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ORIGINAL RESEARCH ARTICLE

The Global Landscape of Manufacturers of Follow-on Biologics: An Overview of Five Major Biosimilar Markets and 15 Countries

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Abstract

Background Current knowledge is limited about which manufacturers are active in the global field of biopharmaceutical product development and how many unique follow-on biologics are approved in global markets.

Objective This study aimed to provide a cross-sectional overview of manufacturers of follow-on biologics approved in 15 large countries from different regions of the world, as well as in five major biosimilar markets with long established biosimilar frameworks.

Methods We screened national drug databases to identify follow-on biologics and their manufacturers approved in 15 countries in Asia, Africa, Latin America and the rest of the world, as well as five major biosimilar markets: the European Union (including the UK), USA, Canada, Australia and Japan.

Results This study identified a total of 304 follow-on biologics from different manufacturers for 18 active substance classes included in the analysis. Of these, 67 products are approved as biosimilars in at least one of the five major biosimilar markets. A total of 140 (46%) follow-on biologics are manufactured in India or China, of which only eight (seven from India and one from China) are approved as biosimilars in any of the five major biosimilar markets. This study found that the majority of follow-on biologics are only approved in the respective country of manufacturing. A small number of manufacturers, primarily from India and Argentina, supply their products to other regions in the world. As some countries have less stringent regulatory approaches for biosimilars, or have only recently implemented biosimilar guidance in line with World Health Organization standards, follow-on biologics could have been approved that would not be considered biosimilars according to the World Health Organization standards.

Conclusions With this study, we try to contribute to discussions on creating more transparency about global approvals of follow-on biologics and promoting access to high-quality biosimilars in countries around the world.

1 Introduction

Biological medicines, hereafter referred to as 'biologics', are therapeutics that have changed the medical landscape drastically over the last three decades. In contrast to traditional small-molecule medicines, biologics involve more complex manufacturing methods, such as recombinant

Key Points

A total of 304 unique follow-on biologics for 18 active substances have been identified, of which 67 are approved as biosimilars in any of the major biosimilar markets.

Almost half of all follow-on biologics are manufactured in India and China, of which only a few are approved in major biosimilar markets.

We advocate for more transparency about globally approved follow-on biologics and aim to stimulate policy discussions on ensuring worldwide access to safe and effective biosimilars.

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DNA technology. Biologics therefore require sophisticated manufacturing methods to ensure consistent product quality and safety and efficacy profiles over the product lifespan. Because of the heterogeneous nature of biologics and the limitations of existing analytical methods to fully characterise physico-chemical properties, challenges remain for fully characterising and detecting minor differences in quality, for example due to manufacturing changes, and should therefore be adequately assessed for possible impacts on clinical safety and efficacy [1–4].

The complex properties of biologics underline the challenges to develop follow-on products after the expiry of patent and regulatory data protection of the innovator product. To this end, a dedicated route for regulatory approval of follow-on biologics has been established called the 'biosimilar' pathway, which involves a distinct regulatory approach that addresses the specific needs of biologics, as compared to small-molecule generics. The biosimilar approach involves a robust comparability exercise to prove that the follow-on biologic is clinically equivalent to the innovator product and does not compromise on safety and efficacy [5]. In the years following the first official approval of a biosimilar in 2006, the European Union (EU) approval of Omnitrope®, regulatory systems of the five major markets, i.e. the EU, USA, Canada (CA), Australia (AU) and Japan (JP), have implemented biosimilar pathways and the World Health Organization (WHO) has defined globally recognised standards [6–10]. In recent years, the biosimilar framework has proved successful in coping with the challenges of regulating complex products and has stimulated the development of biosimilars in these five major markets.

The WHO has an important public health, educational and coordinating function and made great progress in advising that appropriate regulatory frameworks for biosimilars are established and aligned globally [11]. Nevertheless, in many countries, in particular in low-income and middle-income countries, regulatory frameworks for biosimilars have only recently been implemented or are not in line with the revised WHO Biosimilar Guidance. In a recent survey on biosimilar related topics conducted by the WHO, it was noted that the absence of appropriate regulatory frameworks for biosimilars may have led to the approval of many follow-on biologics that do not meet WHO biosimilar standards (i.e. and should therefore not be regarded as biosimilars) [12, 13]. The term *follow-on biologics* is therefore used throughout this article to describe both (i) products that are approved as biosimilars by a stringent regulatory authority, such as the EU (including the UK), USA, CA, AU and JP, and (ii) products that are not biosimilars as so defined but that are approved subsequent to originator reference products and sometimes referred to as *non-innovator biologics* by the WHO. Whether some of these products may or may not conform to the revised WHO Biosimilar Guidelines has not been established as part of this study.

