Biopharmaceutical Innovation on Pharmerging Countries: A Quantitative Analysis and Scenario Prediction

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***Abstract*—The advancement of biotechnology area has allowed the development of biodrugs and its use implemented for the treatment of complex diseases. Countries with an emerging pharmaceutical market are pointed out as responsible for sustaining the sale growth of new medicines Therefore, a technological and industrial mapping of the biopharmaceutical segment was developed through the analysis of patent data extracted from Derwent and WIPO database. Numerical analyzes were performed, implementing an algorithm in MATLAB, in order to predict scenarios. The importance of Merck and Sartorius, both with about 74 biopharmaceutical patents, stands out. The leading position of U.S. (101,873 patents) and Europe (93,013 patents) has been confirmed, although China has demonstrated a relevant position (36,513 patents) over the twenty years of analysis. Also, Brazil will increasingly attract the interest of different countries in protecting biotechnological products (61.27% increase until 2021) in order to exploit the emerging Brazilian market. The analysis pointed out that pharmerging countries do not stand out among the largest holders of biopharmaceutical patents and presents low exploitation of the opportunities of their emerging markets.**

***Index Terms*—biopharmaceutical, innovation, pharmerging country, patents, BRICS**

I. Introduction

Pharmaceutical industry is considered highly oligopolistic and some global companies dominate almost all drug research and development (R&D) in the world. Considering success in this segment is highly dependent on innovation, the U.S. and Europe stand out as pioneers in the pharma industry, with significant participation in the global market, consistent investments in R&D and traditionally dictates the dynamics of the sector [1].

However, is observed the upward relevance of countries with an emerging pharmaceutical market (pharmerging countries), especially BRICS members (Brazil, Russia, India, China and South Africa), which according to IMS Health [2], [3], a global pharmaceutical market auditor, are the potential responsible to keep the sustainable growth of the drug industry. Great prominence is given to China, which, according to [4] should become a leader in the generation of pharmaceutical innovation by 2036.

Biopharmaceutical drugs and other biotech products can become the core of the pharmaceutical industry, requiring significant transformation in technology, operations and strategy [5]. In fact, biodrugs represent a growing share of the world pharmaceutical sector, totaling US$ 228 billion in global sales in 2016 and the CAGR index is expected to reach 8.59% in 2018-2023 period [6].

Therefore, this study aimed to develop a quantitative study and prediction scenario based on patent data as an indicator of biopharmaceutical innovation in order to assess how emerging pharmaceutical markets are being explored.

II. Background

A. The Opportunity of Biopharmaceutical's Market

Molecular complexity is one of the major differences between biopharmaceutical drugs and conventional drugs. The drugs with high molecular mass and complex structure (nucleotides, RNA or DNA and amino acids, peptides and proteins) are called biodrugs [7]. Studies on insulin represent two-thirds of the total and vaccines concentrate 22% of the world's efforts. Although biopharmaceuticals can be very effective in treating diseases, their costs can reach to US$ 1 million per patient [3].

As a cheaper cost alternative to expensive biopharmaceutical therapies, there are the biosimilars, which are generic biodrugs, developed from expired patents. Since generic medicines start from an existing innovation, they require a much smaller investment and get reach the market at a lower cost. The use of biosimilars health systems can expand patient access by offering more treatment options, besides offering a new tool to the government to control rising health spending [8].

Biopharmaceutical drugs number has grown around the world in recent years. From 2013 to 2016, the total of products approved by the Foods and Drug Administration (FDA) and European Medicines Agency (EMA) for use in humans was 73. By 2016, the number of approvals

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reached 1,357, of which 737 were biosimilars, and the global sales totaled US$ 228 billion [3], [7].

In 2018, the biopharmaceutical market was shown to be even more promising, achieving growth rates of 15% above conventional medicines. The annual sales totaled US$ 275 billion, an increase of 6,250% over 1990, account about for 25% of the global pharmaceutical market [9].

B. Pharmerging Countries

Countries with emerging pharmaceutical market have attracted attention in recent years by the fast growth of the local pharmaceutical market, especially by the investments made by national companies in the generic segment, through methods such as reverse engineering. Also, population aging favors the growth of the sector in pharmerging countries as it has a direct impact on the economic growth of these countries due to the change in consumption patterns [10].

