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BIOSIMILARS, ALTERNATIVE WAY FOR EXPIRATION OF PATENTS IN THE BIO-PHARMACEUTICAL INDUSTRY: REVIEW OF MANY COUNTRIES IN RELATIONSHIP TO SYSTEMATIC DEVELOPMENT, REGULATIONS AND MOLECULES APPROVED

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Abstract

The development of biological products has experienced continuous growth over the past thirty years. 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 reviews the literature on biosimilar drugs and covers their therapeutic status, approved biosimilars, and regulatory guidelines in Australia, Brazil, Malaysia, Japan, Singapore and South Korea. The literature suggests that biosimilars are comparable but not identical to the reference product. They are not a generic version of an innovative product and do not ensure therapeutic equivalence. Each country has its own regulatory guideline for biosimilar drugs.

Keywords: Biosimilar; bio-pharmaceutical; intellectual property; regulatory guidelines.

Introduction

For over a decade, the biopharmaceutical industry 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 R&D 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 and balanced access to high-quality drugs [1][2][3][4][5]. In this context, some sources estimate that expirations are responsible for major profitability losses that could reach approximately US $70 billion between 2010-2024 [6][7].This condition has become worse due to the massive loss of exclusivity of patents and is further deteriorated as time passes. In 2012, 7% of worldwide sales (US $53 billion) were at risk as a result of the free entry of generic drugs, which compete directly with the original brands, forcing them to lower their prices or, even worse, to stop producing them.In the period 2009-2014, the pharmaceutical companies of the world losses due to the massive expiration of patents US $120 billion [8].

This situation has motivated large multinational firms and some of their partner contract research organizations) 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 "new life".

More than 55% are products of biological and not chemical origin, opening up a great opportunity for new players in the development of biosimilars, with lower production costs and shorter development time than an original medicine with five to nine years of clinical trials.They design "biosimilars"drugsat a much lower cost than the original molecules, between US $10 million and US $250 million, because of not having to follow the protocols of an unprecedented biological molecule. This results in more affordable drugs for a variety of new therapies [9].

The term "biosimilar" can be 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" [6]. However, a biosimilar product may not differ significantly in terms of the degree of purity, potency, and safety of the product being administered to the patient[10].

The Public Health Service Act from United-States (PHS Act), define biosimilars, under section 351(i)(2), "biosimilar or bio-similarity means that the biological product is highly similar to the reference product not withstanding 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." [11].

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 1), which are composed of chemically-based structures, have a smaller molecular size and single complexity, with a known chemical synthesis process.

Table 1: 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 [9]

The United States, Europe, and Japan are the regions that invest the most in R&D of biological products on the world. Therefore, they are expected to become the most attractive markets for the development of biosimilars. Sackman and Kuchenreuther[12]estimate that the global biosimilars market earned revenues of about US $1.3 billion in 2013.The main biological products that have attracted the development of biosimilars are Avastin, Enbrel, Herceptin, Humira, and Rituxan, which together generate more than US $50 billion annually. In Europe, where 29 biosimilars are authorized and competing with the biological product, they are sold at a price that is 30%lower than that of the original drug.

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. Table 2 looking the data on exclusivity following approval of biosimilars in many countries.

Table 2: Data on Exclusivity Following Approval of Biosimilars.

Country	Data on exclusivity period
Japan	Eight years of data exclusivity
Canada	Eight years of data exclusivity
United States	Four years of data exclusivity/eight years of market exclusivity
Europe	Ten years of data exclusivity
South Korea	Eight years of data exclusivity
Singapore	Five years of data exclusivity
Malaysia	Five years of data exclusivity
Australia	Five years of data exclusivity

Source: [13]

It is also noted that, in the case of the United States, there is a distinction between exclusive data and exclusivity in marketing, ensuring a more extensive commercial level to the manufacturer's laboratory biosimilar protection, regardless of any other research and development laboratories conduct to create the original biosimilar. A particular feature of biosimilar approval in the United States is that there are two levels of approval: the biosimilar drug and the biosimilar "Interchangeable Drug" [7].