Studies on follow-on biologics of erythropoietin, insulin and rituximab approved in India showed significant differences in critical quality attributes when compared with their respective reference products [14–16]. Another example is the pure red cell aplasia case, which was first noted in the EU after a formulation change of the originator epoetin alfa, but which was also observed later with follow-on products of erythropoietin in Argentina, China, India and South Korea [17, 18]. In most regulatory jurisdictions, follow-on biologics adopt identical international non-proprietary names as their reference product, regardless of their approval pathway, which further complicates making a distinction between different products in clinical practice and in pharmacovigilance.

This demonstrates that there is a clear public health relevance for understanding the global policy space around follow-on biologics to be able to discuss potential implications and identify gaps that need to be addressed. However, it is currently unknown how many *unique* follow-on biologics exist in global drug markets, regardless of whether these products fulfil the WHO standard of biosimilars or not. Therefore, policy discussions take place without a clear understanding of the structure of the market and the manufacturers that are active in this field. This means that an important baseline for policy discussions is missing. Hence, the objective of this study was to create a cross-sectional overview of manufacturers of follow-on biologics approved in 15 countries from different regions of the world and five major biosimilar markets with long established biosimilar frameworks.

2 Methods

2.1 Defining the Scope: Study Sample of Biologics to be Included in the Analysis

First, we created a sample list of biologics that are of particular interest of this study, i.e. innovator biologics for which the expiry of patent and data protection has led to the approval of follow-on products. Therefore, we looked into biological product classes for which at least one biosimilar has been approved in any of the five major markets that have implemented WHO guidelines on the evaluation of similar biotherapeutic products in the past 15 years: the EU, USA, CA, AU or JP (from here on referred to as 'the five major biosimilar markets') [19].

Because the WHO guidelines on biosimilars are applied to recombinant biologics in particular, we excluded vaccines, plasma-derived products and their recombinant analogues from the sample list of biologics. However, we added

recombinant human insulin to our sample list, despite no biosimilar being approved in any of the five major biosimilar markets because many follow-on biologics are found in other regions of the world. The full list of recombinant biologics included in this study can be seen in **Table 1**, including the brand name and year of approval of the first biosimilar in each product class.

2.2 Defining the Scope: Selection of 15 Global Countries to be Included in the Analysis

Next, we selected 15 countries for inclusion in the analysis. To select these countries, we looked for publicly accessible national drug databases or other public regulatory information sources that allowed for a comprehensive assessment of national drug approvals. These information sources involved public assessment reports, patient information leaflets and summary of product characteristics. The product-specific metrics that we needed to extract from the databases and information sources included brand names of marketed medicines, marketing authorisation holder (MAH) names, the manufacturer of the active substance and, where available, initial approval dates. Countries were considered suitable for the analysis if this information was available and allowed for systematic identification of national approvals of follow-on biologics. In some cases, information from the website of the MAH or the active substance manufacturer as well as scientific and grey literature were used to complement any missing information. Based on these criteria, we selected 15 countries that were of interest (e.g. countries known to have many local manufacturers such as India), but also represented a good mix of geographic regions from Asia, Africa, Latin America and the rest of the world. **Table 2** shows the 15 countries that were included in this study and the respective information sources for identifying national approvals of follow-on biologics.

2.3 Defining the Unit of Analysis

In contrast to previous studies looking into general marketing authorisation applications of biosimilars, this study adds granularity by identifying and distinguishing between different follow-on biologics [13]. In order to do so, we defined the manufacturer of the active substance as the primary unit of analysis. This was critical to avoid double counting of follow-on biologics

Table 1 List of recombinant biologics (drug substance names) included in this study and overview of first-in-class biosimilar approvals

INN/substance	Brand name (MAH) of first biosimilar	Year (market) of approval of first-in-class biosimilar
Adalimumab	Amjevita (Amgen)	2016 (EU)
Bevacizumab	Mvasi (Amgen)	2017 (USA)
Epoetin alfa	Abseamed (Medice)[c]	2007 (EU)
Darbepoetin alfa	Darbepoetin alfa BS1 (JCR Pharmaceuticals)	2019 (JP)
Etanercept	Benepali (Samsung)	2016 (EU)
Filgrastim	Tevagrastim (Teva)[c]	2008 (EU)
Pegfilgrastim	Fulphila (Mylan)	2018 (USA)
Follitropin alfa	Ovaleap (Theramex)	2013 (EU)
Infliximab	Remsima (Celltrion)[c]	2013 (EU)[d]
Insulin aspart	Insulin aspart Sanofi (Sanofi)	2020 (EU)
Insulin glargine	Abasaglar (Eli Lilly)	2014 (EU)
Insulin lispro	Insulin lispro Sanofi (Sanofi)	2017 (EU)
Human insulin[a]	N/A	N/A
Ranibizumab	Byooviz (Samsung Bioepis)	2021 (EU)
Rituximab	Truxima (Celltrion)[c]	2017 (EU)[d]
Somatropin	Omnitrope (Sandoz)	2006 (EU)
Teriparatide[b]	Terrosa (Gedeon Richter)	2017 (EU)
Trastuzumab	Ontruzant (Samsung Bioepis)	2017 (EU)

