Innovation and capabilities building in biopharmaceuticals in Brazil: a knowledge network analysis

Paper submitted to 47° Encontro Nacional de Economia

Nathalia Alves[1], Marina Szapiro[2], Marco Vargas[3], Jorge Britto[4]

Abstract

This paper aims to provide an initial assessment of the biopharmaceutical innovation system in Brazil by mapping the main linkages and actors that integrate such system and by analyzing the nature of the university-industry relationships established in crucial knowledge areas that support the biopharmaceutical research, development and innovation (RD&I) chain. The analysis is based upon data gathered from the Brazilian National Council for Scientific and Technological Development (CNPq) concerning the 2014-2016 period. 385 public and private laboratories operating in Brazil were identified and 27% of them established linkages with Brazilian Universities and Research Centers. Most of the university-industry collaborations regarded the conduction of basic and applied research in pharmacy, medicine, biochemistry and microbiology knowledge areas. FIOCRUZ, BUTANTAN, USP and UFRJ proved to be central institutions to the network structure. National and multinational companies displayed different patterns of interaction considering the types of relationship established and the knowledge areas involved.

Keywords: Biopharmaceuticals, university-industry relationships; knowledge networks; Brazil.

Resumo

O objetivo do artigo é fornecer uma avaliação inicial do sistema de inovação biofarmacêutico no Brasil, mapeando seus principais vínculos e atores componentes e analisando a natureza das interações universidade-empresa em áreas de conhecimento críticas para a cadeia de pesquisa, desenvolvimento e inovação (P,D&I) biofarmacêutica no Brasil. A análise é baseada em dados do Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) referentes ao período 2014-2016. Foram identificados 385 laboratórios públicos e privados que operam no Brasil e 27% deles estabeleceram vínculos com Universidades e Centros de Pesquisa brasileiros. A maioria das colaborações universidade-empresa envolveram a realização conjunta de atividades de pesquisa básica e aplicada em áreas de conhecimento de farmácia, medicina, bioquímica e microbiologia. Instituições como FIOCRUZ, BUTANTAN, USP e UFRJ mostraram-se centrais para a estrutura da rede de conhecimentos. Empresas nacionais e multinacionais apresentaram diferentes padrões de interação em termos de tipos de relacionamento estabelecidos e áreas de conhecimento envolvidas.

Palavras-chave: Biofarmacêutica; interações universidade-empresa; redes de conhecimento; Brasil.

JEL Classification Numbers: L65, O15, O30

ANPEC Area 9 - Economia Industrial e da Tecnologia

[1] PhD Candidate - Federal University of Rio de Janeiro - PPGE-UFRJ
[2] Full Professor of the Department of Economics – Federal University of Rio de Janeiro - UFRJ
[3] Full Professor of the Department of Economics, Federal Fluminense University – UFF
[4] Full Professor of the Department of Economics – Federal Fluminense University – UFF

1. Introduction

Biopharmaceutical innovation involves a complex and systemic network of heterogeneous agents and institutions, which includes sets of institutional arrangements between industrial activities and supply chains, large and small companies, public and private organizations, Science, technology and Innovations (S,T&I) agencies, regulatory agencies, health political bodies, public policies and intellectual property arrangements, consumers, among many others (MALERBA; ORSENIGO, 2015). The Brazilian biopharmaceutical innovation system is configured around the presence of different actors, such as universities and research centers, public drug and immunobiological research and production laboratories, biotechnology start-ups, multinational pharmaceutical companies, national pharmaceutical companies, national political bodies and regulatory agencies, among many others national specifies (VARGAS et al, 2013; VARGAS, 2017).

The local production of generic drugs in Brazil has significantly increased the share of national firms in the Brazilian pharmaceutical market and it represented an important turning point for the industry's technological learning trajectories. However, the industrial base of Brazil's biopharmaceutical innovation system is still limited, hampering the country's competitive insertion in global biopharmaceutical markets. This scenario points to the need of strengthening the capabilities building processes in new biotechnological platforms in order to effectively enable the domestic production of biopharmaceuticals in Brazil (VARGAS, 2017).