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 Non-proprietary 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"[14], 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[15]. 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 East Asia, 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 Australia, Brazil, Malaysia, Japan, Singapore and South Korea, 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 pharm and bio-pharm industries, even without being the vigour of Europe or the United States, 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. In this context, this paper presents an overview, evolution, and regulations assessment, while it also discusses the beginnings and development of biosimilars in many countries around the world.

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, biopharmaceuticals and biosimilars publications, such as government documents, key legislation documentation, official statistics, technical reports, review articles, and international scientific journals in Japanese, Korean, Malaysian, English, Portuguese and Spanish. The keywords used in the search to process information include biosimilars, development of biosimilars, biopharmaceutical companies, intellectual property, non-patent biologics, regulatory biosimilars, follow-on biologics, generic, molecule, biomedicine, data-marketing exclusivity, evolution and therapeutic. Information search was also conducted through the brand names

and active components of each currently marketed biosimilar. A search of the websites of World Health Organization (WHO), the Food and Drug Administration of the United States (FDA), the European Medicines Agency (EMA), the Ministry of Health, Labour and Welfare (MHLW) of Japan, the Ministry of Food and Drug Safety (MFDS) of South Korea, and the National Pharmaceutical Control Bureau (NPCB) of Malaysia, 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 regulatory authorities also was conducted for legislative decisions, guidance, and evaluation for approved biosimilars. This methodological review led us to obtain results that are analyzed below by each country studied.

Results and Discussion

Australia

Pharmaceutical and Biopharmaceutical Industry

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 [16].

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 [17]. 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[18][19]. 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 [20].

Regulatory Guidelines for Biosimilars

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 and 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. 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).

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.

Biosimilars Approved

Although the guide for biosimilars was published in 2013, the first biosimilar was approved by the regulatory body in 2010. Actually, the TGA has approved thirteen biosimilars to be marketed in Australia (table 3).

Table 3: TGA Biosimilars Approved.

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Aczicrit	epoetin lambda	Anaemia Cancer Chronic kidney failure	Jan 2010	Sandoz
Basaglar	insulin glargine	Diabetes	Nov 2014	Eli Lilly Australia
Bemfola	follitropin alfa	Infertility treatment	Nov 2015	Finox Biotech
Brenzys	etanercept	Ankylosing spondylitis Psoriatic arthritis Psoriasis	Jul 2016	Samsung Bioepis
Grandicrit	epoetin lambda	Anaemia Cancer Chronic kidney failure	Jan 2010	Sandoz
Inflectra	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis	Aug 2015	Hospira (Pharmbio)
Nivestim	filgrastim	Cancer Haematopoietic stem cell transplantation	Sep 2010	Hospira
Novicrit	epoetin lambda	Anaemia Cancer Chronic kidney failure	Jan 2010	Novartis Pharmaceuticals Australia
Omnitrope	somatropin	Growth disturbance due to chronic renal insufficiency Pituitary dwarfism Turner syndrome	Sep 2010	Sandoz
Renflexis	infliximab	Ankylosing spondylitis Crohn's disease Rheumatoid arthritis Psoriasis	Nov 2016	Samsung Bioepis
SciTropin A	somatropin	Growth disturbance due to chronic renal insufficiency Pituitary dwarfism Turner syndrome	Sep 2010	SciGen Australia
Tevagrastim	filgrastim	Cancer Haematopoietic stem cell transplantation	Aug 2011	Aspen Pharmacare Australia
Zarzio	filgrastim	Cancer Haematopoietic stem cell transplantation	May 2013	Sandoz

Source: [21][22]

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 [23]. Table 3 showed that some of the biosimilars approved for marketing in Australia until 2017 are made by local laboratories. This is a clear sign of interest by the authorities and the business sector to develop biosimilars.

Brazil

Pharmaceutical and Biopharmaceutical Industry

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 [24]. 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 [25].

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 [26][27]. 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 [28].

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 [29]. 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 [30].

Regulatory Guidelines for Biosimilars

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 [30]. This new guidance was based on global guidelines, such as those of the FDA, WHO and EMEA, setting the differences between "new biological" products and "biological products" called for Brazilian legislation a "comparator". 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. The applicant needs to present complete data regarding quality issues, but it does not have to be comparative.