EU European Union, *INN* international non-proprietary names, *JP* Japan, *MAH* marketing authorisation holder, *N/A* not applicable

[a]Human insulin included despite no biosimilar approval in any of the five major biosimilar countries because many follow-on products exist in the global market

[b]We only included recombinant teriparatide in our study and therefore omitted recently approved synthetic versions of teriparatide

[c]Multiple approvals on the same date (relating to same follow-on biologics/manufacturer approved under different brand names)

[d]Product has been approved in South Korea before approval in the EU

Table 2 Overview of the 15 countries included in the analysis and respective information sources to assess national drug approvals

Countries	Information source
Asia	
China	National Medical Products Administration (NMPA), Chinese Drug Database (https://www.nmpa.gov.cn/datasearch/search-result.html)
India	Central Drugs Standard Control Organization (CDCSO), list of approved rDNA medicines in India (https://cdsco.gov.in/opencms/opencms/en/biologicals/rDNA/)
Indonesia	The National Agency for Drug and Food Control (BPOM), National Database (https://cekbpom.pom.go.id/)
Malaysia	National Pharmaceutical Regulatory Agency (NPRA), Malaysian Drug Database (https://npra.gov.my/index.php/en/consumers/information/products-search.html)
South Korea	Ministry of Food and Drug Safety (MFDS), Drug Information Database (https://nedrug.mfds.go.kr/searchDrug)
Africa	
South Africa	South African Health Products Regulatory Authority (SAHPRA), South African Health Product Database (https://www.sahpra.org.za/registered-health-products/)
Tanzania	Tanzania Medicines and Medical Devices Authority (TDMA), Regulatory Information Management System (https://imis2.tmda.go.tz/portal/#/public/registered-medicines)
Latin America	
Argentina	The National Administration of Drugs, Foods and Medical Devices (ANMAT), Argentinian Drug Database (https://servicios.pami.org.ar/vademecum/views/consultaPublica/listado.zul)
Brazil	The Brazilian Health Regulatory Agency (ANVISA), National Health Surveillance Agency Drug Database (https://consultas.anvisa.gov.br/#/medicamentos/)
Chile	Public Health Institute of Chile (ISP), Drug Database of Chile (https://registrosanitario.ispch.gob.cl/)
Colombia	The Colombian National Food and Drug Surveillance Institute (INVIMA), Columbian Drug list (https://www.invima.gov.co)
Other (e.g. Middle East)	
Iran	Iran Food and Drug Administration (FDA), Iran Pharmaceutical Statistics (https://www.fda.gov.ir/)
Russia	Directory Vidal, Russian Medicines Index (https://www.vidal.ru/search?t=all&q=&bad=on)
Saudi Arabia	The Saudi Food & Drug Authority (SFDA), Saudi Drug List (https://www.sfda.gov.sa/en/drugs-list)
Turkey	The Turkish Pharmaceuticals and Medical Devices Authority (TITCK), Turkish Drug List (https://titck.gov.tr/dinamikmodul/43)

with multiple marketing authorisation applications, for example because of licensing agreements. For instance, the three European biosimilar approvals of epoetin alfa, Abseamed®, Binocrit® and Epoetin Alfa Hexal®, are produced by the same manufacturer and therefore considered the same product [20–22]. The identification of the manufacturer made it possible to track follow-on biologics throughout all 15 countries and five major biosimilar markets, if approved with different brand names and by different MAHs. For the purpose of this study, we focused on the manufacturer responsible for the drug substance and did not take into account (local) manufacturing sites for final assembly and packaging. We listed all manufacturers where multiple active substance manufacturers were identified.

2.4 Analysis: Search and Identification of Follow-on Biologics

We screened 15 national drug databases of the countries that were selected for this study and searched for the active substance names of all biological product classes from the pre-defined sample list of biologics from **Table 1** to identify follow-on biologics approved in each of the respective national markets. International non-proprietary names and/or Anatomical Therapeutic Chemical codes were used to identify both the innovator and the follow-on product approvals. We also screened for affiliated drug substance names (e.g. "recombinant human growth hormone" in the case of somatropin) if required. We did not distinguish between different indications or formulations. For each identified follow-on biologic, we identified (local) brand names, the name of the MAH and the manufacturer of the active substance. We used automatic translation services where information sources were only available in national languages (e.g. China, South Korea, Iran).

