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Biosimilars approvals by thirteen regulatory authorities: A cross-national comparison

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A R T I C L E I N F O

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A B S T R A C T

Biosimilars are biological medicines highly similar to a previously licensed reference product and their licensing is expected to improve access to biological therapies. This study aims to present an overview of biosimilars approval by thirteen regulatory authorities (RA). The study is a cross-national comparison of regulatory decisions involving biosimilars in Argentina, Australia, Brazil, Chile, Canada, Colombia, Europe, Hungary, Guatemala, Italy, Mexico, Peru and United States. We examined publicly available documents containing information regarding the approval of biosimilars and investigated the publication of public assessment reports for registration applications, guidelines for biosimilars licensing, and products approved. Data extraction was conducted by a network of researchers and regulatory experts. All the RA had issued guidance documents establishing the requirements for the licensing of biosimilars. However, only three RA had published public assessment reports for registration applications. In total, the investigated jurisdictions had from 19 to 78 biosimilars approved, most of them licensed from 2018 to 2020. In spite of the advance in the number of products in recent years, some

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challenges still persist. Limited access to information regarding the assessment of biosimilars by RA can affect confidence, which may ultimately impact adoption of these products in practice.

1. Introduction

Biosimilars are biological medicines highly similar in terms of quality, efficacy, and safety to a previously licensed reference product. According to the World Health Organization (WHO), the development of biosimilars should follow a stepwise comparability exercise, starting with a comprehensive evaluation of quality attributes in relation to a reference product (RP). In addition, similarity should also be demonstrated in non-clinical and clinical studies (Declerck and Farouk Rezk, 2017; World Health Organization, 2018).

Market entry of biosimilars is likely to facilitate access to biological products and to improve the financial strain on healthcare systems, since it is expected that an increase in competition cuts down prices, even for the reference product (Vogler et al., 2021). Accordingly, improving the affordability of biological products provide opportunities to expand access to more patients and/or the resulting savings could be ultimately reinvested to cover new services (Agirrezabal et al., 2020). However, the final savings achieved with the introduction of biosimilars depend on multiple factors, such as demand-side measures to enhance uptake, pricing, and reimbursement policies, which ultimately result in distinct adoption rates in different countries and pharmacological classes (Kim et al., 2020; IQVIA Institute, 2022).

The European Medicines Agency (EMA) has pioneered the regulation of biosimilars with the establishment of its legal framework in 2004 (European Medicines Agency, 2019). Later, WHO guidelines on evaluation of similar biotherapeutic products were issued in 2009 and updated in 2022 aiming to provide globally accepted principles to guide the licensing of biosimilars (World Health Organization, 2009, 2022). The publication aimed to orient regulatory authorities (RA) about the minimal requirements for approval of these products contributing to the development of national frameworks. The establishment of regulations was expected to facilitate marketing authorizations while assuring quality, safety and efficacy of biosimilars (Rahalkar et al., 2021b). A recent survey involving 21 countries observed that the development of guidelines for biosimilars licensing have progressed in recent years (Kang et al., 2021). However, despite efforts to harmonize regulations across different countries, there is evidence suggesting marketing authorization procedures differ and some countries may not follow strict regulatory process to approve biosimilars (Kang et al., 2020). Divergences can be related to the requirement of clinical trials, selection of RP, interchangeability and transparency, with the publishing of public assessment reports (Rahalkar et al., 2021b).

Prior studies characterizing the approvals of biosimilars focused on authorizations in the United States (US) and Europe only (Gherghescu and Delgado-Charro, 2020) while others were restricted to some therapeutic classes (de la Cruz et al., 2017; Díaz et al., 2021). A global survey led by WHO in 2019 revealed major differences in the number of biosimilars approved in different countries (Kang et al., 2021). Understanding the scenario of licensing may identify inequities in the distribution of biosimilars that could ultimately foster new policies to improve timely access to essential biological therapies. Thus, this study aims to present an overview of terminologies, guidelines for biosimilars licensing (year of publication and definitions adopted), and products approved by thirteen RA.

