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Biosimilars in two developing economies of South America (Argentina and Brazil) and one developed economy of Oceania (Australia). Facts, regulations and evolution.

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ABSTRACT

The expiration of patents for biological drugs will lead us to the golden age of biosimilars and provide a competitive edge to medium-sized pharmaceutical manufacturers and contract research organizations. Biosimilars are three-dimensional versions of biological products that share an identical protein sequence and common amino acid sequence with the originals (biological drugs) and have demonstrated a high degree of similarity in physicochemical characteristics, efficacy, safety (including immunogenicity) and quality, but with differences in their manufacturing process in the structure of the active protein. However, these biological medicines offer lower-cost alternatives to the original drugs. This paper provides an overview of the challenges of the biosimilar industry in two countries of South America and one of Oceania with a local history in pharmaceutical industry that should show the experience of each country in relation to its evolution, clinical trials and regulations. Each country has its own regulatory guideline for biosimilar drugs.

Keywords: biosimilar products; biopharmaceutical industry; regulatory guidelines; biological products

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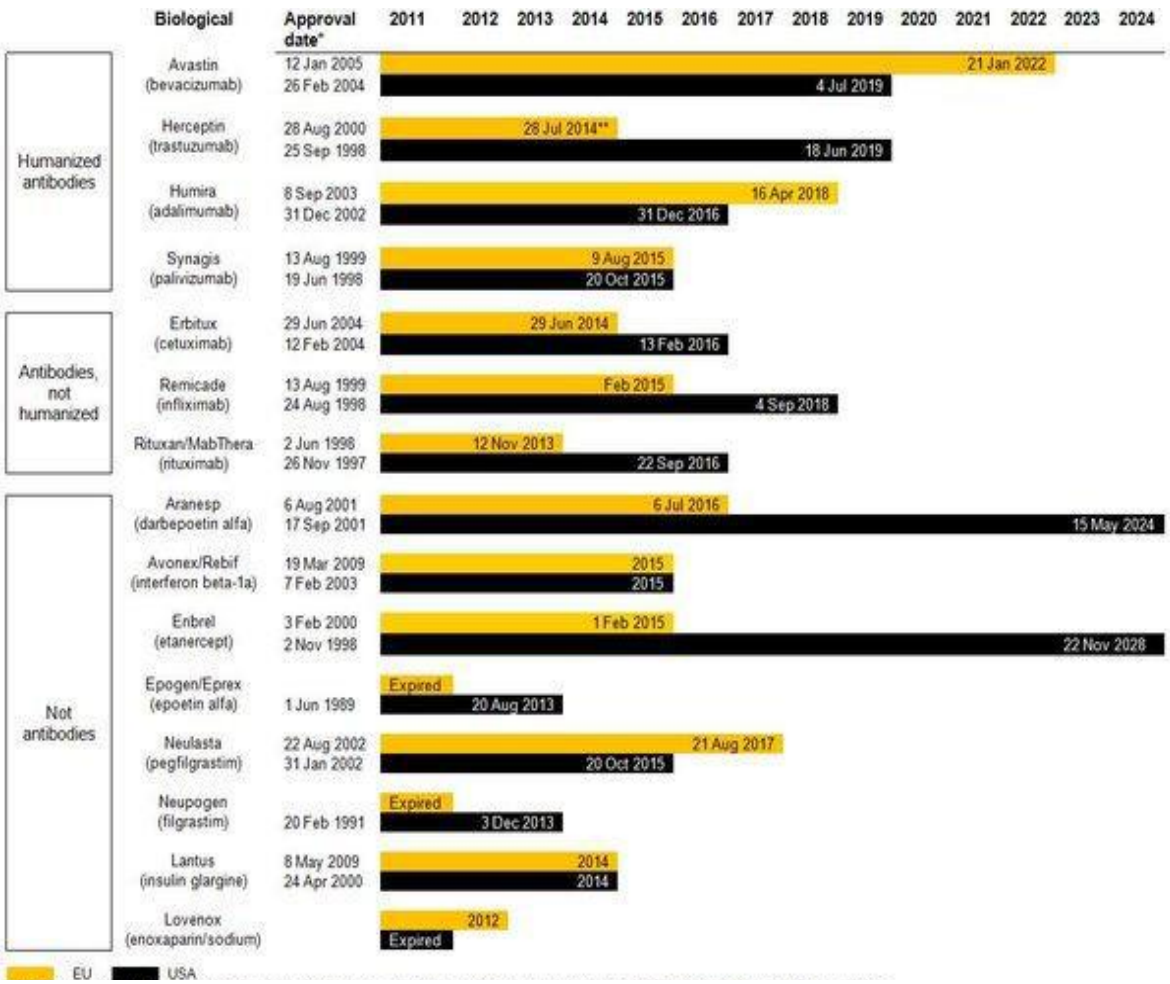
INTRODUCTION

For over a decade, the biopharmaceutical industry (which manufactures biological medical products) has been trying not only to maintain its past high profitability, but also to look for new ways to reduce their production costs and increase the sale of their biological drugs. Because the cost associated with the development of a new molecule of biological origin is extremely high (US $800 to $1.3 billion), the search for strategic alternatives that will enable biopharmaceutical companies to face these high costs of research and development is a strategic priority. Unfortunately, while the costs of developing new biological molecules are constantly increasing, biopharmaceutical companies must confront many other obstacles related to the expiration of the exclusive rights conferred by patents (Bas and Oliu Castillo, 2016). In this context, some sources estimate that expirations are responsible for major profitability losses (Table 1) that could reach approximately US $70 billion between 2010-2024 (Ahmed et al. 2012; Muller et al. 2014).