In a second step of the analysis, we assessed whether follow-on biologics approved in any of the 15 countries included in the analysis are also approved as biosimilars in at least one of the five major biosimilar markets in the EU, USA, CA, AU and/or JP. To this end, we identified all unique biosimilar approvals in any of these five major biosimilar markets. All follow-on products were

then differentiated between products that are available as 'biosimilars' in any of the five biosimilar markets from those that are not available in major biosimilar markets. As such, the five major biosimilar markets with long established biosimilar frameworks served as a reference point to identify follow-on biologics that can be definitely considered biosimilars according to WHO standards. In contrast, follow-on biologics that are not available in any of these five countries warrant further research to assess if they fulfil the WHO biosimilar standards, which was beyond the scope of this study [11, 23].

Finally, we tried to identify the initial approval date for each follow-on product in this study. In most cases, we relied on the first marketing date in the country of origin (the country where the product is manufactured), the information sources from the manufacturing company's website or the scientific/grey literature. Where this information was not available, we relied on the 'oldest' approval date that was found in the respective countries where the follow-on biologic is marketed. The analyses was carried out between December 2021 and April 2022.

3 Results

3.1 Overall Results

This study identified a total of 304 *unique* follow-on biologics from different manufacturers for the 18 active substances included in this study. Of these 304 follow-on biologics, 67 (22%) are approved as biosimilars in at least one of the five major biosimilar markets (EU, US, CA, AU and/or JP) [**Table 3**]. The remaining 237 (78%) follow-on biologics available in one or more of the 15 countries included in this study are not approved as biosimilars in any of the five major biosimilar markets. For each of the 18 active substance classes, we see that a larger proportion of the follow-on biologics are not approved as biosimilars in any of the five major biosimilar markets. The largest difference can be observed for the 'older' biologics for which the first wave of biosimilars have been approved in the EU before 2010, such as epoetin alfa, filgrastim and somatropin, but also human insulin for which, as of yet, no biosimilars exist in any of the major biosimilar markets.

Table 3 Number of identified follow-on biologics per active substance

Product classes (active substance names)	No. of follow-on biologics that are approved as biosimilars in EU, USA, CA, AU and/or JP	No. of follow-on biologics that are not approved as biosimilars in EU, USA, CA, AU and/or JP
Adalimumab	10	11
Bevacizumab	6	17
Epoetin alfa	3	38
Darbepoetin alfa	3	5
Etanercept	4	10
Filgrastim	6	44
Pegfilgrastim	7	13
Follitropin alfa	2	10
Infliximab	5	5
Insulin aspart	2	6
Insulin glargine	2	10
Insulin lispro	1	2
Human insulin	0	22
Ranibizumab	1	2
Rituximab	4	13
Somatropin	2[a]	15
Teriparatide	3	6
Trastuzumab	6	8
Total	**67**	**237**

AU Australia, *CA* Canada, *EU* European Union, *JP* Japan

[a]The marketing authorisation of Valtropin was withdrawn in 2012 in the EU, but it is still available in Brazil, India and South Korea and therefore included in this overview

3.2 Time Trend of Approvals of Follow-on Biologics

The time trend analysis in **Fig. 1** shows that the first wave of follow-on biologics was seen at the end of the 1990s. A total of 38 follow-on biologics have been identified that are approved in different countries around the world before 2006, which is the year of the approval of the first biosimilar Omnitrope® in the EU. These follow-on biologics mostly relate to 'older' generation biologics such as epoetin alfa, filgrastim and recombinant human insulins. We also see an increase since 2015 in the proportion of follow-on biologics that are also available as biosimilars in major biosimilar markets.

With the exception of infliximab (Remsima®) and insulin aspart (Insulin aspart Sanofi®), for all active substance classes, follow-on biologics have been approved in at least one of the 15 countries years prior to the first approval as biosimilar in any of the major biosimilar markets. For some product classes, such as epoetin alfa, etanercept, filgrastim, insulin glargine, insulin lispro, rituximab and teriparatide, initial approval dates of follow-on biologics precede the first approval date of a biosimilar in one of the major biosimilar markets by more than 10 years.

3.3 Type and Origin of Manufacturers of Follow-on Biologics

Table S1 of the Electronic Supplementary Material (ESM) provides an overview of all 304 follow-on biologics identified in this study and the respective manufacturer of the active substance. Of the 304, the majority are manufactured in India (78 [25.7%]) and China (62 [20.4%]), followed by Russia (25 [8.2%]), South Korea (25 [8.2%]), Iran (23 [7.6%]) and Argentina (20 [6.6%]). Only seven follow-on biologics from in India and one from China are approved as biosimilars in any of the five major biosimilar countries.

