Legal & Regulatory Update

Biosimilars in Brazil: Developments in 2015 and Business Perspectives

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ABSTRACT

Brazil is looking into foreign technology to foster innovation in the country's industrial health complex. Biological plants are being built and partnerships with multinationals have been established with the goal to in license technology, manufacture and supply the population with biosimilars made in Brazil. This article brings up-to-date information on the biosimilar market in the country, with a focus on the public-private partnerships and regulatory approvals. With two biosimilars approved in 2015 and the ongoing development regarding the local pharmaceutical companies, there is a good window of opportunity to create new businesses in the soon to be 4th pharmaceutical spender in the world.

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INTRODUCTION

The Brazilian Constitution establishes access to health as a principle. This principle is interpreted by the court as an obligation of the government to provide free public health care to a population of approximately 200 million. Among many responsibilities of the government, the most relevant is to provide drugs and treatment for the people, regardless of the costs involved.

The country has undergone a fast demographic and epidemiological transition, which has a major impact over the public health care system. In 2030, the population will have increased by 10% and the number of elderly people can achieve 40 million. The disease-related mortality is now similar to developed countries, mostly caused by chronic degenerative non-communicable diseases[1].

Imports fulfill many of the medical necessities in Brazil, importation of drugs grew from US$ 1.4 billion in 2002 to US$ 6.5 billion in 2013. While there was a 375% increase in all medication imported, the share of biologics grew by 13.000% during the same period[2]. Biological products represent 51% of the total budget of the Ministry of Health (MoH). They comprise 12% of all medication distributed by SUS (the Brazilian unified health care system), but take up 61% of the total budget. The deficit of the MoH is already US$ 5.5 billion and soon the country will rise from the sixth to the fourth position in pharmaceutical spending, behind only the US, China, and Japan[3]

Considering this scenario, the government developed a program in 2008, called PDPs (*Parcerias para o Desenvolvimento Produtivo*), seeking, among other objectives, to reduce the public health deficit[4]. It is still early to have a measure of the impact of the program in the Brazilian health care system, however, it has potential to become a great landmark.

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PDPs FOR THE DEVELOPMENT OF COMPLEX BIOLOGICAL PRODUCTS IN BRAZIL

The Brazilian pharmaceutical industry has matured with the commercialization of generic drugs. Throughout the years, local generic companies have been importing the API from countries like India and China and very little innovation has characterized the local industry. As a consequence, no real infrastructure and environment for the development of the medicines the country now badly needs has been developed.

To address the lack of infrastructure, know-how and technologies to manufacture biologicals is at the core of the PDPs program. The new guidelines, published in 2014, represent the concern of the government to foster an environment that favors technology transfer and further R&D investments[4].

In this sense, the goals of the PDP program are: (i) to increase the access of the population to medication and decrease the health care budget vulnerability; (ii) to diminish the manufacture and technological dependency of SUS', increasing the production of strategic products locally; (iii) to foment technological development and exchange of knowledge to foster innovation; (iv) to boost the development of local pharmaceutical industry (private and state-sponsored).

Periodically, the government publishes a list of strategic health products for the SUS. This list contains small molecules, biologicals and medical devices, which are usually purchased in a centralized manner by the MoH[5].

Although any institution can submit a request for the inclusion of a new technology to the list, the final decision is a strategic one, which considers the cost/benefit of the new technology. After its publication, which happens on the second semester every year, PDP applicants (state-owned institutions), interested in manufacturing a product can submit a project in partnership with one or more private companies (from the 1st of January to the 30th of April of the following year). Table 1 shows the four phases of the PDP program.

There were more than 100 PDP projects submitted from 2009 to 2014. When the new guidelines of 2014 were published[5], some projects had already been approved and others were under review. The projects that had not been approved had to readjust or, when unable to comply with the new rules, were rejected. Table 2 below shows the ongoing PDP projects (related to biologicals only) and respective phases of development.