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 [31]:

- Registration of the application for approval of a biosimilar (FP1 and FP2).
- 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.
- A history of the state of registration in all of the other countries.
- 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.
- 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 [31]:

- Detailed description of the analytical techniques.
- Comparative analysis of the biological molecules of the biosimilar and those of the comparator.
- Full studies of immunogenicity assays.
- A report of quality attributes of the biological product and the biological comparator.
- Report of comparative studies of stability, and the differences in purity.
- Evaluation of safety and efficacy.
- Pharmacodynamics and pharmacokinetics study.
- Study of cumulative toxicity.
- Clinical comparative studies to demonstrate safety and efficacy.

Biosimilars Approved

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 (2015), manufactured by EurofarmaLabóratorios.

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.

Japan

Pharmaceutical and Biopharmaceutical Industries

The Japanese pharmaceutical market is the second most important one in the world after the United States, with sales of over US $143 billion in 2014 [32], representing 14% of the global pharmaceutical market. Despite this, the sector has been forced to reduce production costs and increase its speed to market products in order to continue obtaining profitability after the Asian economic crisis. This situation caused an expected reduction in investment rates in R&D by the private sector and a decline in the growth rate of the country. Therefore, the government has had to develop strategies to revitalize the industrial sector. This has been achieved through the creation of tax incentives for companies that make further innovations in their products (e.g., biosimilars) above that of generic products or others showing low level of innovation [33]. The biopharmaceutical market in Japan is of great importance to the world. However, most of the products sold there are of foreign origin but manufactured locally under license.

Regulatory Guidelines for Biosimilars

The Ministry of Health, Labour and Welfare (MHLW) is the regulatory body in Japan, responsible for the scientific evaluation of medicines developed by pharmaceutical companies to be used in Japan and for making decisions on approval of drugs, including biologicals.

It consists of three main areas [34]:

(i) Standards for Quality Assurance of Drugs, Quasi drugs, Cosmetics, and Medical Devices.

(ii) Regulations for Buildings and Facilities for Pharmacies and So On.

(iii) Standards for Manufacturing Control and Quality Control of Drugs and Quasi drugs.

There is also the Pharmaceuticals and Medical Devices Agency (PMDA), working together with the MHLW. The PMDA conducts scientific reviews of marketing authorization applications of pharmaceuticals and medical devices and monitoring of their post marketing safety. The PMDA's Office of Biologicals provides consultations concerning clinical trials of new drugs and medical devices and handles biotechnology medicines, including biosimilars [35]. These guidelines are based on the existing processes in Europe and were published by the MHLW in March 2009. This guide also exposes basicrequirements necessary to grant the approval of a new biosimilar product to be marketed in Japan. The following requirements must be met [36]:

(i) Manufacturing process for the biosimilar.

(ii) Should be fully characterized, using analytical methods.

(iii) The dosage form and route of administration of the biosimilar product should be the same as those of the reference product.

(iv) Long-term, real-time, real-condition stability studies should followthe ICHQ5C guideline.

(v) A comparison of quality attributes between the biosimilar and the reference product.

(vi) Nonclinical studies (including pharmacokinetic, pharmacological, and toxicity studies).

(vii) Clinical studies are required whenever the data from quality characterization and nonclinical studies is insufficient to demonstrate comparability with the reference product.

In order to obtain the marketing authorization, it is necessary to have had people of Japanese origin included in one of the efficacy and pharmacokinetic studies.

If clinical data do not include any people of Japanese ethnicity, it is mandatory to show the similarity between a biosimilar candidate and the reference product according to the International Conference on Harmonization Guidelines [37].

The purpose of this guidance (E5R1) is to facilitate the registration of medicines among ICH regions (European Union, Japan, and the United States) by recommending a framework for evaluating the impact of ethnic factors, upon a medicine effect, its efficacy and safety at a particular dosage, and dose regimen. It provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies and supplying medicines expeditiously to patients for their benefit [38].

Biosimilars Approved in Japan.