2. Methods

2.1. Design and setting

This is a cross-national comparison of regulatory decisions involving the approval of biosimilars by RA of thirteen jurisdictions in three continents (America, Europe and Oceania), including: Argentina (*Administración Nacional de Medicamentos, Alimentos y Tecnología Médica* – ANMAT), Australia (Therapeutic Goods Administration – TGA), Brazil (*Agência Nacional de Vigilância Sanitária* – ANVISA), Chile (*Instituto de Salud Pública de Chile* – ISP Chile), Canada (Health Canada), Colombia (*Instituto Nacional de Vigilancia de Medicamentos y Alimentos* – INVIMA), Europe (European Medicines Agency – EMA), Hungary (*Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet* – OGYÉI), Guatemala (*Departamento de Regulación y Control de Productos Farmacéuticos y Afines* – DRCPFA), Italy (*Agenzia Italiana Del Farmaco* – AIFA), Mexico (*Comisión Federal para la Protección contra Riesgos Sanitarios* – COFEPRIS), Peru (*Dirección General de Medicamentos, Insumos y Drogas* – DIGEMID) and US (Food and Drug Administration – FDA).

2.2. Information sources and participants

Data were collected from the websites of the regulatory authorities, except for Guatemala (DRCPFA) where the physical archives were consulted. The research investigated mainly publicly available documents, including registers of approved products, information leaflets, public assessment reports and any other official document containing information regarding the approval of the biosimilar by the RA. The full list of information sources employed in the search is described in Supplementary material.

A network of researchers and drug regulatory experts were invited to participate in data collection, which was conducted by one investigator and further checked by at least one reviewer.

2.3. Eligibility criteria

The study included all the biologicals approved until June 2023, with valid licenses at that point in time and classified as biosimilars or by any related terminology adopted to designate biologicals approved upon comparison to a RP. Biologicals that were developed through an individual pathway and without any indication of a direct comparison to a RP, also called as “me-too”, noninnovator, noncomparable, copy or follow-on biotherapeutic products (non-originators and nonbiosimilar) (de Assis and Pinto, 2018; Castañeda-Hernández et al., 2019; Kang et al., 2021) were excluded.

2.4. Data collection and analysis

The data collection form was structured in two sections, the first section extracted information related to the RA (level of transparency and guidelines for biosimilars licensing), while the second section included data related to the approved biologicals, including biosimilars and RP. The level of transparency was assessed according to the sub-indicator Registration and Marketing Authorization – MA05.03 of the WHO Global Benchmarking tool (World Health Organization, 2021a) by checking the publishing of public assessment reports for approved registration applications in local language.

The data related to the biologicals covered the following fields: international nonproprietary name, product description (strength/concentration and dosage form), brand name, manufacturing company, year of approval, name of the reference product used to demonstrate similarity and whether the approval was based on the decision of another regulatory agency (regulatory reliance mechanisms).

Biosimilars corresponding to the same biological compound, identified by two different brand names, but developed by the same manufacturer and with the same approval date were considered as duplicate registers and were counted as one product.

The collected data was organized in Microsoft Excel spreadsheets and analyzed though descriptive statistics including frequency of biosimilars licensed per jurisdiction, nonproprietary names, brand names, therapeutic subgroups according to Anatomical Therapeutic Classification (ATC) classification and year of approval.

The results were presented descriptively and the terms approval, licensing and authorization were used interchangeably.

3. Results

3.1. Transparency and guidelines for biosimilars licensing

RA presented different levels of transparency. Three RA (EMA – Europe, FDA – US and Health Canada) published summary technical evaluation reports for marketing authorization applications; three (ANVISA – Brazil, COFEPRIS – Mexico and TGA – Australia) had initiated the publication of assessment reports, but this was only applied for part of the evaluated products and seven (AIFA – Italy, ANMAT – Argentina, ISP Chile, DRCPFA – Guatemala, DIGEMID – Peru, INVIMA – Colombia, and OGYÉI – Hungary) had not made available an assessment report for the public in the local language.

With regards to biosimilars, all the RA had published guidance documents establishing the requirements for the licensing of these products. Table 1 describes the terminology, definitions adopted and the year when regulations were issued. RA implemented regulatory guidelines for registration of biosimilars from 2005 to 2016. There was a convergence in terminology and the name biosimilar was adopted by eight RA. ANMAT (Argentina) and INVIMA (Colombia) did not implement a specific term to identify biologicals approved upon demonstration of similarity to a RP.