It is important to point out that some biologicals that are blockbusters in sales, such as etanercept and bevaci-

Table 1: Phases of the PDP program

Phase I: Proposal	Phase II: Project	Phase III: PDP	Phase IV: Internalization of technology
Submission of proposal. The proponent must be the governmental institution (laboratory which will benefit from the new technology). A partnership with one or more private companies is required. The Ministry of Health will analyse the proposal, if approved a term of commitment will be signed between the proponent and the Ministry.	This is the initial stage of development. Project needs to be implemented. The time limit for the development of the project is 10 years. The duration of the project must comprehend not only the development and technology transfer but also the registration at ANVISA. According to the guidelines, ANVISA has 60 days to register a product from a PDP.	Developmentof the project. Technology transfer and closure of contract of acquisition of products between the Ministry of Health and governmental laboratory. For biologics the transfer of the master cell bank into the country is a requirement.	The public laboratory should be in conditions to manufacture the new technology and expand the know how to other units.

Table 2: PDPs for Biologicals[†,‡]

Biological	Brazilian Public Institution	Private Company (Brazil)	Private Company (Foreign)	PDP Phase
Beta interferon 1A	Biomanguinhos	Bionovis	Merck Serono	Phase II
Insulin	Farmanguinhos	Biomm	None	R$122,642,000.00 Phase III, aquisition stage
Filgrastim	Biomanguinhos	Eurofarma	None	Phase II
Filgrastim	Biomanguinhos	Eurofarma	None	Phase I (approved in 2015)
Somatropin	Biomanguinhos	Cristália	None	Phase I (approved in 2015)
Somatropin	Biomanguinhos	Cristália	None	Phase II
Filgrastim	Biomanguinhos	Eurofarma	None	Phase II
Filgrastim	Biomanguinhos	Eurofarma	None	Phase I (approved in 2015)
Taliglucerase alfa	Biomanguinhos	None	Pfizer/Protalix	Phase III
Taliglucerase alfa	Biomanguinhos	None	None	R$ 13,313,903.16 Phase III, aquisition stage
Taliglucerase alfa	Biomanguinhos	None	None	R$ 14,592,000.00, Phase III, aquisition stage
Etanercept	Instituto Vital Brasil/ Biomanguinhos	Bionovis	Merck Serono	Phase II
Etanercept	Bahiafarma	Orygen	None	Phase II
Etanercept	Butantan	Libbs	Mabxience	Phase II
Adalimumab	Instituto Vital Brasil	PharmaPraxis	NA	PDP P, D & I (old guidelines)
Adalimumab	FUNED	Bionovis	Merck Serono	Phase I (approved in 2015)
Adalimumab	Bahiafarma	Libbs	Mabxience	Phase II
Adalimumab	Biomanguinhos	Orygen	None	Phase II
Bevacizumab	Biomanguinhos	Orygen	None	Phase II
Bevacizumab	Butantan	Libbs	Mabxience	Phase II
Bevacizumab	Instituto Vital Brasil	Bionovis	Merck Serono	Phase II
Bevacizumab	Tecpar	None	Biocad	Phase II
Cetuximab	Instituto Vital Brasil/ Biomanguinhos	Bionovis	Merck Serono	PDP P, D & I (old guidelines)
Infliximab	Farmanguinhos	NA	NA	R$ 164,715,908.84 Phase III, aquisition stage
Infliximab	Instituto Vital Brasil/ Biomanguinhos	Bionovis	Janssen-Cilag	Phase III
Infliximab	Bahiafarma	Orygen	Pfizer	Phase I (approved in 2015)
Rituximab	Bahiafarma	Orygen	Pfizer	Phase I (approved in 2015)
Rituximab	Butantan	Libbs	Mabxience	Phase II
Rituximab	Instituto Vital Brasil/ Biomanguinhos	Bionovis	Merck Serono	Phase II
Trastuzumab	Bahiafarma	Libbs	Mabxience	Phase II
Trastuzumab	Biomanguinhos	Orygen	NA	Phase II
Trastuzumab	Instituto Vital Brasil	Bionovis	Merck Serono	Phase II

[†]This table includes only the biologicals PDPs, but excludes vaccines and hemophilic factors There is only one product in stage IV, the Influenza vaccine, a partnership between Butantan and Sanofi Pasteur.

[‡]Three joint ventures were created in Brazil: Orygen is a joint venture between the Brazilian pharmaceuticals Eurofarma and Biolab; Bionovis is a joint venture between União Química, Hypermarcas, EMS, and Achè and Supera (not in this table) a joint venture between MSD, Eurofarma and Cristália, and has a PDP to manufacture the complex generic Glatiramer acetate.

zumab were not in the strategic list for the PDPs of 2015[5] probably because the government considered that the number of ongoing PDPs for both products was already satisfactory and enough to attend its demand.