Since the guide for the development of biosimilars in Japan in 2009 was approved, the sale of ninebiosimilars as shown in table4. The cooperation or strategic alliances with different laboratories, known as outsourcing firms, for the development and further marketing of a product. Such is the case of the already approved biosimilar “Filgrastim BS3” by Sandoz Laboratory, which developed this biosimilar with the collaboration of Sawai Pharmaceutical Co. It is also the case of Nippon Kayaku, which began developing infliximab BS in November 2010, following an agreement with the Celltrion Group for the joint development and marketing of this product in Japan [39].

Table 4: PMDA approved biosimilars

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer /Company name
Epoetin alfa BS	epoetin alfa	Anaemia Renal anaemia	Jan 2010	JCR Pharmaceuticals
Filgrastim BS 1	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	Nov 2012	Fuji Pharma/Mochida Pharmaceutical
Filgrastim BS 3	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	Mar 2014	Sandoz
Filgrastim BS 2	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	Feb 2013	Teva Pharma Japan/Nippon Kayaku
Infliximab BS 1 (Remsima)	infliximab	Crohn's disease Rheumatoid arthritis Ulcerative colitis	Jul 2014	Celltrion/Nippon Kayaku
Insulin glargine BS 1	insulin glargine	Diabetes	Dec 2014	Eli Lilly/Boehringer Ingelheim
Insulin glargine BS 2	insulin glargine	Diabetes	Mar 2016	Biocon/Fujifilm Pharma
Nesp	darbepoetin alfa	Anemia Cancer Chronic kidney failure	Sep 2013	Kyowa Hakko Kirin
Somatropin BS	somatropin	Growth hormone deficiency Turner syndrome	Jun 2009	Sandoz

Source :[39].

Malaysia

Pharmaceutical and Biopharmaceutical Industry

The demand for quality health has been considered crucial by the Malaysian government and its population, and living conditions in this country are improving on a yearly basis. Malaysia currently invests 7.25% of the Gross Domestic Product (GDP) of the country in health. The pharmaceutical industry is one of the sectors that the Malaysian government has prioritized for its promotion and development. An update by the Malaysian Investment Development Authority (MIDA) [40] shows that pharmaceutical companies are mainly small and medium-sized firms engaged in the production of generic drugs, traditional medicines, and herbal supplements, as well as in contract manufacturing for foreign multinational corporations (MNCs). Biosimilars are expected to have a comparable, if not greater, impact on the biopharmaceutical industry than that of generics. Malaysia offers a more competitive cost option to investors due to its

enabling environment. A large number of first-generation biopharmaceutical products are nearing maturity and major biopharmaceutical companies are likely to move these out to countries that offer a good value preposition, like Malaysia [40].

Currently, in Malaysia, local and foreign players are already engaged in activities like the production of active pharmaceutical ingredients (APIs) and applications for good manufacturing practice (cGMP) compliant services at the United States Food and Drug Administration (FDA) and Europe, the Middle East and Africa (EMEA) focusing on monoclonal antibodies and recombinant proteins. Malaysia has also developed specialized parks to cater to the needs of specific industries, which are technology-intensive and research-intensive. Examples of these parks are the Technology Park Malaysia in Bukit Jalil, Kuala Lumpur, and the Kulim Hi-Tech Park in the northern state of Kedah.

Malaysia has been concerned with developing a powerful system of intellectual property protection, in accordance with international standards, akin to protect inventions and foreign and local investors.

Regulatory Guidelines for Biosimilars

The Ministry of Health of Malaysia, through the National Pharmaceutical Control Bureau (NPCB), is the national authority that assures the quality of medicines in the country. The NPCB is responsible for ensuring that all pharmaceutical and biopharmaceutical products developed and commercialized in the country meet the standards of quality, safety, and efficacy as required by law [41].

Unlike other countries that have been studied in this work, there is no elaboration of an exclusive guideline for biosimilars, only an addition to the law previously created for biological drugs (Drug Registration Guidance Document [DRGD]), as a subcategory of biological products. This implies that in order to obtain approval for a biosimilar it must meet all of the quality, safety, and efficiency requirements for any product of biological origin. No distinction is made between a new biological product and the one that has been marketed for many years and is now based in the development of a biosimilar.

