Streamlining breast cancer and colorectal cancer biosimilar regulations to improve treatment access in Latin America: an expert panel perspective

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In a multiday conference, a panel of Latin American experts in biological cancer therapies and health economics were provided with questions to address the barriers restricting access to biosimilars in Latin America, specifically for patients with breast cancer and colorectal cancer, for whom biosimilars can be a path forward to increasing access to care. During the conference, responses were discussed and edited until a consensus was achieved. The regulatory challenges identified in the conference included heterogenous regulations, non-adherence to regulatory pathways, scarcity of market opportunity, inadequate naming of biosimilars by only using international non-proprietary names, imprecise use of interchangeability and substitution, and insufficient traceability and pharmacovigilance. Recommendations were developed to improve the implementation of regulatory pathways and reliable procurement strategies that increase access to these therapies with adequate traceability and outcome measures; efforts from all involved stakeholders will be crucial. These recommendations can serve as a strategy for biosimilar adoption in other countries in a similar situation.

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Introduction

Breast cancer is the second most common cancer and colorectal cancer is the third most common cancer in Latin America.[1] They are responsible for the second and third highest cancer-related mortality in Latin America, with 69 435 deaths from colorectal cancer and 57 984 deaths from breast cancer in 2020.[2] According to the 2019 Global Burden of Disease study,[3] both cancers are cumulatively responsible for approximately 18% of the total disease burden attributable to cancer in the region.

In the late 1990s, biologics revolutionised cancer care.[4] These therapeutic products are manufactured with living systems, including monoclonal antibodies, small proteins, and hormones, among others. They have become an integral part of breast cancer care with the advent of trastuzumab, a monoclonal antibody directed against HER2, which is most notably licensed for HER2-overexpressing breast cancer.[5] Similarly, biologics are often used in advanced treatment of colorectal cancer, including antiangiogenic agents such as bevacizumab, aflibercept, and ramucirumab.[6]

However, a major barrier to widespread access to biologics is their high cost and scarce availability, especially in resource-poor settings. Biosimilars have been developed as an approach to drive down drug costs and increase access to biological therapy by using older biopharmaceuticals that have come off patent.[7]

The definition of a biosimilar is not globally standardised, but the definitions provided by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and WHO share substantial resemblances.[7] In this Policy Review, a biosimilar will be defined as a biological product that is highly similar, and has no clinically meaningful differences in terms of quality, safety, and efficacy, to an already approved product (ie, originator).[8]

Biologics are larger and more complex than small-molecule generics, and therefore production can be difficult to standardise.[9] Approval and authorisation of a biosimilar require sufficient and satisfactory data on pharmaceutical quality, safety, and efficacy standards, all of which are already approved for the originator. Biosimilarity between biosimilars and their originator products in terms of structure, biological activity, and immunogenicity profile is the goal of biosimilar development.[10] Biosimilars have been widely recognised as one of the many strategies to improve the affordability of cancer care globally; however, except for Mexico, Argentina, and Brazil, their uptake in Latin American countries has been slow due to many of factors, including regulatory barriers, different legislature, and market opportunity challenges.[11,12]

In contrast to biosimilars, intended copies (also known as non-comparables, biocopies, biomimics, and non-regulated biosimilars) are copies of originators that have not undergone the stringent regulatory process for biosimilars. They might have clinically significant differences in formulation, doses, efficacy, and safety compared with originators and are not available in highly regulated markets such as the USA, Europe, and Australia. However, they are less expensive than originators and are highly available in less regulated regions such as Latin America.[13] Despite not knowing the risks of using these understudied drugs, intended copies have broadened accessibility of biologics in countries with fewer regulations; for example, in Mexico, 23 intended copies were registered in 2011.[14] Intended copies can also lead to other problems. For instance, Kikuzubam (Probiomed, Mexico City, Mexico), an intended copy of rituximab available in some Latin American countries, was eventually withdrawn from the market because of unacceptable toxicity and concerns of anaphylactic reactions when the

intended copy, Kikuzumab, and the originator product, rituximab, were interchanged.[15,16] Overall, the use of intended copies does not align with WHO guidelines for biosimilars[17] and should be discouraged, since little information exists about their efficacy and safety compared with originators.

Methods

To address these regulatory issues, the Americas Health Foundation (AHF) conducted a literature review using PubMed, Embase, and Google Scholar to identify scientists and clinicians from Latin America who have published in oncology, biosimilars, or health economics from Jan 1, 2014, to Aug 1, 2021. To augment this search, AHF contacted several individuals in Latin America to tailor a list of individuals qualified for proposing region-specific recommendations. As a result, AHF convened an eight-member panel of clinical oncologists and health economists from Chile, Colombia, Ecuador, Guatemala, and Peru. All invitations sent to the eight expert panellists were accepted.

AHF developed specific questions for the panellists (appendix) to address the salient issues concerning the regulation of biosimilars. Subsequently, a written response to each question was drafted by individual panel members and each narrative was edited by the entire group through numerous drafts and rounds of discussion until unanimous consensus was obtained. Two weeks later, the members of the panel reviewed the document to again acknowledge that they were in full agreement.