Brazil has a successful vaccination policy and three big governmental institutions have, traditionally, produced vaccines distributed by SUS, the Fundação Oswaldo Cruz (Fiocruz in the State of Rio de Janeiro*), Fundação Ezequiel Dias (FUNED, in the State of Minas Gerais) and Instituto Butantan, in São Paulo. There are 23 vaccine PDPs on Phase III, acquisition stage, which were not included in table 2. Also excluded were the projects related to hematological factors (there are governmental laboratories specific for hematological factors, Hemobrás and others). In 2015 there were more PDP proposals rejected than accepted (only 8 out of 23 biological-related PDPs submitted were approved). Pfizer had two projects approved on a PDP with the local company Orygen and the governmental laboratory Bahiafarma for the production of infliximab and rituximab; but had one for adalimumab with Orygen and Biomanguinhos rejected. Merck S/A was involved with four PDP proposals with the national company Bionovis but had only one approved, for the production of adalimumab, in partnership with the local laboratory FUNED. Other foreign companies, such as Abbvie and Celltrion (both in partnership with Butantan) faced rejections in PDPs to produce adalimumab and infliximab, respectively. There is room to file an appeal by the applicant of the PDP, which is the governmental institution.

* The units Farmanguinhos and Biomanguinhos are part of Fiocruz in Rio de Janeiro

REGULATORY APPROVALS OF BIOSIMILARS IN BRAZIL

The Brazilian Health Surveillance Agency (ANVISA) was created in 1999 to support the protection of the population's health, through the sanitary control of food and drug related products.[§] The responsibility to protect the health of the fifth largest population of the world is remarkably significant. Since its creation, ANVISA has been facing important regulatory challenges over medical devices and small-molecule products[6,7]. Among these challenges is how to handle and develop the regulatory structure addressing complex biological drugs.

ANVISA's regulation for biologics, Rule #55 of 2010, established the requirements for granting marketing authorization for both new biological and biosimilars (the agency does not officially use the term biosimilars, although this may change). The rule provides three pathways for obtaining marketing authorization for a biological drug:

a. Full data package pathway: submission of full dossier to obtain marketing authorization for a new biological product.
b. Comparative pathway (biosimilars): submission of a comparative dossier containing non-clinical and clinical studies used to demonstrate comparability between the follow on biological product to be approved and the biological used as comparator and studies with information about development and quality control,

§ Art. 6 of Statute #9,782/99.

as well as the comparability result report with the comparator biologic to obtain marketing authorization for a follow-on biological product.

c. Individual development pathway: submission of studies with information about development, production, quality control, and non-clinical and clinical data showing the quality and safety of the product in order to obtain marketing authorization for a follow-on biological product. Non-clinical and clinical studies can be reduced, depending on the amount of data for pharmacological properties, safety and efficacy of the originator product[8].

CELLTRION'S BIOSIMILAR APPROVED IN 2015

In April of this year, Celltrion's Remsima, a copy of Janssen's Remicade (infliximab) was granted marketing authorization via the regulatory comparative pathway (b, above), for the same therapeutic uses of Remicade. It was the first monoclonal-antibody biosimilar in the country.

ANVISA's approval of Remsima followed Celltrion's launch of the product in several countries of the European Union[9]. Celltrion's application for marketing authorization of Remsima was filed in Brazil in November 2012 and approved in April, 2015. ANVISA regularly takes between two to three years to grant a marketing authorization, although this timing will (in theory) be different for products in PDPs. According to the guidelines, the agency has 60 days to revise the processes of PDP products.

ANVISA's report for authorization of Celltrion's biosimilar followed EMA's conclusions about the safety and efficacy of the drug. Celltrion submitted the same data related to manufacturing, quality control and the therapeutic experimentation report filed before EMA: ANVISA's analysis was published and indicated that the only differences between the two biologics was in the glycosylation pattern of the antibodies and the consequent difference in affinity of its binding to the Fc receptor (FcyRIIIa). Similarly to EMA, the agency accepted the argument that there would be no clinical impact regarding these differences. The first mAb biosimilar approval shows that the Brazilian Agency will likely follow EMA's conclusion regarding the effectiveness and safety of biological products. In this sense, obtaining an authorization before EMA will improve drastically the chances of getting approval of the same product in Brazil.