The IMS Health report categorized emerging pharmaceutical markets as Level 1, Level 2 and Level 3 according to with its indexes reached in 2014 and estimated participation in the coming years. Official reports from the pharmaceutical industry indicate that of the 21 pharmerging countries, 5 countries (Brazil, Russia, India, China and South Africa), BRICS members, rank among the top 10 in terms of sales, with China standing out for accelerated growth of the sec-tor. Studies indicate that the sustainable growth of the sector is associated with these countries, due to the increase in domestic demand [2], [3].

The biopharmaceutical sector has pursued this trend, so that the work of Moorkens *et al.* [6] found that among the top 25 pharmaceutical industries, 22 companies are expanding their activities in emerging markets, mainly with a focus on biodrugs development.

III. Methodology

This work consisted of an exploratory study, which integrates bibliographic research and collection and analysis of secondary data.

Firstly, a review of the literature was carried out, using several sources of publication databases such as Web of Science, IEEE Xplore, PubMed and Scopus. The main fields of research encompassed Intellectual Property; Patents; Pharmaceutical industry; Biopharmaceutical industry; Innovation; Pharmerging countries and BRICS.

Technological and industrial mapping was initially developed using Derwent World Patent Index platform and the patent search was made by technology and by country and the indicators were linked to the most innovative companies in the biopharmaceutical sector. Also, it was used Intellectual Property Statistics Data Center, promoted by the World Intellectual Property Organization (WIPO), where a search by origin and by office was developed. It is noteworthy that in the patent study by office, India data were not available in WIPO. The analysis was conducted from 1996 (Brazilian Industrial Property Law was approved) until the last available registration date in the patent banks (2018 – Derwent; 2016 – WIPO).

In order to assess the existence of a potential correlation between R&D investment and innovation, EU R&D Scoreboard reports from 2012, 2015 and 2017 were analyzed. The selected companies were the 12 most innovative (highest patents number) organizations obtained through Derwent. Pearson's correlation test was applied in the Statistical Package for Social Sciences (SPSS) software, considering R&D data and patent protection.

According to the Frascati Manual [11], as well as other studies in the literature [12], [13], patent based indicators provide insight into how innovative a country is, since that R&D is the input of invention activities and patents are the outputs of innovative processes.

After the data collection, numerical analyzes were performed to predict scenarios using MATLAB software. In the forecasts, the polynomial approximation was made by the least squares method, of second degree for Brazil and of third and fourth degree in the case of China, since there is a large numerical difference.

IV. Results and Discussion

A. Biopharmaceutical Patents Study

In the Derwent platform, a search was made using "Biopharmaceutical" term, considering the period between 1996 and 2018 classifying by name of the depositor. The Fig. 1 shows the 15 companies and institutions that hold the most patents in the biopharmaceutical sector.

With the data obtained (Fig. 1), it was observed that within the Pharmacology & Pharmacy area, the company that most hold patents was Merck (Germany), with 74 protections, followed by Sartorious (Germany), with 73 and in the third place appears G&E (U.S.) with 44 registrations.

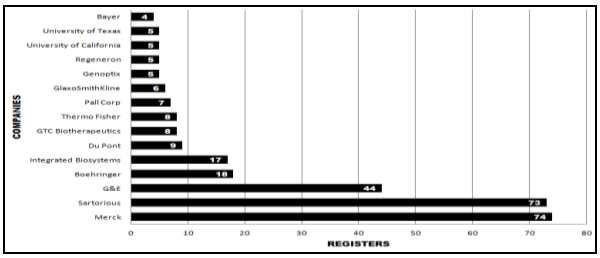

Figure 1. Top 15 companies with the highest number of biopharmaceutical patents granted between 1996-2018.

The presence of traditional companies in other segments, such as 3M (U.S.) and Saint Gobain (France) points out that many patents are linked to new devices and biotechnological processing. It was observed the presence of two U.S. universities in the top 15, which shows the degree of novelty and interest in the area.