See Online for appendix

Search-engine websites of Colombian,[18] Chilean,[19] Ecuadorian,[20] Guatemalan,[21] and Peruvian[22] government agencies were used in our seach of the biosimilars.

Biosimilar availability globally and in Latin America

Biosimilar availability varies widely among and within regions worldwide. In Europe, for example, 67 biosimilars have been approved by the EMA, whereas in the USA, only 33 biosimilars have been approved by the FDA, of which 18 have been launched so far.[23] Market launches in Europe generally occur soon after the originator's patent expires. However, in the USA, launches are delayed for various reasons, including anticompetitive behaviours and other regulatory dynamics that might discourage market uptake of biosimilars.[23] A similar situation to that in the USA has occurred in most Latin American countries.[24]

Mexico, Argentina, and Brazil have established regulatory processes and achieved a solid developmental and manufacturing base, which has increased access to biosimilars. As of 2020, these countries had the most approved biosimilars in Latin America, with 44 products approved in total.[25] However, biosimilar availability in other Latin American countries is expectedly less than in Mexico, Argentina, and Brazil, because regulatory initiatives began later and fewer market opportunities exist. As of 2020, 14 biosimilars were approved in countries in the Andean region (Bolivia, Colombia, Ecuador, and Peru), and 18 biosimilars were approved in countries of the MERCOSUR trade bloc (Chile, Paraguay, Uruguay, and Venezuela).[25]

In this Policy Review, we focussed on several Latin American countries (Colombia, Chile, Ecuador, Guatemala, and Peru) that have different and inconsistent regulatory processes for biosimilars, yet have an inherent need to increase access to biological treatments for patients with cancer. The biosimilars approved for the treatment of breast cancer and colorectal cancer in the five Latin American countries represented by the eight members of the panel are shown in table 1.

Efficacy and safety outcomes of biosimilars compared with originators in breast cancer and colorectal cancer

In 2013, the first biosimilar approved for breast cancer treatment was a trastuzumab biosimilar candidate (trastuzumab-pkrb [CT-P6]) tested in a phase 3 trial.[26] This trial showed that, when used in combination with paclitaxel, the biosimilar was non-inferior in overall response compared with the originator.[26] Since 2017, the EMA and FDA have approved several trastuzumab biosimilars for breast cancer treatment.[27]

Clinical evidence has shown either non-inferiority or equivalence of the four trastuzumab biosimilars already approved for breast cancer treatment in Latin America compared with the originator (table 2).[34]

For many originator biologics with recent or upcoming patent expirations, new formulations with slight variations in presentation have been developed so that patent holders can file continuations (ie, revisions of patent applications or patents for second uses) to extend the originator's patent. For trastuzumab, evidence suggests that the pharmacokinetics of subcutaneous and intravenous trastuzumab are similar.[35] Therefore, in countries with scarce resources and access restrictions to biologics, use of the higher cost subcutaneous originator would only be reasonable if the formulation had shown clinical or real-world benefits compared with the intravenous biologic or biosimilar. However, a systematic review reported that the potential benefits of the subcutaneous formulation (eg, patient convenience) have not been measured or reported and might not be relevant in real-world scenarios.[36]

Bevacizumab (a vascular endothelial growth factor antibody) has a broad use in oncology with several indications. This monoclonal antibody has been approved for treatment of colorectal, brain, non-small-cell lung, and renal cancers, among others. In the USA, plans to manufacture a biosimilar for bevacizumab were announced in 2012, but the product was only approved by the FDA in 2017, for all eligible indications authorised for the originator product (ie, since the release of the

	Trastuzumab-anns*(ABP 890)	Trastuzumab-pkrb* (CT-P6)	Trastuzumab-dkst* (MYL-1401O)	Trastuzumab-qyyp* (PF-05280014)	Bevacizumab-awwb†	MB02†	Source
Colombia	..	2021	2018	2019	2019	2020	INVIMA[18]
Chile	..	2020	2019	..	..	Under review	ISP[19]
Ecuador	2021	2020	..	2021	2021	..	ARCSA[20]
Guatemala	..	..	2017	..	..	..	DRCPFA[21]
Peru	2020	150 mg dose approved in 2020; 420 mg in 2021	2019	2019	2021	..	DIGEMID[22]

INVIMA=*Instituto Nacional de Vigilancia de Medicamentos y Alimentos*. ISP=*Instituto de Salud Publica*. ARCSA=*Agencia Nacional de Regulación, Control y Vigilancia Sanitaria*. DRCPFA=*Departamento de Regulación, y Control de Productos Farmacéuticos y Afines*. DIGEMID=*Dirección General de Medicamentos, Insumos y Drogas*. *Biosimilar to the originator trastuzumab. †Biosimilar to the originator bevacizumab.