3.2. Characterization of biosimilars

Fig. 1 describes the first licensed biosimilar after the introduction of the concept of similar biotherapeutic product by each RA. The first approved biosimilars included somatropin (Omnitrope®, Sandoz) licensed by EMA in 2006, followed by Health Canada in 2009 and COFEPRIS (Mexico) in 2010. Epoetin lambda (Novicrit®, Sandoz) and filgrastim (Nivestim®, originally from Hospira) were licensed in 2010 in Australia (TGA), followed by filgrastim (Zarzio®, Sandoz) in Guatemala (DRCPFA) in 2012 and rituximab (Novex®, Elea Phoenix) in Argentina (ANMAT) in 2013.

FDA (US) and ANVISA (Brazil) approved the first biosimilars in 2015 with the licensing of filgrastim (Zarxio®, Sandoz) in US, infliximab (Remsima®, Celltrion) and filgrastim (Fiprima®, Eurofarma Laboratório) in Brazil. In contrast, the entry of biosimilars in Chile and Peru occurred later, in 2017. ISP Chile approved infliximab (Remsima®, Laboratorios Saval) and insulin glargine (Basaglar®, Eli Lilly), while infliximab (Flixceli®, Celltrion) was licensed by DIGEMID (Peru). In Colombia, two trastuzumab biosimilars were approved in 2018 by INVIMA (Ogivri®, Mylan GMBH and Trazimera®, Pfizer).

Table 2 presents the number of new biosimilars authorized by year (first authorization) and by RA. Most of the biosimilars were approved from 2018 to 2020. In 2018, EMA licensed 13 biosimilars, in contrast to the approvals from TGA (Australia), ANVISA (Brazil), INVIMA (Colombia) and FDA (US) that peaked in 2019 summing eight, 16, 10 and 10 products, respectively. ANMAT (Argentina), ISP Chile, DRCPFA (Guatemala) and Health Canada displayed the highest number of approvals in 2020. Four products (epoetin alfa, filgrastim, interferon alfa-2b and interferon beta-1b) classified as biosimilars by COFEPRIS (Mexico) were originally approved between 1997 and 2001, before the establishment of the national regulation of similarity. However, all of them were included in the list of biocomparable medicines issued by the RA (COFEPRIS, 2020).

The number of biosimilars approved by RA according to the ATC classification and the international nonproprietary name is presented in

Table 1
Terminologies adopted, definitions and year when guidelines for licensing were issued by RA.

Country	Regulatory authority	Terminology	Definition	Year
Argentina	*Administración Nacional de Medicamentos, Alimentos y Tecnología Médica* (ANMAT)	No specific terminology	Medicinal specialties of biological origin whose qualitative and quantitative composition, therapeutic indication and proposed route of administration, have a history in other medicinal specialties of biological origin authorized and registered with ANMAT or another regulatory health authority (Ministerio de Salud, Administración Nacional de Medicamentos Alimentos y Tecnologia Medica, 2011).	2011
Australia	Therapeutic Goods Administration (TGA)	Biosimilar medicine	A biosimilar medicine is a version of an already registered biological medicine (the reference medicine). Both the biosimilar and its reference medicine will have the following similar characteristics (demonstrated using comprehensive comparability studies): physicochemical, biological, immunological, efficacy and safety (Australian Government, Department of Health, Therapeutic Goods Administration, 2018).	2015
Brazil	*Agência Nacional de Vigilância Sanitária* (ANVISA)	Biological product developed by comparability pathway	Biological product which approval was based on a comparability exercise demonstrating similar quality, efficacy and safety to a reference biotherapeutic product (Brasil, Ministério da Saúde, Agência Nacional de Vigilância Sanitária, 2010).	2010

(*continued on next page*)

Table 1 (*continued*)