The manufacturing company that produced the largest number of follow-on biologics is the Indian-based drug manufacturer Reliance Life Sciences, producing follow-on biologics for 12 of the 18 active substances, followed by Intas and Biocon, which are both Indian companies that manufacture follow-on biologics for 10 of the 18 active substances. All follow-on biologics manufactured by Reliance Life Science are not available as biosimilars anywhere in the five major biosimilar markets, whereas two and five follow-on biologics produced by Intas and Biocon, respectively, are available as biosimilars in at least one of the five major biosimilar markets. Furthermore, we discovered that the Russian-based manufacturer Biocad (producing 7 out of 18) and Iranian-based manufacturer Cinnagen (6 out of 18) are the largest manufacturers of follow-on biologics for the 18 active substances outside India. None of their products is available as a biosimilar in any of the major biosimilar markets.

3.4 Global Distribution of Follow-on Biologics

The detailed overview of national approvals of each follow-on biologic in the 15 countries included in the analysis (see

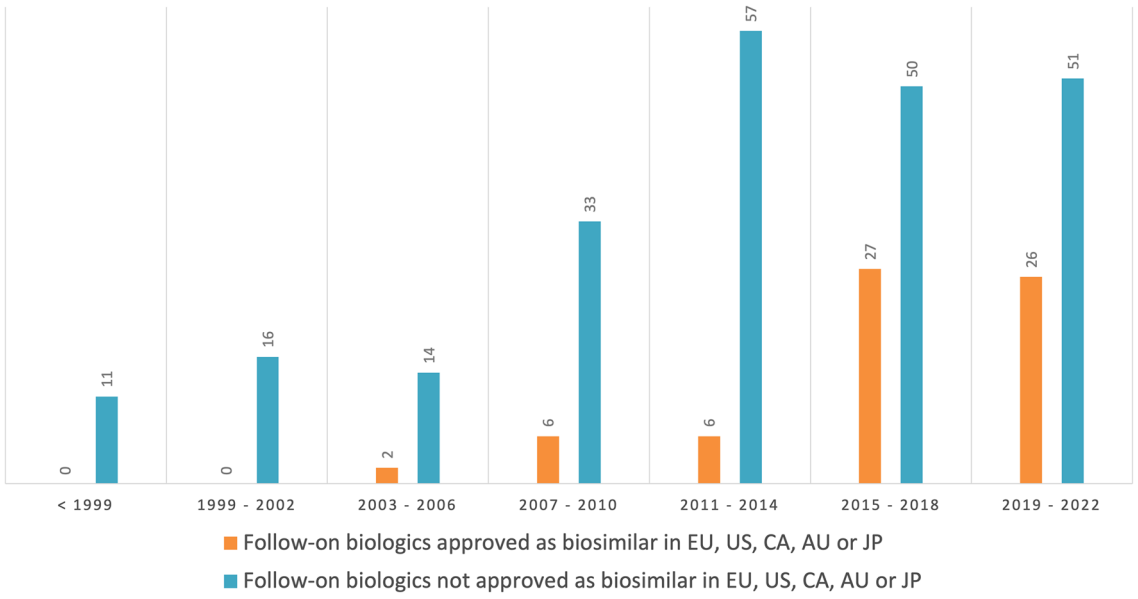

Fig. 1 Time trend analysis of approvals of follow-on biologics approved as biosimilars in major biosimilar markets (European Union [EU], USA [US], Canada [CA], Australia [AU] and/or Japan [JP]) versus follow-on biologics not approved in major biosimilar markets. A total of five products (all not approved as biosimilars in EU, US, CA, AU or JP) were excluded from this Figure because the initial approval date could not be identified

ESM) shows that the vast majority of the 237 follow-on biologics, which are not approved as biosimilars in any of the five major biosimilar markets, are only approved in the same country where they are manufactured. This mostly concerns 'older' generation biologics, such as epoetin alfa and filgrastim.

However, there are several exceptions. A total of 47 of the 237 (19.8%) follow-on biologics are approved in at least two of the 15 countries included in the analysis. Of these, four follow-on biologics are distributed to five different countries. This concerns the two insulin glargine products, one produced by Chinese-based Gan & Lee Pharmaceutical, available under various brands in Argentina, Brazil, China, Indonesia and Russia, and the other produced by Indian manufacturer Wockhardt, available under the brand name Glaritus® in Colombia, Tanzania, India, Indonesia and Malaysia. This is also the case for two human insulin products, one also produced by Indian manufacturer Wockhardt and available as Wosulin® in Brazil, Colombia, Tanzania, India and Russia, and the other manufactured by the Indian company Biocon, which is available under the brand name Insugen® in Brazil, Chile, Tanzania, India and Malaysia.