The requirements for the registration of biologics/biopharmaceuticals are guided by the ASEAN Common Technical Dossier (ACTD) and the Drug Registration Guidance Document (DRGD).The requirements are

(i) administrative information;

(ii) product quality data (clinical analysis);

(iii) product safety data (nonclinical analysis);

(iv) clinical data, demonstrating clinical efficacy and capacity to meet therapeutic claims, through clinical studies.

The process for registering a biosimilar begins with an online submission to the NPCB by the legal representative of the new product. With this, the office generates an appointment for the representative to present all of the information necessary to meet the approval requirements set forth, such as analytical methods and quality validation documentation. With this information, the NPCB consults with experts, usually external, such as academics, clinical advisors, and health and biological experts. Together, they produce an evaluation report that is sent to the Drug Control Authority (DCA) of NPCB, which defines whether or not the biological product can be approved to be marketed in Malaysia [41].

Biosimilars Approved

Since the biosimilar guideline was published in July 2008, in Malaysia, five biosimilars have been approved for marketing. The latest was Insugen, in January 2014, as table 5 shows.

Table 5: DCA Approved Biosimilars in Malaysia.

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/company name
SciTropin	Somatropin	Growth disturbance in children and growth hormone deficiency in adults	Aug. 2010	Sandoz
Binocrit	Epoetin alfa	Renal anemia, cancer, and predonation preparation for autologous and allogeneic blood transfusion	Mar. 2011	Sandoz
Zarzio	Filgrastim	Cancer, HSCT, and chronic neutropenia	Mar. 2012	Sandoz
Nivestim	Filgrastim	Cancer, HSCT, and chronic neutropenia	Aug. 2013	Hospira
Insugen	Recombinant human insulin	Diabetes mellitus	Jan. 2014	Biocon

Source: [42]

Singapore

Pharmaceutical and Biopharmaceutical Industry

Singapore, through its 1975 Act, provided the country with a regulatory framework for the control of the importation, manufacture and distribution of medicinal products in order to provide protection to the public health of the country's inhabitants. This code was called, “Code of Marketing Practices” through the Singapore Association of Pharmaceutical Industry or SAPI[43]. The Code goes hand in hand with the revised Code of Marketing Practices of the International Federation of Pharmaceutical Manufacturers Association (IFPMA) in 2006, is administered by the Marketing Practices Committee. Later, from the 2000s, he entered the biomedical sciences, becoming, in this way, the second largest

manufacturing cluster in the country[44]. In this cluster, we find seven of the world's top ten pharmacies, which have invested in Singapore, while eight of the top ten have settled in this country with the intention of launching their expansion to the rest of Asia. One of the reasons for this is that Singapore's institutional capacities are recognized globally as one of the freest and most transparent economies in the world.

Singapore is a multi-ethnic country that has an ecosystem of pharmaceutical and biotechnology companies integrated with a very interesting platform to develop capabilities that allow it to enter the biosimilars industry. Singapore also has excellent access to multidisciplinary R&D capabilities and competences, which are concentrated in the same geographic sector, where more than 50 leading companies in the biopharmaceutical sector of the world (GlaxoSmithKline, Novartis, Takeda) coexist with a sustained growth of approximately one 30% per year since 2011. This country has emphasized the protection of intellectual property, which gives companies enough peace of mind that investments will be well protected, which also allows them to establish strategies of alliances with institutions National and foreign, public hospitals to develop new medicines in the biosimilars sector. Singapore's high-quality basic and clinical research makes it a leading partner in Asia for R&D collaborations. Between 2000 and 2010, Singapore's biomedical manufacturing output had quadrupled from US$4 to US$16.3 billion and the industry has grown to account for about 5 per cent of the national GDP [45].