Country	Regulatory authority	Terminology	Definition	Year
Chile	*Instituto de Salud Pública de Chile* (ISP Chile)	Biosimilar	Biotechnological medicine that has demonstrated to be comparable in terms of quality, safety and efficacy in relation to a reference biotechnological product, based on exhaustive characterization through comparability studies conducted in equal conditions, including quality, non-clinical and clinical studies, all of them comparative (Republica de Chile, Ministerio de Salud, 2014).	2014
Canada	Health Canada	Biosimilar biologic drug	A biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug (Government of Canada, Health Canada, 2022).	2010
Colombia	*Instituto Nacional de Vigilancia de Medicamentos y Alimentos* (INVIMA)	No specific terminology	Biological medicines that have presented the results of a comparability exercise demonstrating that the biological is highly similar to a reference product (Ministerio de Salud y Protección Social, 2014).[a]	2014
Guatemala	*Departamento de Regulación y Control de Productos Farmacéuticos y Afines* (DRCPFA)	Biosimilar	Biological/ biotechnological medicine that have proved to be similar or comparable in terms of quality, safety, efficacy and immunogenicity to a reference medicine (Gobierno de Guatemala, Ministerio de Salud Pública e Asistencia Social, 2020).	2011
Europe	European Medicines Agency (EMA)	Biosimilar	Biosimilar medicines are medicines similar in quality, efficacy and safety to the reference biological medicines and are not subject to patent coverage (European Medicines Agency, 2018).	2005
Hungary	*Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet* (OGYÉI)	Biosimilar	Refers to EMA	2005
Italy	*Agenzia Italiana Del Farmaco* (AIFA)	Biosimilar	Refers to EMA	2005
Mexico	*Comisión Federal para la Protección contra Riesgos Sanitarios* (COFEPRIS)	Biotechnology medicines biocomparable	The noninnovative biotechnological medicine that proves to be biocomparable to the reference biotechnological medicine in terms of safety, quality and efficacy based on the assessments established by the Law, the Regulation of Health Products and other applicable regulations (Estados Unidos Mexicanos, Presidencia de la Republica, 2011).	2011
Peru	*Dirección General de Medicamentos, Insumos y Drogas* (DIGEMID)	Similar biologic product	Product that is similar to the reference products in terms of quality, efficacy and safety (Gobierno del Estado Peruano, Ministerio de Salud, 2016).	2016
US	Food and Drug Administration (FDA)	Biosimilar	A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product (U.S. Food and Drug Administration, 2022).	2015

[a] INVIMA regulation established an abbreviated comparability route in which last generation analytical techniques are required to demonstrate similarity to a RP.

Table 3. Two therapeutic subgroups were represented in all the markets: the antineoplastic agents and the immunosuppressants. However, there were three classes licensed by a limited number of RA. The antianemic preparations; the pituitary and hypothalamic hormones and analogues; and the ophthalmologicals were approved by four RA.

In total, the investigated jurisdictions had from 19 to 78 biosimilars approved. EMA was the RA with the highest number of approvals, summing 74 biosimilars with marketing authorizations. AIFA (Italy) and OGYÉI (Hungary) had four and three biosimilars approved by national procedures, respectively. In Latin America, Brazil displayed 51 biosimilars licensed by ANVISA, higher than the total approvals from high-income countries, such as Australia (TGA) and the US (FDA).

Adalimumab and trastuzumab were the biosimilars with the highest

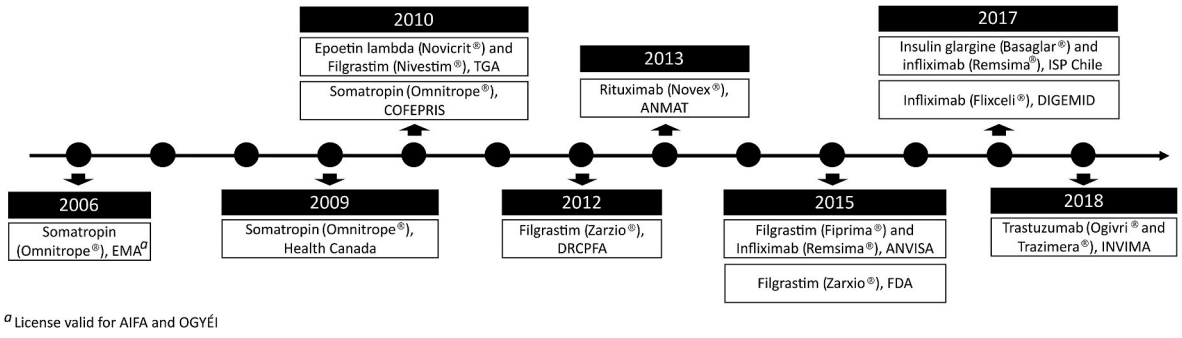

Fig. 1. Timeline for the first approved biosimilars after the introduction of the concept of similiar biotherapeutic product by each RA (nonproprietary name [brand name], RA).