Table 1: **Approvals of breast cancer and colorectal cancer biosimilars by year and country**

biosimilar, the originator product has lost its regulatory exclusivity).[37] If the totality of evidence for bevacizumab biosimilars comprises appropriate comparative analysis, most suitably conducted in patients with non-small-cell lung cancer, then extrapolation to other eligible indications, such as colorectal cancer and other types, can be scientifically justified.[38]

Particularities of biosimilar regulations

The biosimilar approval process differs from the usual generic drug approval processes. For example, the development and manufacturing of biosimilars and generics differ in time, costs, and scientific complexity, and therefore require differentiated approval routes.[15] Moreover, because biosimilars are a follow-on biologic (ie, a copy of the original biologic once its patent has expired), they must follow a specific regulatory process that includes foundational analytical studies, good manufacturing practices, and comparative non-clinical and clinical studies establishing similarity in pharmacokinetics, pharmacodynamics, and toxicity with the originator. Clinical studies are needed to show similar efficacy, safety, and immunogenicity profiles of the biosimilar to the originator.[15] Once these processes are reviewed by a reliable regulatory agency, such as the FDA or EMA, the approval procedure for biosimilars in other countries or regions should be a relatively simple documental process, in which documents already approved by reliable agencies are submitted, and no further analyses or tests are required. Thus, the size and capabilities of a country's regulatory agency should not be a limitation to conducting this documental process that is globally accepted. Concerns about documental processes for approval are associated with different ethnic population groups not being adequately represented in trials used for FDA or EMA approval, since safety and toxicity profiles vary across diverse ethnicities. Under-representation of the Latin American population in clinical trials is a challenge that persists in countries in this region. However, the under-representation of ethnic populations is an issue that exists across the development of all drug classes and is not specific to biosimilars. Thus, pharmacovigilance becomes a crucial tool to assess safety in each of the exposed populations.

	Indication	Trial result
Trastuzumab-anns* (ABP980)	Adjuvant early stage and metastatic breast cancer, and metastatic gastric or esophagogastric junction adenocarcinoma	Non-inferior in breast cancer pCR 48% (95% CI 43–53) for ABP980 *vs* 41% (35–46) for trastuzumab (RR 1·19 [90% CI 1·03–1·37])[28]
Trastuzumab-pkrb* (CT-P6)	Adjuvant early stage and metastatic breast cancer	Non-inferior pCR 46·8% (95% CI 40·4–53·2) for CT-P6 *vs* 50·4% (44·1–56·7) for trastuzumab (RR 0·93 [95% CI 0·78–1·11])[29,30]
Trastuzumab-dkst* (MYL-1401O)	Adjuvant early stage and metastatic breast cancer, and metastatic gastric or esophagogastric junction adenocarcinoma	Non-inferior in breast cancer ORR 69·6% for MYL-1401O *vs* 64·0% for trastuzumab (HR 1·09 [95% CI 0·95–1·24])[31,32]
Trastuzumab-qyyp* (PF-05280014)	Adjuvant early stage and metastatic breast cancer, and metastatic gastric or esophagogastric junction adenocarcinoma	Equivalent in breast cancer ORR 62·5% (95% CI 57·2–67·6) for PF-05280014 *vs* 66·5% (61·3–71·4) for trastuzumab (RR 0·94 [95% CI 0·84–1·05])[33]

HR=hazard ratio. ORR=objective response rate. pCR=pathological complete response. RR=relative risk. *Biosimilar to the originator trastuzumab.

Table 2: **Approved indications for biosimilars for breast cancer treatment in Latin America and associated supporting studies**

Extrapolation

Regulatory agencies, such as the FDA, allow data extrapolation for biosimilars, which means that the scientific rationale considers all the data collected from one therapeutic indication of the biosimilar and extrapolates them to other eligible approved indications on the basis of the originator.[39] Therefore, for biosimilars with several indications, providing clinical trial information for each indication is not necessary,[39] because extrapolation reduces or eliminates the need for repeating indication-specific clinical studies that have already established the safety and efficacy of the originator product.[40]

Switching

Several regulatory considerations should be made regarding switching, which is the practice of a prescriber changing a patient's medication from either the originator to the biosimilar or vice versa, or between two or more biosimilars. From past experience in rheumatology, when patients are switched from one product to another once or several times, the slight differences between biosimilars increase the potential for negative outcomes.[41] These outcomes include loss of efficacy, immunogenicity, and the emergence or worsening of adverse events. Other potential challenges related to multiple switches between products include the complexity of pharmacovigilance and patient-related challenges owing to differences in delivery devices, individual pharmaceutical containers (eg, vials and ampoules), drug formulation, or dose.[41]

Because each biosimilar could have different levels of similarity or equivalence margin, as defined for the specific originator product, a theoretical possibility exists that two biosimilars would not meet a comparability standard if both products were compared head-to-head.[13] For this reason, data from switching studies with an originator and its analogous biosimilar are unique to those particular products and should not be generalised to other switching scenarios between the originator and its biosimilars or between different biosimilars of the same originator.[42]

Early in 2021, data showed that among patients who had previous treatment with the originator product, bevacizumab, most had received the biosimilar in the first line of treatment, indicating that the switch to biosimilar treatment occurred within the same line of therapy.[43] The authors of the study claimed that these findings supported the safety and efficacy of the switch,[43] but further data are needed to support this claim.