More than US$1.05 billion is spent on biomedical R&D annually. After a decade of its foray into the biomedical sciences sector, employment in biomedical R&D has more than doubled from 2,200 to over 5,000 between year 2000 and 2010. Singapore manufactured over US$19 billion worth of medicines and medical devices for global markets in 2011. Singapore has committed US$11.13 billion in continued support of research, innovation and enterprise activities between 2011 and 2015. Out of the US$11.13 billion, US$2.6 billion is dedicated to enhancing existing biomedical R&D infrastructure, integrating multi-disciplinary research and translating basic science into tangible outcomes [46].

Singapore have a world-class clinical excellence and with Government Initiatives has a core of clinician scientists has been built up in Singapore through initiatives such as the Singapore Translational Research (STaR).

Regulatory Guidelines for Biosimilars

Singapore seeks to provide a pro-innovation environment that facilitates the development of innovative therapies, while ensuring global standards of safety, quality and efficacy. This is bolstered by the active involvement of the Singapore

Health Sciences Authority or HAS[44]in defining new regulatory frameworks and pursuing new areas of research in regulatory sciences over the years. In 2009, the HSA Academy was set up to foster greater synergies across the agency's unique conglomeration of diverse scientific and biomedical capabilities. More importantly, it would also serve as an enabler for growing thought leadership in Singapore. In addition to organising scientific meetings and symposia, the academy also seeks to facilitate discussions on cutting edge issues in the forensic and analytical sciences, regulatory science and transfusion medicine. Moreover the HSA, as accredited reference agency, that certifies the tests in laboratory[47].

Biosimilar Approved

Singapore currently has only one approved biosimilar (Infliximab) sinceMarch 2016.

South Korea

Pharmaceutical and Biopharmaceutical Industry

South Korea has been considered as one of the "tiger economies" as a result of the growth experienced by its exports during the second half of the 20th century. There is social health insurance in place since 1977, covering the entire population since 1989, but the country faces a significant challenge due to the aging of the population and the increasing health expenditure [48]. In 2015, the pharmaceutical industry in South Korea became the tenth largest in the world. However, generic production has historically dominated the sector and little attention has been paid to products that are more innovative or require R&D, such as biologicals that need strong investments and involve high risk in their development. This situation has gradually changed over time, through adjustments introduced by successive governments in the country, starting by increasing health coverage in the population and launching institutional initiatives with a high degree of transparency. The public policies implemented in South Korea regarding expenses related to drugs were divided into two different funds. The first one corresponded to a security fund, while the second is related to the Health Care System Reform Act of 2000 or Separation of Prescribing and Dispensing (SPD) of drugs. The changes made to the intellectual property rights and the Free Trade Agreement (FTA) signed with the United States, Europe, and India gave a significant degree of security to the industry, allowing greater foreign investment. The leading pharmaceutical company in South Korea is Dong-A Pharmaceuticals founded in 1932. In order to grow and reach revenues of nearly US $1 billion, the company established strategic alliances with firms such as Bayer and Meiji, which

helped to expand its market and venture into R&D of high-impact biologics. Hence, the company has invested heavily in the development and manufacturing of biosimilars, working with the "Incheon Free Economic Zone" to build a 142,200m^2plant to manufacture biosimilars in the popular Songdo International Business District of South Korea. The company is currently conducting Phase II clinical trials of DA-6034 (a biosimilar derivative of the original drugeupatilin) for the treatment of dry eyes and also is in the Phase III of DA-3031 (a pegylated human recombinant Granulocyte Colony Stimulating Factor, G-CSF, which is biosimilar to the reference pegfilgrastim, Neulasta) for the treatment of chemotherapy-induced neutropenia in cancer patients. In2015, Dong-A Pharmaceuticals sold its products to over 40countries in Europe, Latin America, and Asia [49]

Regulatory Guidelines for Biosimilars

The regulatory body for the approval of medicines in South Korea is the Ministry of Food and Drug Safety (MFDS), which is responsible for scientifically evaluating drugs developed by pharmaceutical companies in Korea.

The legislation for biosimilars and the guideline for evaluating biosimilars were established by the same agency in July 2009.

In addition, specific manuals have been developed to assessand facilitate the development of biosimilars for erythropoietin and somatropin (2011), Granulocyte Colony Stimulating Factor (2012), and monoclonal antibody (2013).The MFDS guideline is harmonized with the World Health Organization guidelines and with the European Union guidelines in its scope and data requirements for authorization.