Table 2
Number of biosimilars licensed by RA according to the year of approval.

Year of approval	Argentina	Australia	Brazil	Canada	Chile	Colombia	Europe	Guatemala	Hungary[a]	Italy[a]	Mexico	Peru	US
1997–2001											4		
2006							1		1	1			
2007							5		5	5			
2008							2		2	2			
2009				1			2		2	2			
2010		2					1		1	1	1		
2011		1											
2012								1					
2013	1	1					4	1	4	4			
2014		1		2			3		3	3	2		
2015		2	2	2							2		1
2016	4	2	1	1			3		3	3			3
2017		3	4	3	2		10	1	12	12	4	1	5
2018	1	6	4	4	2	2	13	4	13	13			7
2019	6	8	16	5	4	10	4	3	4	6	2	3	10
2020	7	6	10	16	6	3	8	7	9	8	1	3	4
2021	3	6	5	9	3	5	9	6	9	9	9	9	4
2022	2	5	5	7	2	2	6	3	6	6	5	3	7
2023			4	1		3	3		3	3	2	2	1
Total	24	43	51	51	19	25	74	26	77	78	32	21	42

[a] Includes all the approvals from EMA.

quantity of registered products summing 64 and 58 approvals, respectively. In the case of adalimumab, there was a marked difference in the quantity of products approved in the studied jurisdictions: EMA had nine approvals, while ANMAT (Argentina) and COFEPRIS (Mexico) licensed three and two adalimumab biosimilars, respectively. In addition, adalimumab, bevacizumab, rituximab, and trastuzumab were the four biologicals with marketing authorizations in all the studied RA. In contrast, ranibizumab biosimilars were approved only by EMA (license valid for AIFA [Italy] and OGYÉI [Hungary]), TGA (Australia), Health Canada and FDA (US).

We observed a noticeable difference in the timing of approvals. In US, FDA licensed the first adalimumab biosimilar in 2016, while in Mexico it was only approved in 2022. With regard to rituximab biosimilars, ANMAT (Argentina) licensed the first product in 2013 and it was only approved in 2019 by ANVISA (Brazil), Health Canada, ISP Chile, INVIMA (Colombia) and DIGEMID (Peru). In Europe, EMA approved adalimumab and infliximab biosimilars in 2017 and 2013, respectively.

Three RA reported that their approvals considered the decisions of other agencies. DIGEMID (Peru) had 15 biosimilars (71.4%) licensed based on EMA's authorizations. In contrast, decisions from DRCPFA (Guatemala) considered the approvals of ANMAT (Argentina), EMA, FDA (US), *Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos* (CECMED, Cuba), ISP Chile, Pharmaceuticals and Medical Devices Agency (PMDA, Japan), Ministry of Food and Drug Safety of Korea and Ministry of Health of Russia. In Italy (AIFA) and Hungary (OGYÉI), the majority of biosimilars were approved on the basis of the authorization by EMA (74/78 and 74/77, respectively).

With regards to the brands with highest number of approvals, Amgevita®/Amjevita® (adalimumab, Amgen), Hyrimoz® (adalimumab, Novartis/Sandoz) and Trazimera® (trastuzumab, Pfizer) were approved by eleven RA: ANMAT (Argentina), TGA (Australia), ANVISA (Brazil), Health Canada, ISP Chile, INVIMA (Colombia), EMA (extensive to AIFA [Italy] and OGYÉI [Hungary]), DRCPFA (Guatemala), COFEPRIS (Mexico), DIGEMID (Peru) and FDA (US). Two brands from Celltrion, rituximab (Truxima®) and trastuzumab (Herzuma®), were approved by ten RA, including TGA (Australia), ANVISA (Brazil), Health Canada, ISP Chile, INVIMA (Colombia), EMA (extensive to AIFA [Italy] and OGYÉI [Hungary]), DRCPFA (Guatemala), DIGEMID (Peru) and FDA (US), in addition to ANMAT (Argentina) and COFEPRIS (Mexico) that licensed Truxima and Herzuma®, respectively.