In fact, in some emerging countries such as Brazil, the pharmaceutical industry developed dependent on imports of drugs and pharmaceutical inputs, investing few resources in R&D. This question reflects in the

biopharmaceutical market, since it is an even more technology-intensive.

In order to check the correlation existence among R&D and innovation Pearson's coefficient (0.637) was obtained, demonstrating that there is a positive linear correlation between these two parameters. Therefore, it is suggested that biopharmaceutical industries increase their investments in R&D to leverage their innovation indicators.

The patents number granted to European countries, U.S. and BRICS, according to WIPO, can be seen in Table I, and the Table II shows the numbers of patents granted to residents in these same countries.

According to Table I, it was confirmed the leading position of the U.S., with 101,873 biotechnology patents, followed by Europe (93,013 protections), with highlights for countries such as Germany, France, Netherlands, United Kingdom and Switzerland. Even if these numbers are related to all biotechnological products, there are patents for biodrugs inserted, pointing out the high degree of innovation in these countries.

TABLE I. BIOTECHNOLOGY PATENTS GRANTED TO EUROPE, U.S. AND BRICS COUNTRIES (1996-2016)

Year	Europe	U.S.	Brazil	Russia	India	China	South Africa
1996	2,635	2,916	0	268	2	18	7
1997	2,993	3,556	1	328	6	26	7
1998	3,003	4,646	0	248	7	37	6
1999	2,96	4,718	4	168	7	31	10
2000	2,66	4,216	1	174	6	121	9
2001	2,881	4,48	8	142	14	153	8
2002	3,133	4,458	20	177	24	85	5
2003	4,32	4,346	6	840	39	292	9
2004	4,351	4,168	27	642	32	575	17
2005	4,24	3,656	7	921	46	657	14
2006	4,807	4,145	24	760	63	924	10
2007	4,041	4,092	8	263	69	1,014	8
2008	4,363	4,221	7	382	77	1,047	12
2009	4,544	4,369	10	308	81	1,191	29
2010	5,028	4,906	21	390	101	1,849	23
2011	5,173	5,162	16	366	88	2,813	11
2012	5,509	5,731	21	352	89	4,515	27
2013	5,954	6,27	35	349	101	5,712	22
2014	6,117	6,83	41	405	84	5,339	15
2015	6,708	7,068	41	417	102	5,016	31
2016	7,593	7,919	50	371	158	5,098	18
Total	93,013	101,873	348	8,271	1,196	36,513	298

Criteria used: Indicator: 5-Patent grants by technology; Type: Total count by applicant's origin; Technology: 15–Biotechnology. Source: own elaboration from the data of the WIPO (2018).

For the BRICS, China is the most prominent country, with 36,513 patents (35,318 of which were granted to residents, as shown in Table II), showing the evolution of its biotechnology industry. These figures demonstrate the country's race to reach satisfactory positions in innovation and thus ensure its competitiveness in the global market and the self-sufficiency of its industries.

Complementation of coordinated policies of subsidized credits and the creation of innovation centers for technology transfer and fixation, with clear production and industrialization objectives were one of the main differentials in the development of Asian countries [14].

Brazil (348 protections), on the other hand, shows stagnant numbers over the years, with oscillations that do not exceed tens, demonstrating low exploitation of the potential of the national market. India has already grown more sharply, with 1,196 patents, filing over 100 patents in certain years.

Russia already has a scenario in which there are a total of 8,271 biotechnology patents and in some years, it reaches almost a thousand, but it undergoes strong oscillations. South Africa already has the lowest number of patents in the countries listed, with 298 and shows the lowest oscillation of the period, which indicates the low rate of innovation in the country.

Some authors present that the success chances through technological recovery are greater, since when taking advantage of a process of technological maturity there is a better use in the processes of learning in production. Other authors suggest that the possibilities for development are greater in the early stages of the new technology's diffusion, since the manufacturing processes parameters are not yet consolidated, and the companies can advance in the imitative development of products, components and processes [15], [16].

According to Table II, it can be observed that in Brazil the number of protections of the residents is lower than that of non-residents, which indicates a fragility, since this fact shows that the national industries have innovated little when compared to the international industries, indicating as well a low level of use of the biopharmaceutical market by domestic companies. Also, there is a great international interest in securing protections in the emerging market.