Another 12 follow-on biologics are distributed to four countries, including a number of monoclonal antibodies. For example, one follow-on product of bevacizumab (manufactured by mAbxience in Argentina), and three follow-on products of rituximab (one manufactured by mAbxience in Argentina, the other two by Indian-based companies Dr. Reddy's and Hetero Biopharma) are each distributed to four countries on different continents. When comparing the largest producing countries, we noticed that follow-on biologics manufactured in India, and to a certain extent Argentina, are more likely to be approved in at least one other country compared with follow-on biologics manufactured and approved in China, Russia and Iran.

Follow-on biologics approved as biosimilars in major biosimilar markets are more commonly approved in any of the 15 countries included in the analysis, compared to follow-on biologics not available as biosimilars in these five markets (see previous section). For example, trastuzumab biosimilar Ogivri® (manufactured by Biocon) is approved in 12 of the 15 countries, insulin glargine biosimilar Abasaglar® (manufactured by Eli Lilly) in 10 of the 15 countries and infliximab biosimilar Remsima® (manufactured by Celltrion/Lonza) in 9 of the 15 countries. We also see a large distribution to other countries in other product classes, such as adalimumab, bevacizumab, filgrastim, rituximab and somatropin.

3.5 Use of Brand Names Varies Across Global Markets

In general, we see that many follow-on biologics are often marketed under different brand names in different countries (see ESM). This is particularly the case for follow-on biologics that are not approved as biosimilars in any of the five major biosimilar markets. For example, rituximab manufactured by mAbxience in Argentina is marketed as Novex® in Argentina, Rituximab Amring® in Tanzania, Rituxikal® in Indonesia and, according to the information available to us, marketed using only the non-proprietary name 'rituximab' in Russia. The same is observed with rituximab manufactured by Hetero Biopharma in India, which is known as Maball® in India and Colombia, but marketed as Rilast® in Russia and Rituxsan® in Indonesia. In addition to the use of different brand names, we see that many of these follow-on biologics are also marketed by different MAHs in different countries, for example rituximab manufactured by mAbxience is marketed by different MAHs in each of the four countries. In contrast, follow-on biologics that are approved as biosimilars in at least one of the five major biosimilar markets are almost exclusively marketed under the same brand names and mostly by the same MAH in any of the other 15 countries.

Similarly to rituximab marketed under the non-proprietary name in Russia, we also noticed many other cases where follow-on biologics are marketed without a brand name (using only the non-proprietary name). In most cases, this relates to older generation biologics, such as epoetin alfa, filgrastim, pegfilgrastim, follitropin alfa, insulins, teriparatide and somatropin, but in some cases this was also observed for monoclonal antibodies such as rituximab (e.g. next to Russia also in India) and infliximab (in Russia).

4 Discussion

4.1 Majority of Follow-on Biologics Are Not Available in Major Biosimilar Markets

This study found that more than three quarters of all follow-on biologics identified in global markets are not approved as biosimilars in any of the five major biosimilar markets of the EU, USA, CA, AU and JP. The majority of these products are manufactured in India and China (ESM). We only identified 67 unique products that were available as biosimilars in any of the five major biosimilar markets. As these countries have long established biosimilar frameworks, these 67 products can all be considered biosimilars approved according to WHO standards. On the contrary, we do not know to what extent the remaining 237 follow-on biologics followed regulatory pathways in line with WHO biosimilar guidance or not (as this was beyond the scope of this study). Nonetheless, several considerations can still be made based on the results of this study.

As the results show, we identified many follow-on biologics have been approved globally before the first biosimilar

approval in April of 2006 (Omnitrope®). Therefore, it is unclear how these products have been compared against their licensed reference product as comparators, and whether these products could be considered biosimilars according to today's biosimilar standards, as official biosimilar guidance was not available at the time of approval [24]. As Table S1 of the ESM shows, this mainly concerns 'older' generation biologics, such as locally produced epoetin alfa, filgrastim and insulins, which have been approved before 2006 in the respective country of manufacturing. This is also supported by the findings of Kang et al., who showed that the majority of follow-on biologics that cannot be considered biosimilars (termed *non-innovator biologics* by the WHO) are found in the product classes of insulins, filgrastim, interferons and epoetin alfa [8, 13]. This may not be surprising as, historically, these older generation biologics comprise smaller and less complex products, which are easier to replicate and may therefore be more likely to trigger generic competition by local manufacturers. Moreover, low-income and middle-income countries may have faced a greater need to develop affordable therapeutic alternatives that opened up the market for companies producing follow-on biologics. At the same time, this could explain the large number of local manufacturers found in China and India owing to the large patient populations in these countries.

We also found several more complex follow-on biologics that were approved in global markets 10 years prior to the first approval of a biosimilar from that product class in one of the five major biosimilar markets. Examples are etanercept and rituximab, with the approval of Yisaipu® in 2005 in China and Reditux® in 2007 in India, respectively. As these products concern relatively complex and large-sized biologics, and specific regulations were not available at the time of approval, the scientific community has raised questions about their biosimilarity and the lack of robust clinical trials [24, 25]. Interestingly, Dr. Reddy's had planned to launch Reditux® as a biosimilar in the EU 10 years ago, but as of today no application to approve Reditux® in the EU has been recorded and clinical trials are still ongoing in Europe and the USA [26].

