, Canada, China, Egypt, EU Member States, Ghana, India, Indonesia, Jordan, Malaysia, Korea, Singapore, Thailand, Zambia

The WHO survey of 21 countries revealed that most LMIC countries do not have regulatory guidelines for the interchangeability of biosimilars, but many have adopted national approaches for this. As summarized in Table 3, most of the countries rely on the decisions made by the prescribers. However, Brazil, Cuba, Ghana, Peru, Russia, and Zambia also consider the clinical evidence provided by the biosimilar manufacturers [19].

It is important to note that both biosimilars and interchangeable biosimilars can constitute as safe and effective treatment options. Some prescribers fear that switching between non-identical but highly similar biologics can lead to loss of efficacy or adverse events. However, several reviews have confirmed the safety of switching from RPs to biosimilars. This includes a systematic review of 178 switch studies, encompassing over 20,000 switched patients, reporting no signs of such switching associated with any loss of efficacy or higher rates of side effects [31].

What are some actual and potential benefits of biosimilars?

Success stories from HICs

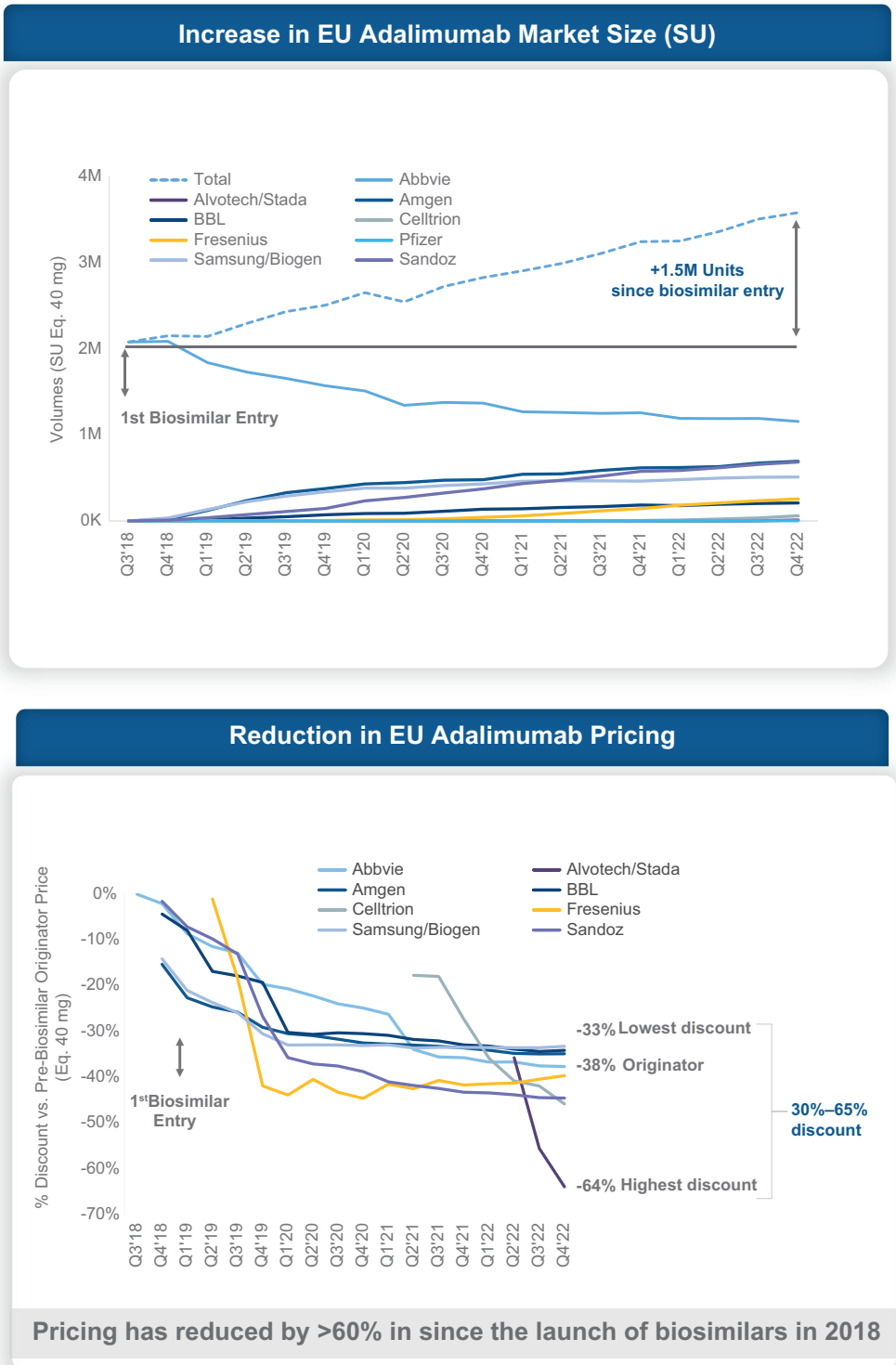
More data on the benefits of biosimilars for healthcare systems and societies are available in HICs, such as the US and European countries, compared to LMICs.