TABLE II. BIOTECHNOLOGY PATENTS GRANTED TO RESIDENTS IN EUROPE, U.S. AND BRICS COUNTRIES (1996-2016)

Year	Europe	U.S.	Brazil	Russia	China	South Africa
1996	619	1,521	0	261	14	4
1997	733	2,201	0	319	19	4
1998	606	3,112	0	240	31	4
1999	484	3,048	0	162	29	7
2000	456	2,634	0	171	119	5
2001	458	2,873	1	112	149	5
2002	505	2,685	0	153	78	2
2003	1,243	2,41	0	808	281	5
2004	1,116	2,149	2	626	559	7
2005	1,296	1,827	1	896	643	12
2006	1,146	2,1	0	750	900	4
2007	589	2,085	1	218	974	4
2008	596	1,902	1	319	1,013	7
2009	600	1,99	3	274	1,144	19
2010	710	2,43	3	345	1,775	18
2011	746	2,449	4	331	2,734	4
2012	783	2,717	0	314	4,421	16
2013	705	2,85	9	279	5,584	7
2014	694	3,071	9	330	5,184	3
2015	823	3,154	12	373	4,838	7
2016	663	3,375	19	228	4,829	0
Total	15,571	52,583	65	7,509	35,318	144

Criteria used: Indicator: 5-Patent grants by technology; Type: resident and abroad count by applicant's origin (equivalent count); Technology: 15-Biotechnology. Source: own elaboration from the data of the WIPO (2018).

According to Table III, the U.S. (82,395 patents) is still the region with the highest biotechnology patents,

followed by China (46,993 patents), which increased by 3 times the number of patents granted in 2010 (2,190 patents) to 2016 (6,467 patents), being the most prominent BRICS country in the biopharmaceutical market.

TABLE III. BIOTECHNOLOGY PATENTS GRANTED IN OFFICE IN EUROPE, U.S. AND BRICS COUNTRIES (1996-2016).

Year	Europe	U.S.	Brazil	Russia	China	South Africa
1996	1,334	2,3	0	312	46	313
1997	1,511	3,19	0	411	55	275
1998	1,255	4,514	0	344	71	269
1999	1,103	4,488	0	290	72	282
2000	991	3,862	2	263	235	112
2001	938	4,326	1	171	262	128
2002	956	3,98	0	241	213	250
2003	1,833	3,665	0	979	563	275
2004	1,749	3,273	2	777	1,019	277
2005	1,844	2,79	1	995	1,159	227
2006	1,601	3,254	0	859	1,348	275
2007	1,052	3,211	1	327	1,46	270
2008	1,084	2,982	6	456	1,494	486
2009	1,126	3,087	38	442	1,695	495
2010	1,245	3,936	51	492	2,190	436
2011	1,353	4,075	52	537	3,285	128
2012	1,335	4,401	24	505	5,392	421
2013	1,295	4,773	66	482	6,972	309
2014	1,195	5,234	84	566	6,564	341
2015	1,39	5,369	103	675	6,431	124
2016	1,205	5,685	151	507	6,467	100
Total	27,395	82,395	582	10,631	46,993	5,793

Criteria used: Indicator: 5- Patent grants by technology; Type: Total count by filing office; Technology: 16 - Pharmaceuticals. Source: own elaboration from the data of the WIPO (2018).

In fact, a study of on investment and development of new strategies for large industries in the biopharmaceutical market point out that companies are already present and positioned in emerging countries, especially BRICS. It is worth mentioning Pfizer's $ 350 million investment to build a global biotechnology center in China, as well as an inauguration of Merck US's BioReliance® End-to-End Biodevelopment Center in Shanghai, China [6].

B. Predictions

Among the countries of the BRICS, China and Brazil stand out. Therefore, the scenario prediction study was applied to these two regions, considering a time horizon of 5 years (2017-2021).