4.2 Failed Biosimilar Approvals and Their Availability in Other Global Drug Markets

In some cases, follow-on biologics that are approved in one or more of the 15 countries analysed in this study have failed to gain biosimilar approval in one of the five major biosimilar markets. This indicates that these products may not be considered biosimilars according to WHO standards. For example, the biosimilar application for Solumarv® from Marvel Lifesciences was refused by the European Medicines Agency in 2016 following major objections that it was not comparable to the reference product (Humulin®) [27]. The same product had however been marketed for many years in different countries around the world such as South Africa, Tanzania, Russia and India under the brand name Biosulin® (see Table S1 of the ESM) [28]. This does not only show that non-innovator biologics (those follow-on biologics that cannot be considered biosimilars according to the WHO) can be found among those 237 follow-on biologics that are not approved as biosimilars in major markets, but also highlights the challenges in developing biosimilars and, therefore justifying the increased stringency of regulatory approaches for biosimilars.

Another factor that could contribute to divergent regulatory approaches for follow-on biologics, as seen with the insulins, is the approach chosen by some regulatory authorities to regulate certain biologics under the traditional regulatory paradigm of small-molecule drugs. Even the US Food and Drug Administration has only brought small biologics, such as insulins, into the regulatory pathway of biologics after March 2020 [29]. As such, some biosimilars, such as Admelog®, have been approved under the abbreviated pathway of 505(b)(2) in the USA whereas they have been approved under the biosimilar pathway in the EU. Other countries are reportedly still regulating certain biologics as chemical drugs [11]. This could further raise questions as to what extent follow-on biologics approved in these countries fulfil WHO biosimilar standards.

4.3 Shift Towards Biosimilar Approvals in Five Major Biosimilar Markets

The time trend analysis from **Fig. 1** shows that, in recent years, a larger proportion of follow-on biologics are approved in at least one of the five major biosimilar markets. About one-third of all global approvals since 2015 concern products that are also approved as biosimilars in the EU, USA, CA, AU and/or JP. This could mean that these newer generation follow-on biologics are more likely to be approved according to WHO biosimilar standards, as they are more widely implemented among global regulatory authorities. Furthermore, generic companies may have matured and learned to develop follow-on biologics according to the current approval standards.

We therefore expect that a large portion of the 237 follow-on biologics, in particular recent approvals, can actually be considered biosimilars according to the WHO biosimilar standards, despite not being available as biosimilars in any of the five major biosimilar markets. Recent approvals of follow-on biologics in South Korea, such as Eucept® (manufactured by South Korean-based LG Chem), are considered biosimilars by the Ministry of Food and Drug Safety because of the available biosimilar guidance in Korea in line with WHO biosimilar standards [30, 31]. The reason that these products are not available in the EU, USA, CA, AU or JP

could therefore be related to commercial, legal and/or strategic reasons. Additionally, in some cases follow-on biologics were approved in local drug markets years before being approved as biosimilars in any of the five major biosimilar markets, which may have been caused by differing patent protection periods in these countries. For example, the initial authorisation of a biosimilar of recombinant teriparatide in 2022, manufactured by Indian-based pharmaceutical company Intas, has already been approved and marketed in India since 2010 [32].

4.4 Local Manufacturers Versus Global Suppliers

The majority of the 237 follow-on biologics not approved as biosimilars in any of the five major biosimilar markets are only available in one of the 15 countries included in this analysis. This mostly relates to follow-on biologics produced for the local market. Only a fifth of the 237 follow-on biologics (47 of the 237) are distributed to other countries, often involving larger and well-known *generic* companies of which the majority are based in India (ESM). Interestingly, whereas a large proportion of Indian manufacturers supply their products to markets beyond India, this study found that the majority of follow-on biologics manufactured in China, Russia and Iran are only approved for the local market.

4.5 Limitations

There are a number of limitations to consider when interpreting the results of this study. First, this study only provides a snapshot of approvals of follow-on biologics, with our study sample restricted to 18 active substance classes and 15 countries around the world plus the EU, USA, CA, AU or JP representing five major biosimilar markets. The market dynamics are however complex and the global product landscape is under continuous transformation. Nonetheless, we believe that this study provides some interesting insights into the dynamics of global approvals of follow-on biologics and the manufacturers that are active in this field. We are aware that more follow-on biologics exist for other active substance classes, such as non-recombinant low-molecular-weight heparins or biologics for which as of yet no biosimilars are available in any of the five major biosimilar markets and were therefore not included in this study. Examples are imiglucerase or the monoclonal antibodies eculizumab, abciximab and omalizumab for which follow-on products are already available in other global markets such as India.