The biosimilar market share has been growing in HICs, with the total European biosimilar market reaching Euros 8.8 billion in 2021 [34]. As of 2022, biosimilar products comprised nearly 66% of the adalimumab share in the EU [35]. Notably, the impact of biosimilar competition led to cumulative savings at list prices of over Euros 30 billion in Europe by 2022 [36]. Figure 1 shows the market expansion and price reduction with the advent of adalimumab biosimilars in the EU.

Significant price reductions have also been associated with the market entry of biosimilars in the US. The cumulative savings in drug spending from the trastuzumab biosimilar launch between Q3 2019 and Q2 2022 was estimated to be US$5.3 billion in the US. Moreover, three years after the launch of the first trastuzumab biosimilar, the price of the RP declined by 19%, and biosimilars accounted for 80% of the share of all trastuzumab products [35].

A 2023 report by the US Department of Health and Human Services highlighted how biosimilar competition reduced costs for Medicare

Figure 1: The launch of adalimumab biosimilars has (A) expanded the market; and (B) reduced prices, making biologics more accessible



CAGR: compound annual growth rate.

Part B and enrollees. Opportunities remain to further decrease Part B and enrollee expenditure via increased utilization of more affordable biosimilars [37].

Biosimilars are not only linked to cost savings, but they also add value through increased access to medicines for patients. For instance, European data showed a substantial increase in the use of biologics and biosimilars when a biosimilar entered the market, which was attributed to reduced costs driven by competition [38]. Physician perspectives on biosimilars have also positively evolved, as demonstrated by a survey of 63 oncologists and immunologists showing more confidence in using biosimilars across various European countries [39].

Actual and potential benefits of biosimilars for LMICs

Despite more data being available for HICs, promising data on the potential and actual benefits of biosimilars also exists for LMICs.

Biosimilars are more cost-effective treatment options than their RPs and competing with RPs can contribute to decreasing RPs' prices and allow more patients to be treated. In Malaysia, for instance, insulin prices have dropped over 40%, and insulinization rates have improved by 30% since 2011, when biosimilars to RHI insulins were made available [40].

A study in Brazil estimated the impact of the lack of access to trastuzumab on the mortality of human epidermal growth factor receptor 2-positive (HER2-positive) patients with metastatic tumours in the national health system (NHS) in 2016. Of the 2,008 women diagnosed with advanced HER2-positive breast cancer, it was estimated that two years later, only 808 would be alive if they received only chemotherapy, 1,408 if

they received chemotherapy plus trastuzumab, and 1,576 if they received the gold standard of chemotherapy plus trastuzumab and pertuzumab [41]. Studies such as this one underscore the importance of adopting biosimilars in countries with sub-optimal accessibility to life-saving medicines, such as trastuzumab.

A recent study conducted in China confirmed equivalent clinical outcomes and lower prices of cancer care biosimilars compared to RPs, suggesting that increasing the uptake of biosimilars can benefit oncology patients. A systematic review and meta-analysis of 39 randomized clinical trials and 10 cohort studies found equivalent clinical outcomes between rituximab, bevacizumab, and trastuzumab and their RPs in China. In 2022, the estimated median weighted average prices for biosimilars of bevacizumab, rituximab, and trastuzumab in China were 74%, 69%, and 90% of the price of the RP, while biosimilars uptake rates were 83%, 74%, and 54%, respectively [42].

Governments, regulators, and physicians consider biosimilars as important treatment options in emerging markets

In 2014, the Colombian Ministry of Health and Social Protection highlighted that eight of its NHS's 10 most used medicines were biologics. If there were just two competitors for each of those eight biologics, the Colombian NHS could have saved 600 billion Colombian pesos [43]. In Mexico, the head of COFEPRIS emphasized in 2017 that biosimilars represent a safe option for the NHS to improve access to treatments for NCDs [44].

Many physicians now believe using biosimilars can reduce costs and increase patient's access to medicines. For instance, according to a survey among Malaysian oncologists, most oncologists (95%) agreed that prescribing a biosimilar would save healthcare costs, increase the accessibility of biologics (91%), and stimulate competition in the biologics market (88%) [45].

What are some barriers to biosimilar access and adoption?

Challenges of various natures remain towards increased access to and adoption of quality-assured biosimilars in emerging markets and, more broadly, in the global South. Insights on key access challenges were gathered mainly via a literature search and were complemented with interviews. A total of three interviewees from three countries, Nigeria (lower-middle-income), Colombia (upper-middle-income), and Taiwan (high-income), were interviewed to gather insights from different local contexts.