Global biosimilar regulatory landscape

Both the EMA and FDA regulations provide robust biosimilar approval frameworks. The USA did not implement a regulatory framework for biosimilar assessment until after the enactment of the Biologics Price Competition and Innovation Act in 2009.[44] Given that the first US biosimilar drug was approved almost a decade after the first one in Europe, the number of authorised biosimilar drugs in Europe far exceeds the number of biosimilars approved in the USA.[23]

In the early 2000s, when members of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (including Europe, Japan, and the USA) began discussing how to approve biosimilars after patent expiry of the originators, Latin America already had about 100 products on the market that were intended copies of originator products and registered as generics.[14] It was not until 2010 that countries in Latin America started distinguishing between the approval process for generics and that for biopharmaceuticals, although nowadays some countries in the region operate under the original guidelines.[14,45]

Biosimilar regulatory landscape in Latin America

The biosimilar regulatory landscape in Latin America is evolving as authorities have begun consolidating defined and standardised pathways for this drug class.[45] Most Latin American countries tend to adopt guidelines on the basis of accepted international regulations, such as the WHO guidelines, which in turn are based on EMA regulations with the aim of providing "globally acceptable principles for the licensing of biological products."[17,46] However, the regulatory situation throughout the region is heterogenous.

Brazil and Argentina have advanced regulations, whereas others, such as Paraguay, Bolivia, Peru, Dominican Republic, and Venezuela, have regulatory plans still in the development phase. In central America, only Panama, Guatemala, and Costa Rica have regulations, which are based on WHO guidelines. Peru and Ecuador have separate regulations for biologic originators and biosimilar products. Chile, Colombia, and Mexico have published regulations for biosimilars, but now have to address the issue of intended copies that do not comply with current regulations. These intended copies were probably registered before the implementation of biosimilar regulations and their approval was based on regulations for generic drugs.[45,46]

Brazil's regulations are particular in that they offer two pathways for approving biosimilars with differing data requirements. The first pathway, the comparative pathway, requires pharmacokinetic and pharmacodynamic studies and phase 3 clinical trials assessed on a case-by-case basis, and allows extrapolation of indications for a biosimilar when approved. The second pathway, the individual development pathway, does not require data of high quality, full sets of pharmacokinetic and pharmacodynamic studies, or head-to-head clinical trials, and it does not allow for extrapolation.[47]

In Mexico, requirements for biologic drug approval, including biosimilars, follow the same process as for any other pharmaceutical product. Colombian legislation allows biosimilar approval through similarity based on analytical chemistry studies alone, even if data from clinical trials do not exist. In Paraguay, draft regulations follow standards similar to Colombian regulations. These regulations might be inadequate to govern the approval of biosimilars and might increase the risks of approving understudied drugs.[45,46]

Given this scenario, a revision of the region's regulatory pathways is needed to ensure that efficient and streamlined processes do not compromise safety assessments. Each country should create a specific regulatory pathway for biosimilars that differs to the approval pathway for generic drugs and biologic originators. These pathways should be based on the recommendations provided by WHO or the processes already implemented by the FDA or EMA. Furthermore, changes to strengthen and harmonise national regulations across the region with international standards might enable more accurate approvals and

effective processes than those currently in place.[46] Several initiatives have been developed to confront this task.

The Pan American Network for the Harmonization of Pharmaceutical Regulations (PANDRH) was established to homogenise or converge the different local regulations. However, the process has been slow and difficult.[46] Harmonising biologic and biosimilar regulations is the objective of the PANDRH's Biotechnological Products Working Group, which was established in 2010, and recommended that the region should follow the WHO guidelines.[48] The *Foro Permanente de Regulación de Biológicos de las Américas* also aims to strengthen the harmonisation process of pharmaceutical regulations in Latin America. We have summarised the biosimilar regulatory status for the countries represented by members of this panel (panel 1).

Streamlining approvals for biosimilars in Latin America

The biosimilar regulatory process in Latin America must be standardised and streamlined for products that are considered biosimilars by international standards to be commercialised in a timely manner. As the regulatory landscape of biosimilars in the region continues to evolve, translating into practice the recommendations outlined by regulatory agencies is crucial. However, the implementation of these regulations poses several challenges, outlined in the following sections.

Heterogenous regulations

The heterogenous biosimilar regulations in Latin America present a major challenge to the region's regulatory landscape in terms of cost, processes expediency, and accuracy of approvals.[14] Additionally, except for Mexico, Brazil, and Argentina, the other Latin American countries do not address extrapolation. When extrapolation is granted by reliable agencies such as the FDA, EMA, or WHO, this practice could contribute to reducing the need to invest in infrastructure and human resources to replicate trials and studies at a local level.[39] Of note, according to the WHO guidelines, a similarity exercise could be requested when a biosimilar is used in instances of increased or reduced immune function or at very different doses.[17] Furthermore, a lack of separation between regulatory pathways for biosimilars and other drugs such as originators or generics makes the approval pathways susceptible to undesirable deviations, leading to, for example, the approval of intended copies.[39]

Non-adherence to regulatory pathways

Inadequate training and poor availability of personnel for biosimilars assessment could result in decreased adherence to and suboptimal application of the proposed regulations. In turn, this non-adherence could either delay the approval of biosimilars or result in the approval of intended copies, which do not meet the required criteria for biosimilarity.[15]