Table 1: Patent Expiration of Biological Products in USA and EU, 2011-2024.



Source: GaBi Online Sheppard et al. Bernstein Research (2012)

This situation has motivated large multinational firms and some of their partner contract research organizations (CROs) to develop an alternative way of profitability, with a fresh biopharmaceutical business. Thus, they test best-selling biological molecules (known as blockbusters) whose patents have expired, or are about to expire, in order to give these molecules a 'second and new life' (Table 2). They design 'biosimilars' at a much lower cost than the original molecules, between US $10 million and US $250 million, and with six to nine years of clinical trials. This results in more affordable drugs for a variety of new therapies (Zelenetz et al. 2014).

Nonetheless, the existing definitions of biosimilars are different depending on the country or region. However, an interesting definition is established by (Ahmed et al. 2012): '*Biosimilars are defined as biologic*

products that are highly similar to reference products, notwithstanding minor differences in clinically inactive components, with no clinically meaningful differences between the biologic product and the reference product in terms of safety profile, purity, and potency.' The Public Health Service Act from United-States (PHS Act), define biosimilars, Under section 351(i)(2), '*biosimilar or "biosimilarity" means that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.' (FDA.gov).*

Table 2: Differences between a Chemical, Biological, Generic and Biosimilar Drug

Parameter	Chemical Drug	Generic Drug	Biological Drug	Biosimilar Drug
Synthesis	Production of original chemical formula	Copy from the original chemical formula	Since the insertion of a gene that plays a cell clone molecule	Development derived from the original biological molecule.
Size	100-1000 Da	100-1000 Da	10.000-300.000 Da	10.000-300.000 Da
Glycosylation Process	Zero	Zero	Several	Several
Molecular Structure	Simple	Simple	Complex	Complex
Ability to Generate Immunity	Low	Low	Medium-High	Medium-High
Drug Development Time	7-10 years	1-3 years	10-15 years	6-9 years
Costs	US $500-800 M	<US $1-2 M	US $800-1300 M	US $10-250 M
Characterization Analysis Laboratory	N/A	There are techniques to identify similarity to the original drug	N/A	No identification technique equality of the molecule. Clinical studies are needed

Source: Adapted from Zelenetz, A. et al. 2011

From the molecular perspective, biosimilars have a sequence of amino acids similar to the original, but its most important difference is the level of the three-dimensional structure of the active protein. It is very important to note that biosimilars are not 'generic drugs' (Table 2), which are composed of chemically-based structures, have a smaller molecular size and single complexity, with a known chemical synthesis process. Such is the case, for example, of aspirin, which measures 0.18 kDa and has been manufactured for over 100 years throughout the world. In contrast, the compounds with a biologically-based structures are much more complex, with three-dimensional molecules and a much larger molecular mass, such as: Insulin, measuring 5.8 kDa; the growth hormone, measuring 22.1 kDa; the Erythoprotein, measuring 34 kDa; or the largest and most complex, the Monoclonal Antibody, measuring 150 kDa.

Because of the complexity, size and biological origin of these molecules, they require in-depth clinical studies and must be approved by the competent health agencies in each country to be categorized as biosimilars. However, this increases their production costs (in relation to the generic drugs of chemical origin), since it is not possible to know the exact process by which the original biological medicine is manufactured and the changes and potential consequences that the new biosimilar can have in the body. Therefore, pharmacokinetics and pharmacodynamics tests are key components to measure effectiveness, performance, and safety in patients, as well as the similarity to the original drug (Vital, Kay and Emery 2013).

These characteristics require the unification and homogenization of terminologies and nomenclatures to provide global stability to this burgeoning industry. However, it is extremely complex, since each country or region sets its own rules relating to the approval of biosimilars and the guarantees of exclusivity that come from the expiration of intellectual property. While patents cannot be protecting biosimilars, because they have

expired, there are regulations to ensure a period of exclusivity in marketing, so that their return in guaranteed and R&D should be encouraged for these new types of products. The United States is the only country that divides this exclusivity rights into two categories: data exclusivity (Table 3), which lasts four years, and market exclusivity, which covers eight years. In Australia and Brazil, data exclusivity is granted for five years, while in the European Union it lasts ten years. No information was found for Argentina.

Table 3: Data Exclusivity of Biosimilars in many Countries

Country	Data Exclusivity Period
United States	Four year of data exclusivity / Eight years of market exclusivity
EU	Ten years of data exclusivity
Australia	Five years of data exclusivity
Brazil	Five years of data exclusivity
Argentina	Without information

Source: Adapted from DataMonitor, 2013

Therefore, when referring to biosimilars, we need to address the nomenclature, in order to identify and differentiate them from their biological reference, in terms of their level of traceability and their potential cause of adverse effects that may occur. The nomenclature is incorporated into the WHO (World Health Organization), under a policy called International Nonproprietary Name (INN). Under this policy, an INN should be used to avoid confusion and to better designate a special status to a specific product. However, there are controversies regarding the allocation of INNs because, according to some people, biosimilars should be classified as 'biogenerics', while others try to make the distinction that a biosimilar is not and cannot be identical to the reference product and, therefore, it requires a single unique identifier. The European Union allows and encourages identification through distinguishing brands, while the United States Food and Drug Administration (FDA) does not have the legal authority to require the establishment of brand names for biosimilar. In Latin America (Brazil, for example) it is not required for prescription drugs to have a specific brand in the *'Sistema Unico de Saúde'* (Pineda et al. 2015), while in Australia there is a naming convention for biosimilars, called the Australian Biological Names (ABN).