Weak regulatory frameworks

Despite progress, regulatory frameworks for biosimilars have different maturity levels across LMICs, with some remaining unclear or under development. Heterogenous regulations, non-adherence to regulatory pathways, and imprecise use of interchangeability (as well as insufficient pharmacovigilance) are common challenges [28]. These factors can impede or slow down access to quality-assured biosimilars. In particular, the African region has the highest prevalence of poor-quality medicines, with weak or absent regulatory systems largely responsible for this [46]. WHO estimates that one in 10 medicines in LMICs is substandard or falsified, with most reports of these products coming from Africa [47]. Unsurprisingly, the Nigerian interviewee flagged abuse and misuse of fake, counterfeit, and low-quality biosimilars. Possible identified causes for this issue included underdeveloped regulatory systems, easy access to cheap but low-quality or fake biosimilars, lack of education on biosimilars, not following the prescribers' guide, and difficulty securing follow-up appointments with doctors.

Inappropriate labelling of drugs as biosimilars

In LMICs certain non-innovator biotherapeutic products other than the originators or biosimilars are approved and can occupy a substantial proportion of the market. The dominant product class of human insulin, manufactured in various countries, is a key example of such a biotherapeutic.

A me-too/non-innovative/copy biotherapeutic product, i.e. non-originator and non-biosimilar, is defined as a biotherapeutic product developed on its own and not directly compared and analysed using a licensed reference biotherapeutic product as a comparator. It may or may not have been compared clinically. In the WHO survey, the existence of a regulatory framework for such products in the participating countries was assessed [19]. Brazil, China, Cuba, Malaysia, the Republic of Korea, and Thailand have formulated regulations for such products. Brazil had several such products on its market as non-innovator products, and all that were licensed before March 2002 have been reassessed in terms of efficacy and safety for each indication, that is, four somatropins, one filgrastim, one interferon, and two erythropoietins. On the other hand, China has 98 non-innovator biotherapeutics of 13 products approved by the National Regulatory Authority. However, there is no plan for their re-evaluation. These products range from the older ones like interferon and erythropoietin to newer monoclonal antibodies (mAbs) like adalimumab and bevacizumab. The complexity of this situation becomes a barrier to the uptake of biosimilars as it decreases confidence in biosimilar uptake.

Dependence on importation

Given the difficulties in encouraging local manufacturing, many LMICs are highly dependent on importing biosimilars from other countries, making them vulnerable to shortages and contributing to illegal transactions and circulation of substandard and falsified medicines, such as in the African region. However, as noted by the Nigerian interviewee, stakeholders in LMICs are often interested in exploring partnerships with biosimilar companies to secure local manufacturing and procurement agreements.

Low awareness of biosimilars

Different stakeholders may still be unaware of the use of biosimilars in some LMICs. Prescribers may lack the confidence to prescribe biosimilars, and patients might lack trust in biosimilars. The Colombian interviewee stressed that patients tend to think that biosimilars may have quality issues and noted that such negative perception is likely to originate from the HCPs, which ends up influencing patients. A survey among Nigerian pharmacists published in 2022 suggests a lack of knowledge of biosimilars, as most pharmacists incorrectly responded that a biosimilar is structurally identical to its RP [48].

Lack of effective policies encouraging access to and use of biosimilars

The lack of policies and guidance encouraging access to and use of biosimilars may also contribute to sub-optimal biosimilar

use. The Taiwanese interviewee noted a need for a clear policy to encourage hospitals to adopt biosimilars into their formularies. According to the interviewee, hospitals still prefer to use the RPs as not much educational awareness and/or effective incentives are given to use biosimilars.

To summarize, better access to biosimilars in LMICs is not only a matter of availability but also education, training, capability building, capacity management, better distribution infrastructure, and distribution systems. The LMIC drug regulators should focus on reducing counterfeit or low-quality biosimilars, black-marketing, unethical marketing, product manipulation, and corruption at various levels [49].

Boxes 2, 3 and 4 present a summarized version of the interviews held with former government officials or people affiliated with governments and familiar with the reimbursement of biosimilars in Nigeria, Colombia, and Taiwan.

Policy recommendations

Policy recommendations for accessing and using quality-assured biosimilars in LMICs are outlined below. These recommendations should be considered as general guidance and not as 'one-size-fits-all' policies. Not all recommendations may be relevant to all LMICs, and these should always be tailored to the local contexts and economies in different countries.