Market opportunity

Competition policies can be formulated in a way that they facilitate price competition for clinically substitutable medicines and have generally led to lower prices of biosimilars compared with their originators, contributing to cost savings. However, reducing costs requires enforcement of robust competition policies that prevent companies from using strategies that could impair competition. Examples of anticompetitive behaviours have been widely documented and include the introduction of pseudo-generics, collusion, developing a slightly reformulated product after a patent expires to

Panel 1: **Regulatory pathway for biosimilars**

Chile

In 2011, Chile's *Agencia Nacional de Medicamentos* (ANAMED), a department of the Institute of Public Health, announced the draft guidance for the evaluation of biosimilars in Chile. The Ministry of Health issued *Technical Guideline Number 170* in 2014, approved by *Decree Number 945 of 2014* (and its amendments), which outline the regulations for the biosimilar registration pathway (*TG Number 170*). According to the guideline, the approval process is based on a standalone procedure, which includes submission of preclinical and clinical trials.[49]

Colombia

In 2014, Colombia's Ministry of Health issued *Decree Number 1782 of 2014*, in which the requirements for the sanitary registration of new (pioneering) and known biologic (biocompetitors, biosimilars, or biogenerics) drugs were defined, by establishing three approval pathways: a complete dossier route for originator biologic drugs and two routes for biosimilars (the comparability route and the abbreviated comparability route), all of which include immunogenicity tests. The abbreviated route allows pharmaceutical companies to use available information on safety and efficacy of a product without the need to expose animals and humans to unnecessary experiments.[50]

Ecuador

A specific regulation for the approval of biosimilars has existed since 2013. It was further modified in 2019 (*Acuerdo Ministerial Número 00385-2019* issued by the Ministry of Public Health), to be aligned with international guidelines. The main challenge is providing free homologation for products already approved in other countries, some of which do not meet best practices.[51]

Guatemala

In 2019, the Ministry of Public Health adopted *Normativa 67-2019* for the approval of biologics, biotechnology, and biosimilars. This pathway allows the extrapolation of biosimilars approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), and recommended by WHO. The main challenge is that Guatemala does not have a strong mechanism for pharmacovigilance.[52]

Peru

In 2011, the Peruvian health authorities established separate regulations for pharmaceutical drugs (ie, chemically synthesised) and biotechnology drugs. In 2016, the *Supreme Decree Number 013-2016-SA* was released. This regulation is intended to give more specific requirements for biologics and biosimilars, and to complement the general requirements covered in *Supreme Decree Number 016-2011-SA*. The approval of biosimilar drugs requires the filing of additional documents such as the comparison with the originator according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This pathway allows the extrapolation of biosimilars approved by the US FDA and EMA, and recommended by WHO.[53]

maintain market exclusivity, and filing patent clusters to delay biosimilar entry.[54] The current scarcity of biosimilars in most Latin American countries is partly due to industry strategies delaying the market competition and the market share of biosimilars. Regional manufacturing could be a solution for those Latin American countries that might be considered small and unattractive markets.

Naming

Regulations to standardise the naming of biosimilar products do not exist in Latin America. Naming is the basis of product identification and is therefore essential for traceability and pharmacovigilance. Thus, not naming a biosimilar reduces the ability to document long-term product safety and differentiate the active biosimilar component from the originator. In Latin America, the absence of clear terminology could be a consequence of not differentiating biosimilars from generics, so they are given the same name as the originator. By contrast, this distinction between products has already been implemented internationally.[9]

Inadequate use of interchangeability and substitution

In the context of biosimilars, several terms must be differentiated (panel 2). Although automatic substitution should not be encouraged, a potential benefit for biosimilars might be that a planned substitution of an originator for a biosimilar could be made to increase access to this type of therapy and reduce health costs.[55] The substitution issue is also closely tied to naming, considering that physicians prescribe biologics by a unique identifier. Regional and national clinical practice guidelines should establish which biosimilars can be interchangeable with their originator product. Product substitution is of great concern in Latin America because of the purchasing process of medications that exists in most countries in the region—a process that is based on international non-proprietary names.[46] Because the naming of biosimilars is not correctly established, then such a mechanism can create a spontaneous interchangeability and possibly automatic substitution because patients will receive the readily available medication. Some procurement methods that could mitigate the risk of interchangeability between biosimilars, such as defining different percentages on purchasing units from the biosimilar available on the market, are used elsewhere (eg, USA and Europe), but they are not yet implemented in Latin America. Another option would be to develop real-world studies of the biosimilars already on the market.

Panel 2: **Definitions of key terms**

Substitution
The pharmacist can dispense an alternative biologic to the prescribed biologic. No previous approval of the prescriber is required.

Automatic substitution
The pharmacist must dispense the least expensive or preferred biologic regardless of the prescribed biologic. No previous approval of the prescriber is required.

Switching
Practice in which a prescriber changes a patient's therapy from an originator product to a biosimilar or vice versa. In the USA, switching is synonymous with interchangeability. Interchangeability: when a prescriber sees a biosimilar as therapeutically interchangeable with the originator.