The global biosimilars market was estimated in US $2.29 billion in 2015 and is expected to reach US $6.22 billion by 2020, with a sustained growth of 22.1% between 2015 and 2020 (marketsandmarkets.com 2015). However, this expected growth is almost exclusively for Europe and the United States. Nevertheless, there are other countries interested in the development of biosimilars in South America and Oceania, with the intention of joining this lucrative global market and, thus, access better conditions for investment by companies and society in the biopharmaceutical sector.

The research question for this article is related to the expectations and the evolution of countries like Argentina and Brazil, (the two countries with more experience in industrial pharma in south America), and Australia (the country with more experience in industrial pharma in Oceania), regarding the production, regulation and evolution of biosimilars, taking advantage of the worldwide reality of the expiration of intellectual property on biological drugs. The paper have the intention to inquire whether the countries studied, despite having a very important background in the pharma and biopharma industries, are able to develop a biosimilar production industry according to their skills and capabilities developed in a mature industry, but highly innovativeness as those based on chemistry and biology.

MATERIALS AND METHODS

To assess the current status of biosimilars in the countries of interest, an information gathering strategy was designed, based on online searches of secondary sources using PubMed, pharma and

biopharmaceuticals publications, such as government documents, key legislation documentation, official statistics, technical reports, review articles, and international scientific journals in English, Portuguese and Spanish. This method allowed establishing the framework, regulations and diagnosis of the development of biosimilars for each country. The countries chosen represent the most advanced biopharmaceutical markets in developing countries of South America (Argentina and Brazil) and Oceania (Australia).

Information search was also conducted through the brand names and active components of each currently marketed biosimilar. The websites of the WHO, FDA, EMEA (European Medicine Agency), the Brazilian Health Surveillance Agency (ANVISA), the National Drugs, Food and Medical Technology Administration (ANMAT), the Australian Therapeutic Goods Administration (TGA), the Australian Pharmaceutical Benefits Scheme (PBS), the Council of Australian Therapeutic Advisory Groups (CATAG) and overall regulation authorities were also reviewed to find legislative decisions, guidance and evaluation of approved biosimilars. Information was also obtained on the main companies developing biosimilars in the countries of interest, allowing us to have an appreciation of the history of the biopharmaceutical industry and the changes required for the development of these new drugs.

RESULTS AND DISCUSSION

Argentina

Pharmaceutical and biopharmaceutical industry in Argentina

According to the World Bank, Argentina's investment in R&D is extremely low in comparison to other more developed countries, with just 0.65% by 2011. But the perspective improves when it is compared with other countries in the region, such as Chile, which only has 0.42%. Niosi and Bas (2014) conducted a thorough research into the biopharmaceutical sector, which shows that, although there are some public funds to support the biopharmaceutical research industry, these are extremely insufficient to drive the development of new molecules in an environment where costs and risks are very high. These public funds are piloted through agencies, like the Argentinean Technological Fund (FONTAR) and the National Fund for the Development of Micro, Small and Medium Enterprises (FONAPyME). On the other hand, Argentina has a National Biotechnology Plan since 2007 but, in practice, it has never fulfilled the function for which it was created. However, a new government comes to assume the administration of the country (President Mauricio Macri), giving it a fresh air with expectations of investment in R&D and more sustained growth, making the effort, among other things, to integrate this country to the OECD.

The local pharmaceutical sector represents 5% of the foreign currency received by the country from exports, with a return of profits that is twice that obtained from commodities. According to Mincyt (2015), Argentina is one of the three markets in the world where companies with domestic capital produce more than 50% of medicines. As for the production of 'active compounds', Argentina has the competencies and skills needed to manufacture three types of active pharmaceutical ingredients (APIs) -biological, biotechnological and synthetic-, but clearly not to the extent required by the domestic industry to supply itself. Therefore, it is necessary, to import inputs to complete the production cycle. However, Argentina's recent internal policies from for imported inputs of any kind require companies to establish complex trading strategies, since they practically dictate that for every dollar imported another dollar must be exported, which makes any development scheme very difficult, especially if the conditions of local supply are not given or guaranteed. Another pitfall is that, in Argentina, innovative products are often easily copied, so the current patent law does not meet the international standards of protection of heavy investments made by this industry, which causes uncertainty for investors (Mysler 2012).

In 2014, Argentina spent US $6.1 billion on pharmaceutical products, which were developed in its 110 domestics plants and 17 foreign plants found in its territory. Until 2011, Argentina produced a total of 650 million doses of drugs per year, of which 63% were manufactured by laboratories with national capitals, while exports in the same period reached US $850 million. Of this total, US $55 million came from APIs and biopharmaceutical products. Some Argentinean laboratories that develop and produce biopharmaceuticals are: Instituto Malbrán, Elea, Instituto Massone, Beta, and Biosidus (Maito 2012). Considering that the biosimilars market in Latin America reached in 2013 an approximate US $123.1 million (Sashidhar 2014), Argentina, due to its historic leadership in the pharmaceutical and biopharmaceutical industry, is called to be

one of the key players in the production and sale of biosimilars in South America, even more so if we consider that monoclonal antibodies cost approximately US $200,000 per year it has an approximate cost of US $200 annually monoclonal antibodies.