Strengthening regulatory systems

Regulatory requirements for biosimilar licensing in LMICs should be strengthened to facilitate approval of safe and quality-assured biosimilars. Following examples from WHO and stringent regulatory authorities, i.e. the US FDA and EMA, can help LMICs in this engagement. In Africa, establishing the African Medicines Agency (AMA) could help pool regulatory resources among countries, facilitate access to quality-assured medicines, and help fight counterfeit medicines [46, 50]. As of October 2023, 27 African countries had ratified the AMA treaty, and other countries had signed and were expected to ratify it [51]. Finally, while it is key for regulatory pathways to be stringent enough to ensure only effective, safe, and high-quality biosimilars can enter the market, streamlining requirements when there is sound evidence to do so can contribute to accelerating biosimilars' development.

Strengthening pharmacovigilance

Pharmacovigilance systems should be strengthened to monitor, and report suspected reactions or adverse events appropriately. Given biosimilars' complexity, pharmacovigilance is important to evaluate their long-term safety [52].

Providing guidance for prescribing biosimilars and increasing education on biosimilars

Providing clear guidelines for prescribing biosimilars can help to increase prescribers' confidence in prescribing biosimilars. Additionally, increasing patient education on biosimilars, especially in countries where these may be linked to low levels of trust, can mitigate possible nocebo effects, wherein the symptoms or adverse events are mainly due to patients' negative perceptions about the product rather than its mechanism of action, efficacy or safety [53]. As highlighted by the Nigerian interviewee, initiatives from multiple stakeholders (including members of government, non-governmental organizations, healthcare professionals, and the media) can educate the patients on key topics such as counterfeit biosimilars (and how to potentially recognize them) and the importance of following treatment guidance from trusted sources.

Strengthening national policies to increase access and adoption of biosimilars

Depending on the local context, national policies should be implemented to support increased access to and adoption of biosimilars. Relevant national policies could include promoting higher reimbursement levels for biosimilars and providing incentives to prescribe biosimilars, as narrated by the Taiwanese interviewee.

Encouraging local manufacturing

Encouraging local manufacturing can facilitate stable supply and availability, and consequent access, to biosimilars in the LMICs. Global companies may increase their manufacturing presence in LMICs or may improve the manufacturing capabilities of other local manufacturers via technology transfers, which could be part of licensing agreements. Ideally, promoting local manufacturing should be part of a wider plan to improve business conditions in certain LMICs.

Encouraging stakeholders' initiatives promoting access to biosimilars

At both local and global levels, various initiatives led by different stakeholders can improve access to biosimilars in the LMICs. Company-led initiatives can involve partnerships with local authorities, patient support programmes, and free access to patients. Initiatives led by international organizations such as the WHO PQP can support countries to acquire quality-assured biosimilars.

Potential selection criteria for quality-assured biosimilars

Following a biosimilar's regulatory approval, public and private payers make purchasing decisions to choose amongst potential biosimilars. Acknowledging that a biosimilar's price and affordability requirements remain key factors for payers in LMICs, there are additional criteria beyond price to help stakeholders choose quality-assured biosimilars.

Product characterization and quality

The manufacturing process of each biotechnological medicinal product undergoes several changes during its life cycle, which may have a substantial impact on the product. Therefore, the new and previous versions should be deemed to be comparable by appropriate tests, usually physicochemical, structural, and *in vitro* functional tests [54]. The demonstration of comparability does not have to mean that the pre-change and post-change products are identical but that they are highly similar, and that the existing knowledge is sufficient to conclude that the observed differences have no adverse impact on the safety or efficacy of the medicinal product [18]. The advancement in protein structure characterization and other processes has led to many improvements in the manu-

Box 2: Summary of interview 1 (Nigeria)

Brief overview of job role relating to access to biosimilars.

- Medical practitioner with a humanitarian agency (NGO) working for the Federal Ministry of Health, State Ministry of Health, and local Government agencies.
- In Nigeria, 80%–90% of the population feels comfortable with the regular consumption of medicines. Many times, the medicines, both generics and biosimilars, are bought directly from the pharmacies without a physician's prescription *(Healthcare spending in Nigeria is predominantly a private affair, with out-of-pocket spending accounting for 70 per cent of total health expenditure)*.*

What are the most common conditions for which you think biosimilars are taken? Biosimilars are not generic drugs and are needed to cure specific diseases.

- Let's talk about breast cancer. This is a very common disease in Nigeria, where most of the females at their reproductive age have that belief of taking any medication that helps with breast cancer. Some medical supply agencies in Nigeria directly, advise patients to take biosimilars.

Which regulatory agencies look after approval for medicines in Nigeria?

- In Nigeria, we have two agencies that are looking into this—NAFDAC (National Agency for Food and Drug Administration and Control) and NDLEA (National Drug Law Enforcement Agency). They keep emphasizing and telling people to avoid taking drugs, except based on the physician's prescription. However, the physician-to-patient ratio is so skewed that not everyone can meet the consultants/specialists. One physician can treat 200 patients in a hospital in a day. This is the reason why people are not limiting themselves to the physician or the health professionals' advice before they take any particular drugs.
- Three categories of healthcare exist in Nigeria: primary healthcare, secondary healthcare, and tertiary healthcare. Government agencies and international agencies are supporting Nigerian doctors and health workers. However, many doctors who graduate in Nigeria leave for other countries for better opportunities.