4. Discussion

In this study, all RA had published guidelines for the licensing of biosimilars presenting definitions that were aligned with the WHO's Guidelines on the approval of biosimilars which stipulated that similarity requires head-to-head comparison of a biosimilar candidate to an already licensed RP proving comparable quality, efficacy and safety (World Health Organization, 2022). In contrast, seven out of 13 RA had not published public assessment reports for medicines registration applications in local language.

Despite the increase in biosimilars approvals in the last few years, a remarkable difference in the quantity of biosimilars authorized by RA

Table 3
Numbers of biosimilars[a] approved by RA according to therapeutic subgroup and nonproprietary names.

ATC code	Therapeutic subgroup/ Nonproprietary names	Argentina	Australia	Brazil	Canada	Chile	Colombia	Europe	Guatemala	Hungary[b]	Italy[b]	Mexico	Peru	US
A10	**Drugs used in diabetes**		**3**	**7**	**6**	**1**		**6**	**2**	**6**	**6**	**4**	**1**	**3**
	Insulin aspart		1		2			3		3	3			
	Insulin glargine		2	4	2	1		2	2	2	2	4	1	2
	Insulin human			1	1									
	Insulin lispro			1	1			1		1	1			1
	Isophane insulin			1										
B01	**Antithrombotic agents**		**1**	**5**	**4**		**1**	**1**		**4**	**4**		**2**	
	enoxaparin		1	5	4		1	1		4	4		2	
B03	**Antianemic preparations**		**1**					**5**		**5**	**5**	**1**		**1**
	Epoetin alfa							3		3	3	1		
	Epoetin lambda		1											
	Epoetin zeta							2		2	2			
	Erythropoietin													1
G03	**Sex hormones and modulators of the genital system**		**2**			**1**		**2**		**2**	**2**	**1**	**1**	
	Follitropin alfa		2			1		2		2	2	1	1	
H01	**Pituitary and hypothalamic hormones and analogues**			**2**	**1**			**1**		**1**	**1**	**1**		
	Somatropin			2	1			1		1	1	1		
H05	**Calcium homeostasis**		1		1		2	5		**5**	**6**			
	Teriparatide		1		1		2	5		5	6			
L01	**Antineoplastic agentes**	**15**	**13**	**15**	**15**	**8**	**16**	**18**	**16**	**18**	**18**	**11**	**9**	**12**
	Bevacizumab	4	4	4	6	1	5	8	5	8	8	4	2	4
	Rituximab	5	3	5	4	3	5	4	5	4	4	4	2	3
	Trastuzumab	6	6	6	5	4	6	6	6	6	6	3	5	5
L03	**Immunostimulants**		**8**	**6**	**7**	**2**	**2**	**15**	**1**	**15**	**15**	**9**	**1**	**9**
	Filgrastim		3	3	3	2		7	1	7	7	3		3
	Interferon alfa-2b											1		
	Interferon beta-1b											2		
	Pegfilgrastim		5	3	4		2	8		8	8	3	1	6
L04	Immunosuppressants	**9**	**13**	**16**	**16**	**7**	**4**	**18**	**7**	**18**	**18**	**5**	**7**	**15**
	Adalimumab	3	8	8	8	4	4	9	5	9	9	2	4	9
	Eculizumab							2		2	2			
	Etanercept	2	3	4	3	1		3		3	3	1	1	2
	Infliximab	4	2	4	5	2		4	2	4	4	2	2	4
S01	**Ophtalmologicals**		**1**		**1**			**3**		**3**	**3**			**2**
	Ranibizumab		1		1			3		3	3			2
	Total	**24**	**43**	**51**	**51**	**19**	**25**	**74**	**26**	**77**	**78**	**32**	**21**	**42**

[a] Not all products listed are biosimilars as defined in the WHO, EU and USFDA guidelines.
[b] Includes all the approvals from EMA.

was observed. EMA had the highest number of licensed biosimilars, while ANVISA (Brazil) and Health Canada were the RA with highest number of approved biosimilars in the Americas region. In Chile and Peru, the licensing of biosimilars started only in 2017.