Regulations for biosimilars in Argentina

The regulatory body for the approval of drugs in Argentina is the National Drugs, Food and Medical Technology Administration (ANMAT), which was created in August 1992 by decree 1490/92. This agency is responsible for ensuring the quality of medicines, food, medical products, diagnostic reagents, cosmetics, dietary supplements and house cleaning products, as well as for the authorization, registration, standardization and monitoring of products used in human medicine, food and cosmetics.

For the approval of biosimilars, ANMAT has created several laws between 2010 and 2011, including the following:

- ANMAT 7075/11: It establishes the conditions and requirements for the registration of drug products of biological origin.
- ANMAT 7729/11: It approves the requirements and guidelines for registration of medicinal preparations of biological origin, whose qualitative and quantitative composition, therapeutic indication and route of administration proposals have backgrounds in other medical specialties of biological origin, authorized by and registered with the ANMAT or other Health Regulatory Authority equivalent to the ANMAT (biological reference medicine or comparator), for which there is actual marketing evidence and sufficient characterization of its risk-benefit profile level.
- ANMAT 3397/12: It approves the specific requirements for the submission of applications for the authorization and registration of biological drugs and/or monoclonal antibodies obtained by recombinant DNA methods.

Before examining in further detail the requirements for the approval of a biosimilar in Argentina, it is necessary to provide clarification regarding the terminology used. ANMAT defines a biosimilar as a '*biological product*' and the biological product, from which the biosimilar is derived, as a '*comparator*'.

Together, these three laws regulate the requirements that the owner of biosimilars must meet with the health authority (ANMAT 2011, 2012):

- Physicochemical, pharmaceutical and biological information for demonstrating a similar behavior, in terms of identity, potency and purity of the product to be registered with that used as a comparator.
- Comparability analysis to determine similarity in quality, between the biosimilar and the comparator biological product.
- Identification of a marketing reference biological product authorized by ANMAT.
- Preclinical and clinical studies to measure the nature of the active molecule, information behavior '*in vivo*' or main active molecule, relationship between adverse effects and molecular characteristics and, finally, post-marketing information.
- Compared impurity profiles.
- Full report on the stability of the active molecule in at least three batches.

Biosimilars approved in Argentina

According to the website of mAbxience, and to numerous sources, marketing of a Rituximab biosimilar developed by this company was approved in Argentina in 2014. However, Laboratorio Elea is reported to have produced Novex, a rituximab biosimilar, approved in Argentina in October 2013 (http://www.gabionline.net/Biosimilars/General/Biosimilars-of-rituximab). The company affirm that currently has two development and production facilities, in León (Spain) and in Buenos Aires (Argentina). In December 2014, it launched its first biosimilar in the Argentinian market, Rituximab. (http://www.mabxience.com/mabxience-promotes-the-biosimilar-industry-in-biolatam-2015/). However, on the website of ANMAT, there is no evidence that this has happened and the information could not be corroborated by the regulatory body. Nevertheless, a systematic search for secondary information was carried

out in order to determine the existence of this product in the Argentinean market. The results of this search lead us to conclude that Argentina currently has no biosimilar approved for marketing.

There are some intentions, however, to develop biosimilars in Argentina. One of them is the new agreement between the Argentinean company mAbxience, and EPIRUS Biopharmaceuticals to develop and distribute its infliximab biosimilar. mAbxience will be responsible for regulatory filings and marketing of the biosimilar in select markets in Latin America, such as Argentina, Chile, Ecuador, Paraguay, Uruguay and Venezuela (Epirusbiopharma 2015).

Another interesting point is to analyze the developments in biosimilars being made in Argentina. To that end, current clinical studies were searched, revealing a clear impact of biosimilars in this country's landscape in the near future. These developments are:

- Study of RTXM83 Plus CHOP Chemotherapy Versus a Rituximab Plus CHOP Therapy in Patients With Non Hodgkin's Lymphoma
  Sponsor: mAbxience S.A
  Phase: III

- Bioequivalence Study Bevacizumab Biosimilar (BEVZ92) Versus Bevacizumab (AVASTIN®) in First-line Treatment mCRC Patients.
  Sponsor: mAbxience S.A
  Phase: I

- GP2013 in the Treatment of Patients With Previously Untreated, Advanced Stage Follicular Lymphoma
  Sponsor: Sandoz
  Phase: III

- A Randomized, Multicentre, Open Label, Evaluator Blinded Study to Evaluate Safety and Efficacy of Folitime® of Gemabiotech S.A., Versus Gonal-f ® of Merck Serono, in Patients With Infertility Submitted to ART
  Sponsor: Gema Biotech S.A.
  Phase: III