How are patients affording biosimilars, as these are expensive, and from where are they accessing them?

- It depends on the category of the people. The rich go to the specialists and take medicines based on the physician's prescription. However, the poor are taking low-quality biosimilar medications that are sold by some companies at very discounted rates.

How do you think these low-quality biosimilars manage to enter the system? What about the regulatory framework?

- Many drugs bypass the regulatory bodies or enter through porous borders. There are many medications we have now in Nigeria that are approved by NAFDAC; however, some of these get through with minimum regulations.

What would help win the decision-makers from biologics over to quality biosimilars?

- One, the national regulatory agency, NAFDAC, has to tighten the approval process to wean out companies that bring fake or low-quality biosimilars into the system.
- Second, NDLEA has to strictly enforce its presence even at the local government level.
- Thirdly, a lot of sensitization, awareness, and communication needs to happen at every level, including at the community level. Physicians, Healthcare workers, media, and NGOs should be engaged in creating awareness of low-quality medicines and their harmful effects.

What would be the list of quality criteria for biosimilar selection that you currently follow for your purchasing decisions?

- We have a Biosimilar Guidance Document. (*As part of its mandate for assuring the quality, safety, and efficacy of regulated products in Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) sets nationally accepted norms and standards for the evaluation of these products.)**
- A biosimilar comparability approach is followed, supported by analytical characterization, and the comparability exercise at the quality level may allow for a reduction of the non-clinical and clinical data requirements as compared to a full dossier.
- Global companies coming to Nigeria with their biosimilars should have valid approvals from their regulatory agencies. Also, the sites should be inspected for manufacturing processes to ensure that the biosimilars are of high standards.
- Since 90% to 95% of the medicines in Nigeria are imported, the government should encourage global companies to start manufacturing biosimilars in Nigeria. More control over quality can be had in this way.

In your opinion, what should be the ideal criteria for governments to select quality biosimilars? Is there anything else that you would consider? Such as a high number of approvals in other countries, inspection history, or even data on the product's adverse events.

- NAFDA has processes for that. In addition, there are laboratories here in Nigeria that make sure that the drugs have been tested in their laboratory for quality.
- Biosimilars approved in Europe, or the US are considered to be of high quality.

What challenges and barriers stand in the way of better adoption of quality biosimilars in Nigeria?

- Foremost is the price, then availability. Lastly, there is a lack of awareness and sensitization among both physicians/clinicians as well as the consumers in the community.

Why do you think there is a lack of availability?

- There are two issues: the high availability of poor-quality biosimilars or fake biosimilars and the limited availability and high cost of high-standard biosimilars.

What could stakeholders other than the regulators, such as the industry, healthcare professionals, and patients, do to contribute towards increasing patient access to biosimilars?

- These stakeholders need to engage in creating sensitization towards high-quality biosimilars. They need to engage with the Federal government, the local government, and the traditional leaders in the community to help through campaigns or training and create more awareness.

Box 2: Summary of interview 1 (Nigeria) (*Continued*)

Are you aware of any publication, either in English or even in the local language, that talks about all these problems using data convincingly?

- This can be a very good approach. It will be good to broadcast and send messages in the local languages of the communities. These communications can be sent to the communities, the hospitals, and the healthcare sector.

Could you summarize very briefly the steps from regulatory approval to market access?

- This can happen in two ways. If the pharma company has a direct contract with the government, the government becomes the custodian of those medications. The Federal Ministry of Health buys drugs from these companies and then, after the clearance, distributes them to every state based on the needs of the state or community. So, the drugs move from the Federal Government to the State government, from the State government to the local government authorities.
- For the private companies, once NAFDAC approves the drugs, they go to the dealers and negotiate with them. They also advertise heavily to the beneficiaries and convince them to buy their products, sometimes even before the drug comes on the market. Challenges arise when once the government comes with the original one, it becomes very difficult for the government to convince the people because private companies have already followed the right channel in terms of advertising and have sensitized people into buying their product

*The italicized content has been added separately to bring in more context and clarity.

Box 3: Summary of interview 2 (Colombia)

Brief overview of job role relating to access to biosimilars.

- The interviewee was an erstwhile senior resource at the Colombian Ministry of Health. He was involved in developing pharmaceutical policies in Colombia.

What is the process of accessing biosimilars in Colombia? What factors are considered?