Remsima's approval was obtained by 'Celltrion Healthcare *Distribuidora de Produtos Farmacêuticos do Brasil Ltd.*', a local subsidiary of Celltrion Inc. The government has not issued any specific guidelines, but the price to be approved for Celltrion's Remsima will be an important parameter for the next coming biosimilars. In the case of PDPs, the project submitted must have information regarding prices, this issue will be discussed below. Celltrion sought to have a PDP for infliximab, right after it got the approval.

Recently, as reported by ANVISA, the first biosimilar 100% Brazilian, was approved. It will be manufactured by the national pharmaceutical company, Eurofarma, under the name Fiprima. The national filgrastim was also approved via the comparative regulatory pathway, being compared to Granulokine. In Europe, the degree of adoption of filgrastim biosimilars varies greatly between different countries, from 3.8% in France to almost 10 times more in Germany (31%), it will be interesting to observe what will happen in Brazil[10].

BUSINESS PERSPECTIVES

Despite the positive development concerning the authorization of the first mAb biosimilar in Brazil, some questions are arising regarding how new biological products and biosimilars will interplay in the public health care system. When PDP projects are submitted they must contain the prices proposed for the products that will be developed, which must be compatible with SUS or prices found in the international market (countries that are regulated by the Drug Market Regulation Chamber CMED). Table 3 has a list of all processes regarding biologicals that are being revised at the moment by ANVISA and are likely to enter the market in the next year.

Table 3: Biologicals with processes at ANVISA

Biological	Private Company
Trastuzumab	Cristália
Trastuzumab	Celltrion
Rituximab	Accord
Etanercept	Bionovis
Etanercept	Cristália
Insulin glargine	Eli Lilly
Insulin glargine	Aspen Pharma
Filgrastim	Accord
Filgrastim	Sandoz
Somatropin	Cristália

If the PDP projects approved by the government work well, and some will, the market will soon be flooded with Brazilian biosimilars which will be available among foreign biosimilars, biobetters and innovative drugs. It is important to mention that the inclusion of medicines in the strategic list of medications for SUS is based on studies that take into consideration the cost-benefit of drugs that are in the market. Therefore, innovative medicines, with no history, are not listed. The medical community in Brazil is sophisticated and in many cases, there is a clear disconnect between what they want for their patients and what is provided by SUS. The scenario is, to say the least, rather complicated for the government. There is an increasing number of lawsuits filed by people against the government seeking state of the art treatment with breakthrough drugs. From 2010 to 2014 the government spent more than USD 800 million with these lawsuits, a growth of 500%. Most of these lawsuits seek drugs that are not approved in Brazil but represent the only hope for several patients with life threatening conditions.

In 2015 the government had plans to buy approximately 3 billion USD in drugs, the governmental program, Brasil Maior[11], opened a market of R$ 35 billion reais[12], but this program will be substituted sometime soon.

With many patents expiring during this decade, world market estimatives go from $2 billion dollars to ten times this value[13]. Although some believe that the financial results so far have been poor, it is a bit too early to judge. According to the Biotechnology Information Institute the current pipeline is of 588 biosimilars, 434 biobetters and 133 reference biologics, in a total of 1155 products[14]. There are a lot of incentives for the local pharmaceutical companies to innovate and internationalize. Brazil does not have the easiest business environment in South America, but being the largest market, it can be a first good choice to start in the continent. If the biosimilars produced by the PDPs will contribute significantly to the reduction of the MoH deficit is yet to be seen but there is no doubt that they will, and already are, contributing for a more dynamic business environment in the industry: partnerships, in-licensing and co-development.

CONCLUSIONS

Many articles quote 2015 as an important year for the market of biosimilars, with the first approval in the USA and many patents expiring or about to expire. In addition, it was possible to have more data from of the development of the European market for biosimilars[10]. In Brazil it has definitely been an important year, with two approvals by ANVISA, the first biosimilar monoclonal antibody (Remsima) and the first 100% Brazilian biosimilar (Fiprima). With the ongoing PDPs and a lot of investment being made in new biological plants, it will be interesting to follow the next developments in the country. The shape of the biosimilar market in the soon to be 4th pharmaceutical spender in the world will have an influence not only in Latin America but in businesses around the world.

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