The authorization process for marketing a biosimilarin South Korea begins with the submission of a file by the owner of the product (legal representative of the manufacturer's laboratory) to the MFDS offices. This file must have the following complete documentation [50]:

(i) Comparability exercise data.

(ii) Comparative nonclinical studies to detect significant differences.

(iii) Comparative clinical trials (pharmacokinetics and pharmacodynamics studies, efficacy and safety trials).

For the approval of a biosimilar in South Korea, it is sufficient to demonstrate the similarity in safety and efficacy between the biosimilar and the reference product, in a particular clinical indication. If this is done correctly, the biosimilar authorization for another clinical indication can be obtained.

Biosimilars Approved

Since the guide for biosimilars was published in July 2009, in South Korea, seven biosimilars have been approved for marketing as table 6 shows.

Table 6: MFDS Approved Biosimilars.

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Brenzys	etanercept	Ankylosing spondylitis Psoriasis Psoriatic arthritis Rheumatoid arthritis	Sept 2015	Merck/Samsung Bioepis
Davictrel	etanercept	Ankylosing spondylitis Psoriasis Psoriatic arthritis Rheumatoid arthritis	Nov 2014	Hanwha Chemical
Herzuma	trastuzumab	HER2+ breast cancer Advanced (metastatic) stomach cancer	Jan 2014	Celltrion
Omnitrope	somatropin	Pituitary dwarfism Prader-Willi syndrome Turner syndrome	Jan 2014	Sandoz
Remsima	infliximab	Ankylosing spondylitis Crohn's disease Psoriasis Rheumatoid arthritis Ulcerative colitis	Jul 2012	Celltrion
Renflexis	infliximab	Ankylosing spondylitis Crohn's disease Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	Dec 2015	Merck/Samsung Bioepis
Truxima	rituximab	Chronic lymphocytic leukaemia Non-Hodgkin's Lymphoma Rheumatoid arthritis	Nov 2016	Celltrion

Source: [51]

Enbrel (etanercept) is the best-selling biological drug in South Korea, with sales exceeding US $4.7 billion in 2014, representing a lucrative market for the development of biosimilars.

Conclusion

Much of the biopharmaceutical industry is betting towards a future in biosimilars, giving a second life to biological molecules that are reaching the end of their period of intellectual property protection. At the same time, a means to increase their profitability in the medium term, which new biological molecules tend to lack. The production and

marketing of biosimilars involve lower risks and costs and should be a very powerful means of encouraging emerging economies where developing an all-new drug is extremely costly. All countries discussed in this paper, have backgrounds in the pharmaceutical and biopharmaceutical industry, which allows them to have the necessary 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 developing countries, there are not enough public and private investment funds to conduct the necessary clinical trials. On the other hand, the protection of intellectual property shows no signs of maturity comparable to developed countries that are highly developed in relation to the institutional and technological environment, although, interestingly, they show some delay in the effective implementation of clinical trials in their own countries and, consequently, in the development of biosimilars.

This is reflected in their participation in various clinical trials of biosimilars around the world, which are actually little more than 130. Of these, Japan is involved in only nine and contributes to 6%, while South Korea owns seven clinical trials, with a contribution of 5% and, finally, Malaysia falls behind with only five trials and 2.5% of the total contribution. This does not mean that companies in these countries do not develop clinical trials in other countries or in their own research departments. There is evidence that the South Korean company Celltrion, for example, develops clinical trials in other countries. Perhaps the associated costs and regulations involve a major setback and make them more profitable in countries with less regulatory restrictions, as in the case of emerging countries. Australia has a vision on biosimilars from a public angle, with the opportunity to encourage competition in the pharmaceutical market. Meanwhile, Brazil 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. Biosimilars are excellent news, not only for biopharmaceuticals, but also for patients due to the reduction of costs and prices up to 36% in comparison to the original drug. The great boom of biosimilars is to come in the next few decades, but there is still a need to unify criteria and regulations globally in order for their success to be full and widespread.

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