Absence of traceability and insufficient pharmacovigilance

Biosimilar traceability is essential to differentiate the originator from the biosimilar and satisfy basic clinical and public health needs, such as patient safety. Although traceability strategies are largely missing in Latin America, they are essential to improve pharmacovigilance. For example, International Nonproprietary Names are intended to provide a unique standard name to a drug to avoid prescribing errors, and are widely used for biologics but not often used for biosimilars.

Pharmacovigilance activities vary greatly from one Latin American country to another, with poor resources restricting the use of such systems in many countries and adverse events often being underreported.[25] Additionally, monitoring to measure the effect of biosimilar use on patients is not routinely done. To address these issues, appropriate indicators should be implemented.

Economic considerations

In Europe, in 2018, breast cancer represented the second highest cancer expenditure and colorectal cancer was the third highest.[56] In 2010, in the USA, the estimated cost of breast cancer was US$16·5 billion and colorectal cancer was $14·5 billion, making them the two most expensive cancers.[57] A study on the costs of breast cancer treatment in the USA reported that direct annual costs of breast cancer per patient ranged from $48 477 to $182 665 for the period 2009–12, depending on stage.[58] A scarcity of studies on comprehensive cancer expenditure in Latin America creates a substantial knowledge gap; however, one systematic review of the published literature on direct and indirect costs related to breast cancer in Latin American countries reported average annual direct treatment costs per patient with breast cancer of $13 179–28 910.[59] Breast cancer and colorectal cancer expenditure represents a large financial burden;[59] thus, cost solutions need to be examined to achieve more efficient budget allocation in health-care spending and increase access to care in resource-poor settings.

In Europe, 30–35% of direct cancer costs correspond to pharmaceuticals.[60] This proportion is expected to increase in the near future because of at least two reasons: the pharmaceutical development pipeline is highly focused on oncological drugs for advanced disease;[61] and the reduced

capacities of general practitioners in the health-care system to perform timely diagnostics in cancer obliges them to provide high-cost drugs instead of less expensive curative surgical or medical procedures.[62] For example, long waiting times for colonoscopies might explain why many patients with colorectal cancer are diagnosed at late stages in some countries. Additionally, curative surgical procedures are limited to patients with early stage breast cancer, which is often diagnosed during screening.

The COVID-19 pandemic has had a major adverse impact on health-care performance worldwide.[63] The high demand for health-care services among patients affected by the virus has led to interruptions and delays in cancer care.[64] For example, a Chilean study showed a pronounced reduction in the number of new cancer diagnoses during the pandemic, which will result in an excess of cases that will probably be diagnosed at more advanced stages in the coming years.[64]

Therefore, cancer costs are expected to keep increasing due to innovation in high-cost pharmaceuticals, epidemiological consequences of the pandemic, and a pressing need for increased early detection of cancer.

Biosimilars

The Latin American market for biosimilars was valued at $517 million in 2018, and is expected to reach $3·9 billion by 2025, at a compound annual growth rate of around 33% during this period, making it attractive for global biosimilar producers.[61] Biosimilars are well recognised drugs with the potential to substantially lower therapeutic expenditure in oncology. High-quality biosimilars can positively affect the financial sustainability of health-care systems while improving access to cancer care and alleviating the pressure on high-cost biologics.[45] Biosimilars might cost up to 30% less than their originators when they enter the market after patent expiry of the originators.[65] Studies on biosimilar pricing in Europe have reported discounts ranging from 5% to 35% compared with originators, with discounts of up to 75% noted in some cases.[59,61] However, in contrast to generics or low molecular-weight drugs, no single guideline exists in terms of price control or regulation for biosimilars.[66]

A German study explored the saving potential of biosimilars compared with the originators.[67] For trastuzumab, the annual saving potential ranged from €95·9 million to €120·5 million if all patients received the least expensive trastuzumab biosimilar (ie, trastuzumab-qyyp).[67] Additionally, other studies predicted cumulative potential savings of €50–100 billion between 2012 and 2015 in France, Germany, Italy, Spain, the UK, and the USA after the introduction of biosimilars in the market.[66]

Studies on biosimilar pricing do not exist for Latin America; however, the effect of biosimilars on savings could potentially be proportional to product access, benefiting patients who would otherwise not have access to biologic therapies, especially in countries where cost is already a major issue.[66] Additionally, the introduction of lower-cost biosimilars could expand the possibility of treating extrapolated indications in a cost-effective way. With current drug pricing, trastuzumab is not considered cost-effective for treatment of HER2-positive breast cancer in several Latin American countries. However, a lower-cost alternative could support decisions for drug reimbursement and improve patient access to HER2 therapy in the region.

Furthermore, the savings that the health-care systems would accrue from the increased use of biosimilars could be redirected to improve other aspects of care such as prevention programmes and early diagnosis.