- The process for the arrival of a biosimilar in Colombia is first to have a licence or sanitary registration with INVIMA (National Institute for Food and Drug Surveillance). Colombia has one of the most advanced regulations in the region. The guideline/decree that establishes new biologics and biosimilar registrations was established in 2014.
- A biosimilar registration in Colombia can be established through three routes to have a sanitary registration or licence. First is the complete filing, where the manufacturer must effectively deliver everything from analytical characterization to preclinical studies to clinical studies. The second route is the biosimilar comparability route, and the third is the abbreviated comparability route. The biosimilar comparability guidelines were based on the WHO guidance.
- Colombia has had several biosimilars on the market for a long time such as rituximab, trastuzumab, infliximab, and almost all have entered through the biosimilar comparability route and not the abbreviated route.
- In Colombia, the government is not directly involved in purchasing medicines. *(Colombia's healthcare system operates a public health insurance plan called Entidades Promotoras de Salud (EPS) which is administered by various insurance companies, including SURA, Comfenalco, and Coomeva)*.*
- Biosimilars are either bought directly by the insurance company that negotiates with the product laboratories or by the health centre, which acquires the medicine and later bills the insurer. Either of the two buyers take care of all aspects, whether to obtain the originator biologic or the biosimilar and also the quality and the price. For quality, they usually use data from comparability studies.

How do bidding decisions or reimbursement of biosimilars work in Colombia?

- The bids for biosimilar purchases are made by pharmaceutical managers working for companies that may have contracts with the insurers or directly by the insurance companies.

What perceptions and fears are perceived in the way of a better and faster adoption of biosimilars?

- The first barrier is obtaining sanitary registration, which is becoming a very long and expensive process since registering a biosimilar can take three to five years.
- The other problem is doctors' distrust of generic drug products, especially biosimilars, as these are more complex.
- However, that does not mean that it cannot be done, as currently, in the country, there are eight biosimilars of rituximab in the market, and these are beginning to gain market share.
- There is an important point: you can initiate the process of registration of a product that still is under patent, though you cannot market it.

What would help decision-makers switch from biologic products to quality biosimilars approved in regulated markets?

- First, it is the quality and the evidence of it. In addition to the comparability studies, the pharmacovigilance reports and real-world evidence also help. More robust evidence is if other regulatory agencies have approved these biosimilars, particularly if these are the strict regulatory agencies of the EU, Japan, Korea, Australia, the United States, and Canada. It also helps if regulators in Latin American countries, such as ANVISA in Brazil or the Public Health Institute (ISP) in Chile, have reviewed the evidence.

While approving a biosimilar, are the company's manufacturing capacity to guarantee supply, adverse events, and inspection history also considered?

- All of this is a part of the approval process, not only the characteristics of the product but also the entire manufacturing process; the producer must have Good Manufacturing Practices (GMP). INVIMA either accepts certification of GMP from a European agency, the United States, or Japan or sends inspection teams for a GMP inspection.

Box 3: Summary of interview 2 (Colombia) (*Continued*)

Do you have any recommendations for improving the processes?

- Colombia has a regulatory framework that favours the arrival of biosimilars, and the biosimilars market is well organized, in general. It works quite well and is competitive. For a country to have eight different rituximab molecules is because there is interest and benefit for all, though not all of them are marketed at the same level.
- What could promote the purchase and dissemination of the biosimilars is to convince the buyers that it is a quality product, provide information on the countries that are already using it, which key regulatory authorities have approved the product, and provide follow-up information on pharmacovigilance in the countries where it is already being used. Also, providing the opinion of the doctors about where it is being used becomes very important in positioning the product.
- Provide information upfront on the production capacity and the guarantee that this supply of production and quality will be sustained over time. Whoever is going to want to buy would want to have all the data, such as detailed safety data, pharmacovigilance reports and real-life evidence.
- In general, comparability tells you that they are comparable but there are very few studies that tell you that a therapeutic substitution or switching can be done.

What actions could the government be taking to increase patient access to quality biosimilars in Colombia?

- The government can speed up the sanitary registration process in INVIMA. The other measure is the regulation of prices of biosimilars, to avoid price erosion when too many biosimilars enter the market.

What is the perception of patients about biosimilars?

- In general, the patients' acceptance of generics and biosimilars is good if the doctor prescribes them. However, evidence from other Latin American countries says that patients tend to have a perception that biosimilars may have quality issues, which may influence the patients in Colombia.

Does the government carry out post-approval quality control tests?

- Yes, and this quality control has two aspects, one, if within the pharmacovigilance framework, there appears to be any sign that indicates the drug had a problem, INVIMA regulatory agency could carry out additional tests to show if there was any change. The other thing is that in the process of approval of the sanitary registry, INVIMA could place the condition on the biosimilar manufacturer that it has to carry out phase IV studies of the safety or effectiveness of the biosimilar in real life.

How can other interested parties contribute to increasing the interest of patients, payors, and prescribers in biosimilars?