Brazil

Pharmaceutical and biopharmaceutical industry in Brazil

According to the World Bank, the investment in R&D in this country is the highest in South America, with a little boost, in the 2000 decade, to go from 0.85% to 1.21% of its GDP in 2011. Since the strong introduction of generic drugs in Brazil in 2001, the local pharmaceutical industry has undergone a large transformation. This has increased the general availability of many medicines, despite Big Pharma's threats to reduce their investments in Brazil's pharmaceutical sector. Even with a decrease in investments, the pharmaceutical industry in Brazil has reached a remarkable level, becoming in 2009 the 10th most important producer of drugs in the world. From 2007 to 2011, retail drug sales increased 82.2%, going from US $5.8 billion to US $10.6 billion during the same period (PWC, 2013). On the other hand, if we look at the biopharmaceutical sector, we can see that there has also been a remarkable breakthrough, mainly by greater investments and involvement of the government of Brazil for at least two decades. The country's public laboratories have a strong presence in the human health sector, with FIOCRUZ (The Oswaldo Cruz Foundation, established May 25, 1900, is a government foundation under the supervision of the Brazilian Ministry of Health) being the most important government laboratory in the health sector, with 15 institutes spread throughout the country. Many of them work in the biopharmaceutical field through its Bio-Manguinhos Institute of Technology in Immunobiology, a branch of FIOCRUZ and the largest producer of vaccines in Latin America (Niosi and Bas 2014).

Until 2008, the cooperation relations between public research institutions and private companies, resulted in the creation of more than 12 biopharmaceutical companies, seven of them with national capitals, including: Aché, Blausiegel, Cristália, Eufarma, Fiocruz, Prodotti and Silvestre Labs (Padilha, Kropf and Baetas

2009; Basso, Grossi and Pelegrini 2013). The Brazilian Government is actively encouraging the local production of follow-on biological products via its Productive Development Partnership (PDP) initiative. The Ministry of Health, which coordinates the PDP initiative, hopes to generate US $225 million in savings per year by stimulating innovation, technology transfer and development of Brazilian-based companies (Feijo et al. 2012). In 2013, the Ministry of Health announced 27 new partnerships between public and private laboratories resulting in the domestic production of 14 biologicals (Gabi Online 2015).

The needs of the population to access quality medicines forced the government of this country to increase the import of drugs through the Ministry of Health, prompting the government later on to invest in the development of domestic products, including biosimilars. In 2011 alone, the Brazilian government spent US $5 billion in importing medicines to satisfy the country's basic needs (Gadelha 2011). The market share for biotherapies in 2010 was only 2% of all prescription drugs, but more than 40% of these drugs were covered by the public budget of the Ministry of Health. In 2010, Brazil spent US $220 billion in health care. This included US $21.6 billion for pharmaceutical drugs and US $2.4 billion for biologicals (Castanheira, Barbano and Rech 2011).

Law number 9.279, dated 14 May 1996, aimed to respond to the requirements of the Agreement on Trade-Related Aspects of Intellectual Property Rights and introduced the term *pipeline patents* to refer to patents that had already been granted abroad and were now brought to Brazil (http://www.dannemann.com.br/dsbim/uploads/imgFCKUpload/file/Pipeline_patent.pdf). Some pharmaceutical products benefited from this law. One of them is Viracept®, a drug manufactured by Roche, which used this law to guarantee its patent on 7 March 1997 in Brazil, although the original deposit occurred in the United States in 1993. However, it is also common to observe pharmaceutical products that have not benefited by this law and, consequently, lost their patents. The most famous example is the case of Viagra® (Pfizer), which remained twelve years in the Brazilian market until its patent was revoked, in 2010, by the Brazilian Superior Court of Law. Nowadays, at a price 60% cheaper, this drug is produced as a generic medication by EMS (Basso, Grossi and Pelegrini 2013). Moreover, the joint ventures – Bionovis and Orygen – formed to develop biosimilar drugs under the PDP policy in Brazil have been important actors in the partnerships agreements for development biosimilar industry in this country.

Regulations for biosimilars in Brazil

The regulatory body for the approval of drugs in Brazil is the Health Surveillance Agency (ANVISA) created in 1999 by Law 9.782 of the Ministry of Health. This agency is responsible for issuing licenses for performances to different pharmaceutical companies, the registration of pharmaceutical products, and for establishing all regulations relating to clinical trials and pricing of medicines.

The first guide in Brazil, that developed some topics (general guidelines) on biological products, was published in 2002 (RDC 80/2002). From that date on, there have been several modifications and additions of new regulations to address specific pathways and to establish the monitoring and licensing of these products. All these modification, decanted into the creation of a new resolution in 2010, the RDC 55/2010 (Castanheira, Barbano and Rech 2011). This new guidance was based on global guidelines, such as those of the FDA, WHO and EMEA (though rather more simplified), setting the differences between 'new biological' products and 'biological products.' The latter definition includes the development of biosimilars. It is important to mention that, in order to properly interpret this legislation, a drug of biological origin, in which the biosimilar is developed according this guide, is called a 'biological comparator.' At the same time, two regulatory pathways are established for follow-on biological products: a comparative pathway and an individual development pathway. In the latter, a reduced dossier can be submitted. The applicant needs to present complete data regarding quality issues, but it does not have to be comparative.

It is important to mention that in Brazilian legislation, as in Argentina, a biosimilar is called a 'biological product' and the biological product is called a 'comparator,' from which the biosimilar is derived.

For the approval and marketing of a biological product (biosimilar) in Brazil, the holder of the product must present information in two separate areas: administrative and legal and technical specifications. According to the RCA 55/2010, the former include (ANVISA 2010):

- Registration of the application for approval of a biosimilar (FP1 and FP2).