It is recognized that the expansion in the availability of biosimilars is needed to improve affordability of biological therapies. To this aim, the implementation of regulations for biosimilars licensing is crucial to promote access to biologicals with assured quality, safety and efficacy (Rahalkar et al., 2021b; Wadhwa et al., 2022). It is worth mentioning that approval does not always indicate availability, which will depend on the commercial launch of the biosimilar, and funding decisions made by the health providers (Barszczewska and Piechota, 2021; Outterson et al., 2022), licensing is an essential requirement for accessing medicines in a country. As a consequence, the absence or delay in authorization of biosimilars may represent lack of availability of cost-effective treatments for major health problems.

It is worth mentioning that the high prices of biological therapies, such as immunosuppressants and antineoplastic agents, threaten its accessibility. Considering that adalimumab (including etanercept and infliximab as therapeutic alternatives), bevacizumab, rituximab and trastuzumab are listed as essential medicines by the WHO (World Health Organization, 2021b), the approval and introduction of new biosimilars for these therapeutic groups are urgently needed to improve affordability of first line treatments for key conditions, especially in low-resource settings (Barszczewska and Piechota, 2021). In spite of that, our results indicate an inequity in terms of number and timing of the approvals of biosimilars in the studied jurisdictions.

The observed differences in the timing of licensing and in the therapeutic classification of biosimilars approved may be due to different patent rules or to global market strategies of the manufacturers (Kang and Knezevic, 2018). In US, the existence of high number and overlapping patents is cited as a reason for delayed biosimilars approval in the country (Goode and Chao, 2022). In addition, previous studies suggest that manufacturers tend to postpone the launching of their products in markets with lower expected prices or smaller market sizes (Büssgen and Stargardt, 2022; Outterson et al., 2022).

In contrast, for some biologicals, the observed variations can be attributed to different classification systems adopted by RA. For instance, in US, teriparatide is not regulated as a biological, thus it was not counted as biosimilar product. Similarly, teriparatide was not approved as biosimilar by OGYÉI (Hungary) where two products were licensed as hybrid and one as generic. In countries where there was no specific terminology to identify biosimilars, additional criteria have been set. In Argentina, only biological products with the corresponding RP in the market were included, while for Colombia, the list covered only the biologicals with information of the corresponding RP in

INVIMA's website. In both cases, biologicals that were approved before the publication of regulation establishing similarity were not included in the study.

For biologicals products licensed before the guidelines establishing similarity by the RA, WHO recommends a reassessment since they are unlikely to be biosimilars (Kang and Knezevic, 2018; World Health Organization, 2018; Kang et al., 2021). In this study, four biosimilars were approved by COFEPRIS (Mexico) before the national regulations were issued, nevertheless, these products were reassessed and classified as biosimilars during the extension of their registries. In Mexico, all medicines should undergo an extension of the registration every five years. In 2014, the Official Mexican STANDARD NOM-257-SSA1-2014 on biotechnological products established that in the case of extensions of the sanitary registries of medicines with a registration issued before the 2011 reforms and guidelines on biosimilars entered into force, such products should be subject to the evaluation of each application by COFEPRIS, according to the product classification as innovative or biosimilar medicine (Estados Unidos Mexicanos, 2014). However, since there was no public information regarding the evaluation process conducted, it is uncertain whether the biologicals approved before regulations have been reexamined according to the accepted principles for establishing similarity.

Uncertainties related to the extension of the head-to-head comparison conducted between the biosimilar candidate and a RP to demonstrate high similarity are not new. A previous survey led by the WHO reported that some countries may not follow a strict regulatory process to approve biosimilars (Kang et al., 2020). Although the use of the term biosimilar is recommended only for the products that have been evaluated in accordance to the similarity guidance principles, biological products may be misclassified as biosimilars without proving similarity to a RP (Kang et al., 2020). Furthermore, the co-existence of non-innovator biologicals with limited or no comparison to a RP in the market may impair the identification of true biosimilars (Kang et al., 2020, 2021).

In addition to the products reported here, Brazil (ANVISA) has an alternative route to approve noninnovator biological (excluded from the present study), in which comparability exercise may be abbreviated called standalone development pathway (Garcia and Araujo, 2016). In this case, the requirements of phases I and II studies can be waived or they may not be comparative (de Assis and Pinto, 2018), as a consequence these products should not be considered biosimilars. In order to distinguish noninnovator biological approved through this pathway from the biosimilars, there is a statement in the product information leaflet attesting that the product licensing followed the comparability route. Despite that, this distinction may be challenging. Thus, the identification of biologicals could be further improved with the publication of assessment reports for all registration applications or by implementing a distinct labeling for biosimilars.