Mechanisms to increase access to high-cost drugs, including biosimilars

To ensure the financial sustainability of health-care systems despite high-cost drugs, alternative access

***Panel 3*: Recommendations to address challenges related to biosimilars in Latin American health-care systems**

(1) Developing homogeneous and comprehensive regulations

Regulations in Latin America could be improved to make them more homogenous and comprehensive than those currently in place (table 3).

(2) Increasing traceability and pharmacovigilance

Government, regulatory authorities, medical societies, academia, and health-care providers should implement strategies to ensure traceability through the manufacturing, distribution, and prescription processes of biosimilars by means of a well-documented identification system. Government and regulatory entities should coordinate traceability and pharmacovigilance efforts to strengthen both aspects. Professional personnel must be adequately trained to report, analyse, and monitor adverse effects of biosimilars to improve information analysis systems.[14] Monitoring of outcomes with adequate indicators should be implemented to measure the effects of biosimilar use. These indicators could include access to therapies, health outcomes, and cost savings.

(3) Increasing market opportunities and improving procurement strategies

Governments, manufacturers, regulatory authorities, medical societies, academia, and health-maintenance organisations should create a welcoming procurement environment for biosimilars by fostering access strategies and explicitly including biosimilars in local clinical practice guidelines. Increasing participation of multiple stakeholders in the benefits obtained from biosimilar cost reductions might favour the adoption of more cost-effective drugs. It is also possible to develop co-payment and reimbursement policies to involve patients in the decision-making process regarding the use of either originators or biosimilars.[74] Governments should monitor biosimilar procurement and effects through indicators such as patient outcomes, access trends, and cost savings that can be used to guide future procurement decisions.

(4) Increasing educational opportunities

Medical societies, academia, governments, regulatory authorities, patient advocacy groups, and non-governmental organisations should provide educational content to the medical community and patients in an effort to increase their confidence in biosimilars and dispel prejudices and misconceptions on the efficacy or safety of this drug class.

To overcome these issues, all aspects of biosimilar use should be addressed in national and regional guidelines on colorectal cancer and breast cancer, including interchangeability. Additionally, existing patient groups can benefit from these educational opportunities to increase their knowledge on disease and treatment options.[23]

	Recommendations	Responsible stakeholders
Adapt to international standards	Regulatory pathways for biosimilars should be updated according to international standards on the basis of the recommendations provided by WHO or the processes already implemented by the US FDA or EMA. Biosimilars do not require local completion of extensive phase 3 and phase 4 clinical studies and can be approved on the basis of non-inferiority evidence alone. However, expanding the role of pharmacokinetic and analytical studies of these compounds is crucial	Governments, regulatory agencies, academia, medical societies, NGOs, manufacturers, and health-care providers
Standardise regulatory pathways throughout the region	Implement strategies to harmonise biosimilar regulations by leveraging the initiatives already in place, such as the PANDRH's Biotechnological Products Working Group and the *Foro Permanente de Regulación de Biológicos de las Américas*. Strategies include: establishing a regional position through a space for regulatory convergence, where different drafts of WHO guidelines are disseminated and discussed; training and experience exchange between different local regulators; and regional cooperation in terms of cost, processes expediency, and accuracy of approvals	Governments, NGOs, and regulatory agencies
Extrapolation	Extrapolation of approvals from agencies such as the EMA or US FDA should be considered by Latin American regulatory authorities when no substantial clinical differences between the biosimilars and the original compounds are found and biosimilarity is established. Extrapolation reduces or eliminates the need for repeating local and indication-specific clinical studies that have established the safety and efficacy of the originator product[36]	Governments, regulatory agencies, academia, medical societies, NGOs, and health-care providers
Separate pathways for biosimilars	Implement a specific pathway for biosimilars that is different from the approval pathways for generic drugs and biologic originators	Governments, regulatory agencies, and NGOs
Invest in training and expanding human resources	Invest in educational programmes for regulatory personnel. Because the biosimilar approval requires specific regulations, people in charge of reviewing applications must be specifically trained for this purpose. Establishing regional working groups to assist national regulatory authorities in biosimilar approval could be useful	Governments, regulatory agencies, academia, medical societies, manufacturers, and health-care providers
Naming	Implement a naming convention to clearly identify and differentiate between biosimilars and originators	Governments, regulatory agencies, and manufacturers
Implementation and adherence	Once implemented, adherence to these regulations is of upmost importance. Adequate implementation of biosimilar regulations requires concerted efforts by all stakeholders to overcome organisational, normative, and information technology challenges	Governments, regulatory agencies, academia, medical societies, NGOs, manufacturers, and health-care providers.

EMA=European Medicines Agency. US FDA=Food and Drug Administration. NGO=non-governmental organisation. PANDRH=Pan American Network for the Harmonization of Pharmaceutical Regulations.