According to Fig. 2, there are two very different scenarios in relation to the volume of biotechnology patents, with Brazil on a smaller scale, below one hundred patents. On the other hand, China reaching almost seven thousand patents in 2021. China and Brazil start in 1996 with relatively similar numbers and scenarios, with just over a dozen patents and no patent on biotechnology respectively. China during the period shows a very aggressive growth, especially due to the strengthening of its public policies aimed at the advancement of science and technology and arrives in 2016 with 5,098 patents only in that year and Brazil appears in that period with only 50, which shows its stagnation in the biotech industry, even with an enormous market potential.

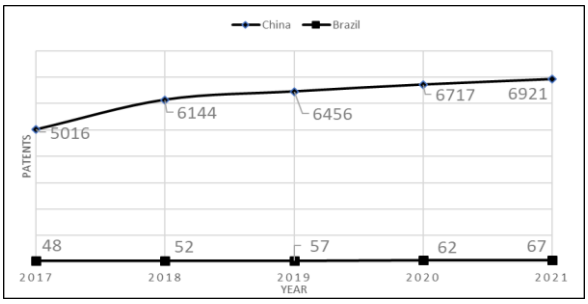

Figure 2. Scenario prediction for grant of biotechnology patents to China and Brazil.

Although China has a prominence against Brazil in the amount of biotechnology patents, the relative variation points to an increase in the number of protections of 39.58% for Brazil versus 37.98% for China, considering the indexes for 2017 and 2021. This estimate suggests that China will continue to drive biopharmaceutical innovation and could endanger European and North American leadership.

In the study by office (Fig. 3), the difference between the regions was very expressive, so an increase in the granting of patents was 61.27% in Brazil versus 14.78% in the China. These data indicate that Brazil will increasingly attract the interest of different countries in protecting biotechnological products in order to exploit the emerging Brazilian market. In fact, in Brazil, partnerships between national and foreign pharmaceutical companies, involving technology transfer and local biosimilars manufacturing, are advancing to allow the increase of expensive drugs for the treatment of complex diseases [8].

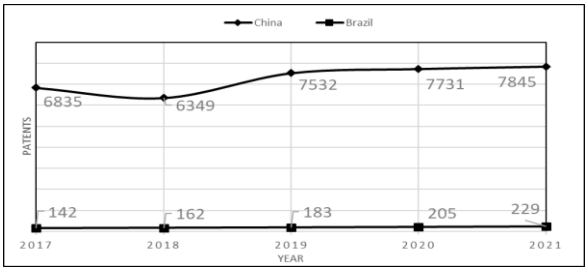

Figure 3. Scenario prediction for grant biotechnology patent in offices in China and Brazil.

V. CONCLUSION

It is a consensus that countries with emerging pharmaceutical markets open a sustainable growth opportunity for the sale of medicines in the world. The present study pointed out that this market opportunity has not been explored by national industries in terms of innovation, so no organization was observed among the 15 largest holders of biopharmaceutical patents according to Derwent data. About the number of patents, the European countries and the U.S. are leaders in the segment, demonstrating their technological capabilities in terms of innovation. Then there is China, which has increased its relevance in the last 20 years in an intense way, which serves as a means of comparison between

leading and emerging market countries, since it jumped from 18 biotechnology patents in 1996 to 5,098 protections in 2016, being foreseen a scope of 6,921 biotechnology patents in 2021.

The other BRICS member, Brazil, appear with smaller numbers and with a large part of their patents granted to foreign companies, which shows the importance of these markets and the level of local innovation that must be improved to have a better chance of competing with other countries.

Therefore, it is suggested that countries with emerging pharmaceutical markets adopt bold, audacious and effective public policies aimed at leveraging innovation in the productive sector, especially in the biopharmaceutical segment, to gain advantage and have new possibilities to exploit the potential of market they currently have.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

B. Eng. Gabriel Guerra da Silva Freire developed the theoretical formalism and obtained the data. B. Eng. Karina Fernandes de Oliveira and B. Eng. Gabriel Guerra da Silva Freire analyzed the data. B. Eng. Karina Fernandes de Oliveira wrote the manuscript with support from Prof. Igor Polezi Munhoz and Prof. Alessandra Cristina Santos Akkari. Prof. Igor Polezi Munhoz performed numerical simulations. Prof. Alessandra Cristina Santos Akkari conceived the original idea and supervised the project. All authors had approved the final version.

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