Regarding transparency, the WHO recommends that relevant documents supporting RA decisions should be available for the public in order to enhance trust (World Health Organization, 2021a), issue that can be especially challenging for biosimilars and that may hinder uptake (Kang and Knezevic, 2018). Public assessment reports describe the scientific reasoning applied to the decision to approve or deny an application, thereby contributing to inform stakeholders about the scientific principles underlying licensing, which can ultimately address knowledge gaps and dispel misinformation regarding similarity (Barbier et al., 2022). In addition, manufacturers also benefit with the publication of assessment reports, since they contribute to making regulatory process clearer and predictable (Papathanasiou et al., 2016).

An additional issue highlighted by our results is related to reliance, an approach to strengthen regulatory capacity, that potentially improves the use of limited resources through cooperation, allowing RA to focus on country-specific activities (Guzman et al., 2020). This mechanism facilitates timely access to safe, effective and quality-assured medicines. In spite of its benefits, the adoption of reliance reviews models is still limited in biosimilars development and evaluation (Rahalkar et al., 2021a,b).

In Europe, biosimilars are mainly approved via a centralized procedure, by EMA (Barbier et al., 2022). However, some biosimilars may be nationally authorized, such as low-molecular weight heparins (European Medicines Agency, 2019). In our study, Italy and Hungary had biosimilars authorized by the national authority, AIFA and OGYÉI, respectively. With non-European countries, reliance from other RA was reported for only two jurisdictions (Guatemala, DRCPFA and Peru, DIGEMID). Interestingly, a previous survey revealed that ANMAT (Argentina), INVIMA (Colombia) and COFEPRIS (Mexico) had regulations to approve new medicines through reliance (Durán et al., 2021). Thus, it is uncertain whether the decisions to approve biosimilars were not based on other RA or if the corresponding information was not publicly available.

The main strength of this study is that it covered the situation of biosimilars approval in different countries and regions involving a cross-national collaboration of researchers and health professionals working in the regulatory/government sector. In contrast, as the publicly available information was limited for some RA, it is possible that some biosimilars approved were missed in data collection while others products included may have their registration cancelled. In addition, it was not possible to confirm whether all products listed as biosimilars are biosimilars as defined in the WHO, EMA and FDA guidelines. Due to the lack of publication of assessment reports by most of the RA, it was not possible to investigate the extension of non-clinical and clinical studies presented to demonstrate similarity, which may have resulted in the inclusion of biologicals that should not be considered biosimilars. In any case, these situations were deemed few, due to the comprehensive search conducted exploring all the information published by the RA.

5. Conclusions

In conclusion, this study presented an overview of biosimilars approved by RA from three continents revealing marked differences in terms of quantity and type of products available. In spite of the advance in the number of products in recent years, some challenges still persist. Lack of transparency and limited access to information regarding the assessment of biosimilars by RA can affect confidence, which may ultimately impact adoption of these products in practice. In addition, strategies that facilitate the identification of biosimilars should be prioritized in order to allow the public to distinguish the biologicals that have been submitted to a comprehensive demonstration of similarity from other noninnovator biologicals.

Author Contributions

The study was conceptualized and designed by LCL. All authors participated in data collection and analysis for at least one regulatory authority. ANMAT (Argentina): MC, MAU and GHM; TGA (Australia): LP; ANVISA (Brazil): CGSOC, FCA and FLSM; Health Canada: TBR; ISP Chile: JCL, JRS and DSV; INVIMA (Colombia): AA and MAMB; DRCPFA (Guatemala): LIGA and LAOT; EMA and OGYÉI (Hungary): RB; EMA and AIFA (Italy): IC, MB, MT and UK; COFEPRIS (Mexico): SVD and SECS; DIGEMID (Peru): LYRT and YGA; FDA (US): EE, BL and GAH. Data collected was further compiled by FLSM. The first draft of the manuscript was written by FLSM and revised by the other authors. All authors read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2023.105485.

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