Table 3: **Recommendations for making biosimilar regulations in Latin America more homogeneous and comprehensive**

mechanisms to biological therapy have been explored. These mechanisms include the regulatory instruments previously discussed, legal instruments such as price regulation, and, most recently, managed entry agreements.[61]

Managed entry agreements aim to provide access to treatments for patients through an arrangement where health-care payers and manufacturers share the financial risk.[68] Although most of these mechanisms have been used for innovative pharmaceuticals, they could also be applied to biosimilars, which cost less than originators but are still expensive. Therefore, the sustainability of health-care systems could be ensured by using managed entry agreements for both originators and biosimilars that have proof of quality, safety, and effectiveness.[69] In Latin America, these contracts have been successfully implemented in Uruguay.[70] These agreements can be categorised into financial and performance-based risk-sharing arrangements (PBRSAs).[69]

One example of financial arrangement is the subscription-based model (ie, the so-called Netflix scheme), which has been implemented by the *Fondo Nacional de Recursos* in Uruguay for patients with breast cancer.[71] In this model, the payer (eg, the government) purchases a subscription from the manufacturer and, in return, the pharmaceutical company provides a set of services or pharmaceutical products to a specific population.

PBRSAs consider financial risk and the uncertainty in health outcomes. In the real world, new approvals are based on average treatment effect estimates, which mask the individual effect at the patient level. First-order uncertainty (ie, the lack of understanding of health outcome variability among a homogeneous patient group) can only be revealed at follow-up.[72] If payers pay for a new product based on average estimates, PBRSAs assume a financial loss, and these losses are the resources allocated to patients who did not benefit from the technology. From a health system perspective, this mistaken allocation forgoes health care because resources could have been better used elsewhere in the system, for other necessities.[72] Two types of PBRSAs have been proposed. The first scheme is coverage with evidence development, in which funding is tied to the ability of research development to resolve specific evidence gaps. The second is performance-linked reimbursement schemes, where financial transfers are conditioned on the achievement of specific predefined outcomes.[69]

Finally, as seen in countries such as Argentina, access to and availability of biosimilars could be improved by

Search strategy and selection criteria

Articles relevant to the consensus discussion and references cited in this Policy Review were identified by searching PubMed, Embase, and Google Scholar for publications using the terms "biosimilars", "Latin America", "biosimilars for breast cancer", "biosimilars for colorectal cancer", "biosimilar access", and "biosimilar regulations" from Jan 1, 2014, to July 1, 2021. The identified articles were either published in English or Spanish. Additional articles were compiled from the references of the identified papers and from searches of the authors' own files. Particular attention was given to papers that reviewed or summarised the topics in question, or that were related to activities in Latin America. The final references were selected according to their relevance to the scope of this Policy Review.

giving equal market opportunity to regional manufacturers that meet international standards on development and manufacturing.

Conclusions

Biosimilars are an effective and equivalent alternative to originator biologics, which contribute to the sustainability and financing of health-care systems and favour access to biologic therapies with the same safety, efficacy, and quality as the original product.[73] In this Policy Review, we addressed specific issues related to poor access to biosimilars in the health-care systems of Latin America, including regulation and procurement. The region faces continuously increasing cancer expenditure, partly as a consequence of the COVID-19 pandemic; thus, an immediate need exists to streamline regulatory processes to allow for more biosimilars to reach the population for whom they were developed. Our proposed recommendations comprehensively address the challenges identified (panel 3, table 3). Although this analysis used biosimilars for treatment of breast cancer and colorectal cancer as a case study, the identified issues and provided recommendations are relevant for all biosimilar products regardless of their cancer target. The recommendations are not intended as a unified solution for the Latin American region and should be tailored on a country-by-country basis; nonetheless, their relevance could provide a way forward for other low-income and middle-income countries outside Latin America.

Contributors

ET, HG, DH, ML, WM, MR-R, NCS, NV, and MAE wrote the original draft of the manuscript and contributed to the literature search. ET, ML, WM, NV, and MAE reviewed the data and information provided by the other authors. ET assigned and followed up on tasks, and was the point of contact for all authors. MR-R and EM conceptualised the Policy Review and contributed to the contributed to the reviewing and editing of the original draft. MR-R developed the methodology. EM contributed to the design of tables and panels. All authors critically revised the article, had full access to all data, gave final approval of the version to be submitted, and accept full responsibility for the content of this manuscript.

Declaration of interests

ET reports honoraria from Abbott, Bayer, Janssen, Heel, Medicamenta, Merck, MSD, Novartis, Pfizer, Roche, and Sanofi, outside of the submitted work. HG reports consulting fees and honoraria from Bristol Myers Squibb (BMS), MSD, Roche, and AstraZeneca, outside of the submitted work. DH reports honoraria from MSD, Roche, Tecnofarma, and Pfizer, outside of the submitted work. WM reports grants from Pfizer and Amgen, and honoraria from Pfizer, Amgen, and Novartis, outside of the submitted work. MAE reports grants from *Fondo Nacional de Desarrollo Científico y Tecnológico*, *Agencia Nacional de Investigación y Desarrollo*, *Asociación Chilena para el Estudio del Dolor*, Roche, Boehringer Ingelheim, LivaNova, AbbVie, GSK, Novartis, BMS, and Novo Nordisk, consulting fees from UN Office for Project Services, Inter-American Development Bank, WHO, Alliance for Health Policy and Systems Research, and UNDP, and honoraria from Merck, MSD, Grünenthal, Novartis, AbbVie, Boehringer Ingelheim, and Roche, outside of the submitted work. All other authors declare no competing interests.

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