- A certificate issued by ANVISA for the compliance with good manufacturing practices by the manufacturing laboratory.
- Original copy of the payment to the sanitary surveillance.
- Certificate of the economic capacity of the company and its operating license.
- Copy of the Certificate of Technical Responsibility, issued by the regional council of Brazilian pharmacies, which confirms that the applicant or manufacturer has a technical director in charge of quality.
- A history of the state of registration in all of the other countries (where appropriate).
- Copy of proof of registration in the country of origin of the biological product.
- Copy of the label model approved by the competent health authority of the country of origin, accompanied by a certified translation of the use instructions.
- Declaration that the biological product 'comparator' (original biological medicine) is the same that was used in the entire test for the development of the biosimilar.

The technical and analytical specifications required for the approval of a biosimilar in Brazil include (ANVISA 2010):

- Detailed description of the analytical techniques used to detect differences between the biological product (biosimilar) and comparator biological product.
- Comparative analysis of the biological molecules of the biosimilar and those of the comparator.
- Full studies of immunogenicity assays.
- A detailed report on the steps of comparability, to detect differences between the quality attributes of the biological product and the biological comparator.
- Report of comparative studies of stability, and the differences in purity.
- Evaluation of pollutants and their impact on the quality, safety and efficacy.
- Complete study of pharmacodynamics and pharmacokinetics, for each therapeutic indication.
- Study of cumulative toxicity.
- Clinical comparative studies to demonstrate safety and efficacy.

Biosimilars approved in Brazil

After being approved in Europe and the United Kingdom, *Remsima* of Celltrion became the first biosimilar approved in the Brazilian market by ANVISA (RDC 55/2010), based on the route of comparability, which showed sufficient evidence of similarity between the biosimilar and biological reference product, *Remicade.* This product will be marketed in Brazil by the firm Hospira. The second biosimilar approved in Brazil is *Fiprima,* manufactured by Eurofarma Labóratorios (Table 4).

Table 4: Biosimilar Approved in Brazil

Product Name	Active Substance	Therapeutic Area	Authorization Date	Manufacturer Company Name
Remsima	Inflimax	Rheumatoid arthritis, Ankylosing spondylitis, Psoriasis, Psoriatic arthritis, Crohn's disease in adults and children, Fistulizing Crohn's disease (advanced), Ulcerative colitis and Rectocolitis	April 2015	Celltrion/Hospira Amarey Nova (Latin American Partner)
Fiprima	Filgastrin	Neutropenia	October 2015	Eurofarma Laboratórios

Source: ANVISA 2015

Despite having two biosimilar approved for marketing, there are several local developments being made in the field of biosimilars, which will reach the market in the coming years. These lines of research and development stages are detailed below:

- Bioequivalence Study Bevacizumab Biosimilar (BEVZ92) Versus Bevacizumab (AVASTIN®) in First-line Treatment mCRC Patients.

  Sponsor: mAbxience S.A.

- Study of RTXM83 Plus CHOP Chemotherapy Versus a Rituximab Plus CHOP Therapy in Patients With Non Hodgkin's Lymphoma

  Sponsor: mAbxience S.A.

- GP2013 in the Treatment of Patients With Previously Untreated, Advanced Stage Follicular Lymphoma

  Sponsor: Sandoz

- Safety and Efficacy Study of BCD-021 Compared to Lucentis® in Patients With Neovascular Wet Age-related Macular Degeneration

  Sponsor: Biocad

Another aspect that shows the future development of biosimilars is the recent agreement signed between Libbs Pharmaceutical (Brazilian company) and mAbxience biotechnology company (with a plant in Argentina), of the Insud Group. This agreement includes an investment of US $100 million by Libbs for the construction of a new plant for biopharmaceutical development. Meanwhile, mAbxience will be in charge of biotechnology transfer, particularly for second generation (monoclonal antibodies). It is estimated that this new plant, called Libbs Biotec, will be completed in 2016 and will be responsible for developing the productive process of seven biosimilars, including purification, culturing, filling and packaging of biosimilars as well as all quality control operations. Among the therapeutic indications, it is expected to cover leukemia, non-Hodgkin lymphoma, colorectal cancer, and autoimmune diseases such as rheumatoid arthritis and juvenile idiopathic arthritis.

Australia

Pharmaceutical and biopharmaceutical industry in Australia

The referendum of 1946 gave rise in 1947 to the new Pharmaceutical Law, which aimed to provide free health services to the Australian population. Some of the benefits under the Pharmaceutical Benefits Scheme (PBS) began to be available since mid-1948. However, the PBS has undergone evolutionary changes as a result of the National Health Act passed in 1959, which introduced a wider range of medications (Medicine Australia, 2008).

In the last 20 years, Australian governments have implemented three programs to promote the development of the Australian pharmaceutical industry. These are the:

1- Factor (f) scheme under the Development Program of the Pharmaceutical Industry,
2- Investment Program in the Pharmaceutical Industry,
3- Pharmacy Partnership Program (P3).

The pharmaceutical industry in Australia is dominated by multinational pharmaceutical companies with varying degrees of involvement in R&D, manufacturing and distribution of drugs, while most of the local pharmaceuticals dedicated to the manufacture of generic medications.