Second, the information provided in this study is dependent on the completeness of information databases and other relevant regulatory documents that were used for the analysis. Moreover, the analyses was particularly challenging where regulatory information required automatic translation services, for example China, South Korea and Iran, or where available information sources from different countries provided ambiguous answers, for example where multiple/different manufacturing sites were listed or changed because of name changes or mergers. Furthermore, the available information on initial approval dates of individual follow-on biologics was limited. In many cases, the dates published by regulatory authorities only referred to the last renewed licencing dates, which made the identification of initial approval dates sometimes difficult, especially for *older* approvals.

4.6 Policy Implications and Recommendations

This study aimed to provide a holistic overview of globally approved follow-on biologics and their manufacturers based on an analysis of 15 large countries from different regions of the world and five major biosimilar markets. The fragmentation of available information to perform a study like this clearly shows the need for more globally concerted efforts to improve transparency about manufacturing and approvals of follow-on biologics anywhere in the world. The lack of clear understanding of the global market of follow-on biologics can have serious implications for various stakeholders, including patients, which shows the public health relevance of this study.

This study does also highlight a number of implications from a national perspective, in particular with regard to clinical practice and pharmacovigilance. The use of different brand names in different countries could pose potential challenges for the identifiability of follow-on biologics, especially for drug safety monitoring of individual products at the global level [33, 34]. Furthermore, the use of identical international non-proprietary names for both biosimilars and non-innovator biologics (i.e. follow-on biologics that cannot be considered biosimilars according to the WHO) could create challenges for clinical practice with regard to switching from one product to another. This can become even more precarious if these products coexist in the same market [35]. The WHO has made great efforts to create globally harmonised standards for biosimilar approvals. We therefore see an important role for the WHO as a neutral and global institution to collect and provide information on approvals of all follow-on biologics found in the global market. We also advocate for greater regulatory reliance to facilitate faster and broader access to high-quality biosimilars around the world. This could especially be valuable for speeding up access in low-income and middle-income countries with limited regulatory capacity, and at the same time could reduce redundancy in regulatory assessments when biosimilars are launched in the broader global market [36].

We support the WHO guidance on the roles and responsibilities of the national regulatory agency in the recently revised biosimilar guidelines, and in particular to not

describe as "biosimilars" those follow-on biologics that have not been approved as biosimilars according to the WHO guidelines [5]. Based on the findings from this study, we therefore recommend follow-up studies to investigate the potential existence of non-innovator biologics in global markets. The group of 237 follow-on biologics not approved in major markets is of particular interest here and warrants further investigation. In the end, this study wants to contribute to discussions on how to improve and accelerate global access to safe and high-quality biosimilars that are imperative for healthcare systems around the world.

5 Concluding Remarks

An increasing number of follow-on products have been approved globally since the expiry of market exclusivity of many innovator biologics. This study identified a total of 304 unique follow-on biologics from different manufacturers for the 18 active substances analysed. Of these 304 products, only 67 are approved as biosimilars in any of the five major biosimilar markets of the EU, USA, CA, AU and JP. The remaining 237 follow-on biologics identified in this study mostly relate to locally manufactured follow-on biologics approved in national markets. Almost half of all follow-on biologics identified in this study are manufactured in India or China, of which only a few are approved as biosimilars in any of the five major biosimilar markets. We also identified a number of manufacturers, primarily from India and Argentina, that supply their products to other regions in the world. As some countries still lack or have only recently implemented stringent regulatory pathways for biosimilars, it is unclear whether follow-on biologics followed WHO biosimilar guidance and can therefore be considered biosimilars. Because of the potential existence of follow-on biologics, not being biosimilars, we advocate for more transparency about the scientific grounds of regulatory approvals of individual follow-on biologics found in the global market. This study tries to contribute to better knowledge about manufacturers active in this field. We hope that this can facilitate better coordination among global regulatory authorities and ensure worldwide access to safe and effective biosimilars approved in line with WHO biosimilar standards.

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Authors' Contributions KK and PS developed the methodology for this study. KK collected the data and performed the analysis. KK and PS drafted the manuscript. MG, JH and VA reviewed the manuscript.

Declarations

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Conflicts of interest/competing interests KK and PS have no conflicts of interest that are directly relevant to the content of this article. MG declares that he has no conflicts of interest (besides being employed by the not-for-profit organisation IFPMA). VA and JH are employed by pharmaceutical companies, but declare that they have no conflict of interest directly related to the article's content. IFPMA represents research-based pharmaceutical companies and associations around the world. Some IFPMA members develop, manufacture and market biosimilars. IFPMA supports science-based regulatory frameworks for biosimilars to ensure patients' safety.

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