- Communication can do a great job of advocating quality biosimilars amongst health personnel and patients. The message is that biosimilars, though not the same, demonstrate the capability of achieving the same effectiveness and safety as the originator.

Who should carry out these communication campaigns for patients and doctors?

- A great effort for these communication campaigns would be to bring together the government, academia, industry, doctors, and patients. INVIMA carried out a project called 'Demonstrate Quality' that aimed directly at showing the quality of the products and increasing their credibility. Unfortunately, that programme rigour has since declined. Definitely, new ideas must come from the government and from stakeholders who want to increase the biosimilar shares in the market.

*The italicized content has been added separately to bring in more context and clarity.

facturing and product testing that a biosimilar manufacturer can measure up to 100 critical quality attributes (CQAs) across 40 or more biochemical, analytical, pharmacological, or functional assays to ensure bio-similarity [29]. The national control laboratories at LMICs should ensure that adequate tests are carried out to check that the biosimilar products comply with WHO specifications to provide assurance to prescribers, payors, and patients on the product's quality prior to release in the market [20].

Regulatory approval in developed countries

A biosimilar's regulatory approval by a regulatory authority that is a part of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), such as the US FDA, EMA, and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, could increase LMICs stakeholders' confidence in the quality of a biosimilar. Additionally, the WHO PQP allows LMICs to adopt pre-qualified biosimilars with confidence.

Adverse events

In addition to considering the adverse events that emerge from the clinical trials, pharmacovigilance data and results from post-marketing studies can provide additional useful information on the safety of a biosimilar.

Availability of real-world evidence (RWE)

RWE, even from the HICs, can further reassure payers about a product's safety, efficacy, and quality. The RWE can provide information on the use of a biosimilar in populations not included in clinical trials, such as diverse ethnic groups, and potentially information on the biosimilar's use in other indications (not explored as part of the original clinical trials).

Product packaging

Clear packaging and barcoding on the product's per-dose packaging can help limit medication errors [55] and potentially help distinguish between quality-assured biosimilars and fake or counterfeit biosimilars.

Related devices/delivery mechanisms

The possibility of administering the biosimilar via patient-friendly devices or delivery mechanisms (for instance, insulin pens) can be valuable and improve HCPs' and patients' experience.

Capability, capacity, and presence of the manufacturer

The manufacturer's capability, capacity, and geographical pres-

Box 4: Summary of interview 3 (Taiwan)

Brief overview of professional background and current position in National Health Insurance Administration (NHIA).

- Professional background was in pharmacy with a specialization in the field of pharmaco-economics. The interviewee had experience related to health insurance reimbursement including related to the work of the (Pharmaceutical Benefit and Reimbursement Scheme) joint committee in the NHIA. He had more than eight years of experience related to health insurance reimbursement.

Any connection with the reviewing of biosimilar applications?

- Yes, any biosimilar to be included in the reimbursement of health insurance is also sent to the expert meeting and the joint committee to make a decision. It is very relevant to be included in the list of health insurance reimbursements.

If a new biosimilar enters the Taiwan market, regarding the whole process, from the evaluation and review of the listing to the health insurance and even to the procurement at the hospital end, could you please tell us about the process and details as far as you know?

- Any biosimilar that would like to enter Taiwan, the first step will be to go to the Taiwan Food and Drug Administration (TFDA) to obtain a drug licence. TFDA will have a specific meeting to review relevant data and materials for drug licences. Once biosimilar obtains the drug licence, it can apply for listing in the health insurance benefits. The manufacturer must send the required data to NHIA. In the NHIA internal expert review meeting, the clinical efficacy, safety, and prices of the biosimilar will be discussed first, and then the joint meeting will have a follow-up discussion for the final decision. In addition to expert committee members and representatives of government agencies, there will also be representatives of various hospital associations, representatives of various levels of medical institutions, and representatives of patients who can be present. As Taiwan has a national health insurance system, most medical institutions have a contract with health insurance. Therefore, each pharmaceutical firm negotiates with the drug review committee of each hospital to enter the hospital and be on the health insurance reimbursement list.

As for TFDA, what criteria will be reviewed if biosimilar manufacturer wants to obtain the licence?

- In principle, the efficacy and safety are reviewed as per the biosimilar guidelines of TFDA.

However, as mentioned, health insurance will also review the efficacy and safety of the products. Is there any difference between the content and the method of the TFDA review?

- In fact, NHIA's review for the reimbursement of biosimilars now largely relies on the relevant review conducted by TFDA for drug licences. NHIA also discusses the pricing of the biosimilar, which, under the current framework of health insurance, is basically the price of its reference drug (originator) at a 15% discount. If a manufacturer wants to be listed in the health insurance, sometimes they provide some corresponding discount.

You just mentioned a 15% discount for health insurance, but when it comes to hospitals, how can these biosimilars be used by hospitals?