The performance of the industry today is partly due to significant growth during the 1980s and 1990s, which coincided with the Factor (f) plan of the Federal Government. At that time, the industry experienced significant growth in investment levels, exports and spending in R&D, all of which were supported by the Factor (f) scheme (https://medicinesaustralia.com.au/files/2009/12/Australian-Pharmaceutical-Industry-Report-2007.pdf).

Actually, Australia is a relatively small and new pharmaceutical market (ranking 15th in the world) with a good reputation for producing a small volume of high-quality biopharmaceutical products, which leads it to simultaneously import pharmaceutical technology. In this scenario, most companies are multinationals, and only four of them develop 70% of the drugs. (Lim 2014; Harris, Nicol and Gruen 2013). A 2013 report reveals that the Australian government reimburses drug prices to pharmaceuticals companies. Furthermore, it is fair to assume that, on average, medicines in Australia are 19% cheaper than in the rest of the OECD (OECD 2013).

Regulations for biosimilars in Australia

The regulatory body for therapeutic goods in Australia is the Therapeutic Goods Administration (TGA), a division of the Australian Government Department of Health and Ageing that is responsible for regulating therapeutic goods, including medicines, medical devices, blood and blood products, including biosimilars. In July 2013, this agency prepared a guide called 'Evaluation of biosimilar' as a first approach to biosimilars, with the purpose of identifying the necessary data to support applications for the registration of biosimilars and to clarify the scientific and regulatory principles used by the TGA to evaluate those applications.

The TGA defines a biosimilar as '*a version of an already registered biological medicine that has a demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies.'* Although referred to as biosimilars in Australia, the term *'similar biological medicinal products'* (SBMPs) is derived from the European Union guidelines adopted by the TGA (Australian Government 2013).

In order to obtain approval for a biosimilar, it is critical to demonstrate the degree of similarity between the biosimilar and the biological reference medicine. To accomplish this, the holder of the drug must submit the following information:

- Pre-Submission Planning Form (PPF)
- Administrative information
- Risk management plan guideline
- Chemistry, manufacturing and quality control data
- Preclinical data
- Clinical data
- Comparability study according to ICH Q5E (Comparability of Biotechnological/Biological Products Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process).

  The analytical techniques required to demonstrate the degree of similarity include:
- Physicochemical properties: **Primary structure:** Edman degradation; peptide mapping with Liquid Chromatography with MS detection (LC-MS); C-terminal sequencing and amino acid analysis. **Secondary structure:** Peptide mapping with reduced/non-reduced hydrolysis and Edman degradation or MS analysis to show disulphide bonding and other structural forms and near ultraviolet (UV) Circular Dichroism CD. **Tertiary and Quaternary structure:** far Ultraviolet (UV); Circular Dichroism (CD); NMR; FTIR and X-Ray crystallography.
- Biological activity: ***In vivo* activity** (measuring therapeutic effect in animals); *In* ***vitro* activity** (measuring therapeutic effect in cells): cell proliferation or inhibition of proliferation; cell senescence; measurable changes in cell size or content (e.g. mRNA). Enzyme assays, Receptor-binding assays, Promotion or inhibition of coagulation by chromogenic or turbidometric techniques.
- Content, purity and impurity profile: **Protein content:** Protein assay (e.g. Keldahl, Lowry, Bradford); Absorbance at 280 or 230 nm; High Performance Liquid Chromatography (HPLC); Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE). **Purity:** High Performance Liquid Chromatography (HPLC); Reverse Phase High Performance Liquid Chromatography; Size Exclusion High Performance Liquid Chromatography (same as GF-HPLC); Ion Exchange High Performance Liquid Chromatography HPLC (IE) or Hydrophobic Interaction HPLC (HI); Capillary Electrophoresis (CE) and Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE).
- Immunochemical (if applicable e.g. monoclonal antibodies): **Binding specificity:** ELISA; Surface Plasmon Resonance (SPR); histochemical staining, immunoblotting and Western blotting. **Binding avidity:** SPR; binding assays and competitive ELISA.

When the TGA receives the information detailed above and approves the pre-submission planning form (PPF), it meets to work together with three advisory committees under the Ministry of Health, in order to review and issue a document with the final decision approving or rejecting the biosimilar. The advisory committees are:

- The Advisory Committee on Prescription Medicines (ACPM)
- The Pharmaceutical Subcommittee (PSC)
- The Advisory Committee on the Safety of Medicines (ACSOM)

An interesting point of this guide is that once the TAG assesses all the information, and finds that there is insufficient evidence or results that show a high degree of similarity between the biosimilar and biological reference product, the holder of the drug can withdraw the request for a biosimilar and submit it for evaluation as an original biological medicine. If the holder chooses this path, it is necessary to provide additional information, in accordance to the medication guide for biological products.

Australian Biological Names (ABN)

According to the Therapeutic Goods Regulations of 1990, all medicines are required to use Australian Approved Names (AAN), in their product information (PI) and in consumer medicine information (CMI). In the case of a biosimilar, this will be drawn from the Australian Biological Names (ABN).

As a biosimilar is not identical to the reference biological product, and small differences between the biosimilar may lead to significant differences in the clinical behavior, it is necessary to have an additional classification that allows distinguishing and clearly identifying the biosimilar from its reference product. Because of this, the TGA indicates that the ABN for a biosimilar should be composed of:

- The reference product ABN, thus identifying the reference product with which the biosimilar has demonstrable comparability.
- A biosimilar identifier, consisting of: the prefix *sim(a)* and a three letter code issued by the WHO International Non-proprietary Name (INN) Committee, according to its draft policy.