- The health insurance price is the same for all hospitals. When hospitals purchase drugs, they will talk with the pharmaceutical firms for another agreement, in which the pharmaceutical firm may provide an appropriate discount to the hospital.

What hindrances are perceived in the way of a better and faster adoption of biosimilars?

- The main problem for biosimilars in Taiwan is that the market share of biosimilars is not very high. In fact, Taiwan does not have a very clear policy to encourage hospitals to adopt biosimilars, so the biosimilar market share is not very high. Hospitals still prefer to use the originator biologics.

What do you think is the reason for this situation?

- The first is that the originator actually has a high market share. Hospitals, unless you have a good reason, do not have to change from the originator to the biosimilar. For example, in some European countries, the government encourages the use of biosimilars; maybe the health insurance agency gives specific profits to hospitals. However, with no such policy here, competing well with the originator becomes difficult.

It had been mentioned that the pharmaceutical firm would have to contract with the hospital individually and set a procurement price. When hospitals evaluate the procurement of such a biosimilar, what are the factors they consider?

- First, for example, if they can get a good discount. Second, the main disease areas for biosimilars are oncology and some specific immune diseases. If the patient is used to the originator, he/she does not want to change. Most important is the demand by the hospitals. Even if the biosimilar is listed in a hospital, if no physician prescribes this biosimilar, the firm gets no market either.

Is there any other challenge or obstacle to the use of biosimilars in the Taiwan market?

- At present, there is no clear policy that encourages the use of biosimilars, so the hospitals may not want to change to biosimilars without specific reasons. This is a big obstacle.

What actions do you think the government can take to improve the use of high-quality biosimilars?

- There has been some discussion on biosimilars in the past two years in relevant societies. Of course, we have actually referred to many global examples of encouraging biosimilars. Regular communication and continuous education are very important to let doctors know the quality of biosimilars compared with the originators so that they have confidence in biosimilars and are more willing to use them. Another way is to modify the policy. For example, in some countries, the first step is to let the patient use a biosimilar when starting a new patient. There are many similar situations across the globe. The EU is the first to vigorously promote the use of biosimilars.

Box 4: Summary of interview 3 (Taiwan) (*Continued*)

What can pharmaceutical companies do to improve the use of biosimilars?

- Taiwan is still a national health insurance system, so biosimilars have to be included in the health insurance reimbursement first and then listed in the hospital. The crux of the problem is that NHIA still fully reimburses originator drugs, and the patient has no intention to use biosimilars.

NHIA has been discussing copayment before. If the rules of copayment come up, do you think it will help biosimilars?

- It depends on how the copayment policy is designed. Because what we are talking about is still an overall copayment. It depends on the design of the copayment policy to know the impact on biosimilars, or the government should have a strong policy to adopt biosimilars to a large extent.

ence can impact the availability of a biosimilar. Payers could consider the following characteristics of the manufacturer: experience and reputation with biosimilars; records related to products' quality; supply conditions such as the number of manufacturing centres; manufacturing location; supply chain resilience; positive history related to shortages and recalls; capability to maintain adequate production; and counterfeit protection [56, 57].

Additional services offered by the manufacturer

Additional offerings, such as educational materials, can be helpful during treatment initiation and continuation for HCPs and patients.

Conclusion

Biosimilars are more affordable treatment options than their RPs and can help increase access to medicines in LMICs and HICs. Experiences from the HICs confirm several benefits of biosimilars. Biosimilar companies actively market their products in LMICs, creating opportunities to expand treatment options, particularly needed for under-served and under- or un-insured communities. As governments and other stakeholders increasingly recognize the potential of biosimilars in addressing accessibility and affordability challenges, more biosimilars are likely to enter the global market. Increased access to biosimilars can benefit health systems and economies by increasing competition and reducing the prices of expensive biologics. Despite establishing regulatory pathways for biosimilars in LMICs, focused approaches are required to strengthen the regulatory requirements further and facilitate access to quality-assured biosimilars. Additional challenges related to adopting quality-assured biosimilars persist across LMICs and may include dependence on importation, low awareness of biosimilars, and lack of effective policies encouraging their access and use. Recognizing that affordability remains a critical factor when making decisions around procuring biosimilars, stakeholders in LMICs can consider some characteristics of the product and the manufacturer to ensure the selection of quality-assured biosimilars. Proposed policy recommendations to promote access to biosimilars in this review article include strengthening regulatory systems and pharmacovigilance, providing guidelines for prescribing biosimilars, increasing education on biosimilars, strengthening national policies to increase access to and adoption of biosimilars, encouraging local manufacturing, and encouraging stakeholders' initiatives promoting access to biosimilars.

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Data availability statement

The data supporting the research findings are available from the corresponding author upon reasonable request.

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