The TGA announced plans to revise its proposed biosimilar naming conventions following a July 2014 draft policy from the World Health Organization (WHO), which stated that biological qualifiers will now consist of four letters and will be applied prospectively and retrospectively to all biological products given international non-proprietary names (INNs). Following the WHO's four-letter biological qualifier convention announcement, the TGA will review its naming policy.

Biosimilars approved in Australia

Although the guide for biosimilars was published in 2013, the first biosimilar was approved by the regulatory body in 2010. Since then (September 2015), the TGA has approved ten biosimilars to be marketed in Australia, the last one in August 2015 (Table 5).

Table 5: TGA Approved Biosimilar in Australia

Product Name	Therapeutic Area	Authorization Data	Manufacturer/ Company Name
Aczicrit (epoetin lambda)	Anaemia Cancer Chronic kidney failure	27 Jan 2010	Sandoz
Grandicrit (epoetin lambda)	Anaemia Cancer Chronic kidney failure	27 Jan 2010	Sandoz
Novicrit (epoetin lambda)	Anaemia Cancer Chronic kidney failure	27 Jan 2010	Novartis Pharmaceuticals Australia

Nivestim (filgrastim)	Cancer Haematopoietic stem cell transplantation Neutropenia	16 Sep 2010	Hospira
Omnitrope (somatropin)	Growth disturbance due to chronic renal insufficiency Pituitary dwarfism Turner syndrome	29 Sep 2010	Sandoz
SciTropin A (somatropin)	Growth disturbance due to chronic renal insufficiency Pituitary dwarfism Turner syndrome	29 Sep 2010	SciGen Australia
Tavagrastim (filgrastim)	Cancer Haematopoietic stem cell transplantation Neutropenia	29 Aug 2011	Aspen Pharmacare Australia
Zarzio (filgrastim)	Cancer Haematopoietic stem cell transplantation Neutropenia	7 May 2013	Sandoz
Basaglar (insulin glargine)	Diabetes	21 Nov 2014	Eli Lilly Australia
Inflectra (infliximab)	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	19 Aug 2015	Hospira (Pharmbio)

Source: ARTG. www.tga.gov.au/searching-australian-register-therapeutic-goods-artg.

Under a recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC), doctors and pharmacists will be allowed to give patients the option of biosimilar medicines, just as they can now offer generic versions of chemical treatments. The Australian government estimates that consumers could save approximately between US $560 million and US $880 million over the next five years if the biosimilar drugs are developed and supported. An important issue to consider is that of the ten drugs subsidized by the Pharmaceutical Benefits Scheme (PBS), five are of biological origin, with consequent savings for patients (https://extranet.ama.com.au/sites/default/files/MediaClips/MediaClips-290515.pdf). Table 5 showed that of the ten biosimilars approved for marketing in Australia, two of them are made by local laboratories and one by a foreign laboratory but with locally-based R&D. This is a clear sign of interest by the authorities and the business sector to develop biosimilars. This point is further strengthened when searching for projects in early stages of development. The following clinical studies are being developed in Australia:

- Temozolomide and Irinotecan Hydrochloride With or Without Bevacizumab in Treating Young Patients with Recurrent or Refractory Medulloblastoma or CNS Primitive Neuroectodermal Tumors.

  Sponsor: National Cancer Institute (NCI)
  Phase: II

- Vinorelbine Tartrate and Cyclophosphamide in Combination with Bevacizumab or Temsirolimus in Treating Patients With Recurrent or Refractory Rhabdomyosarcoma.

  Sponsor: National Cancer Institute (NCI)
  Phase: II

- GP2013 in the Treatment of Patients with Previously Untreated, Advanced Stage Follicular Lymphoma.

Sponsor: Sandoz
Phase: III

- Bevacizumab With or Without TRC105 in Treating Patients with Metastatic Kidney Cancer.

Sponsor: National Cancer Institute (NCI)
Phase: II

Study start date: November 2012

CONCLUSION

Biosimilars should be a very powerful means of encouraging emerging economies where developing a new drug is extremely costly and where the necessary conditions for that to happen are not always present (intellectual property, venture capital, regulations). Manufacturing biosimilars drugs is a great opportunity for biopharmaceutical laboratories and CROs that can be more profitable in the medium term with the added benefit in the treatment of patients.

Both South American countries, as well as the country in Oceania, have backgrounds in the pharmaceutical and biopharmaceutical industry, which allows them to have the necessary tools, experience and infrastructure to be successful in the development and manufacturing of biosimilars. However, the public institutional aspect often opens up a gap in the expectations and needs of companies and patients. On the one hand, there are not enough public and private investment funds to conduct the necessary clinical trials and, on the other hand, the protection of intellectual property shows no signs of maturity comparable to international standards.

Australia has a vision on biosimilars from a public angle, with the opportunity to encourage competition in the pharmaceutical market. Meanwhile, South American countries see them as an opportunity for pharmaceutical companies to become more profitable by reducing costs in developing a biosimilar, compared to an original biological molecule and, therefore, lowering prices for patients, thus increasing the profitability and competitiveness of enterprises.

Despite the difficulties seen in both regions, future development of biosimilars can be expected once there are clearer nomenclatures, standard regulations and rules for governments, companies and patients.

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