Biopharmaceutical activities are defined as science-based, once innovation is driven by joint advances in basic and applied research in life and health sciences (DOSI; MAZZUCATO, 2006; PAVITT, 1984). Biotechnology intensive activities may be understood as a set of knowledge building blocks and technological tools that coevolve in time, as an inherently interdisciplinary and pervasive activity. Developing Scientific and technological infrastructure and building bridges to access to external knowledge sources are considered critical to enable biopharmaceutical innovations. New discoveries of products often require combinations of scientific knowledge pieces from different fields – such as general biology, molecular biology and physiology – alongside with industrial and commercial capacity, marketing skills and complementary assets management (CORIAT et al, 2003. ELIASSON; ELIASSON, 1996). This approach emphasizes: (1) the importance of human resources skills; (2) the need of a sufficiently diverse environment in scientific and technological infrastructure; (3) exploitation of synergy effects between combining knowledge fields and technological tools to foster the development of new marketable drugs (ELIASSON; ELIASSON, 1996).

The links between science and technology spheres may articulate diverse and complex configurations given the specificities of each science and innovation systems (CORIAT et al, 2003). The academic literature highlights the importance of universities and research institutes according to three main functions: 1) Education; 2) Research; and 3) Entrepreneurial role of universities (MOWERY; SAMPAT, 2005).

This paper provides an initial assessment of the biopharmaceutical innovation system in Brazil by mapping the main groups of actors that integrate such system and by analyzing the importance and nature of the university-industry relationships in crucial areas to the biopharmaceutical research, development and innovation chain (RD&I). In doing so the paper intends to shed light in the main differences in interaction patterns between national and multinational companies, in view of their demand for R&D projects throughout the different stages of the biopharmaceutical R&D chain, and to highlight the importance of certain S,T&I organizations as the most relevant links due to their centrality in the formation of knowledge networks in biopharmaceutical activities in Brazil.

The paper is organized as follows. Next section presents the methodological aspects. The third section presents the theoretical basis that support the analysis held in the study and a brief overview on the Brazilian scientific and technological infrastructure evolution regarding academic institutions and university-industry relationships. The fourth section is dedicated to the identified industrial actors and the knowledge network analyses resulting from their collaborations with universities and research centers during the 2014-2016 period. The fifth section presents the study main findings, followed by the conclusions and the references.

2. Methodological Aspects

The research is based upon data gathered from the Brazilian National Council for Scientific and Technological Development (CNPq) regarding biological and health sciences. The CNPq database discloses information such as: (1) Number of research groups, research lines, researchers per knowledge areas; (2) General information about enterprises and S&T institutions involved in university-industry relationships, such as: name, identification code, economic activity classifications and geographic location; (3) Types of university-industry interactions defined by final purposes[5]. CNPq disclosures data according to biannual censuses from the year 2000 to 2016, except for the year 2012. To investigate university-industry relationships were collected microdata regarding the period 2014-2016.

Biological and health sciences are composed by 22 knowledge areas[6]. Thirteen closely biopharmaceutical related knowledge field were selected[7]: Biochemistry, Biophysics, General biology, Genetics, Immunology, Medicine, Microbiology, Morphology, Parasitology, Pharmacology, Pharmacy, Physiology and Biotechnology.

It is worth mentioning that as the CNPq dataset is built upon voluntary declarations by the academic research groups. The indicators may be undervalued due to understatement patterns. Also, the dataset is characterized by double counting issues: (1) The same researcher can integrate more than one research group; (2) Enterprises can establish relationships with several research groups; (3) University-industry relationships are classified according to three final objectives. Despite the limitations, the CNPq database is the main reference for university-industry relationship analyses in Brazil.

A sample of Brazilian pharmaceutical and biopharmaceutical enterprises was sort using several sources of information[8]. Alves (2017) provides a list of 137 bioscience firms and 96 biotechnology firms with applications in human health, both constituted as knowledge intensive entrepreneurships (MALERBA; MCKELVEY, 2016). The Brazilian Drug Market Regulation Chamber Annual Statistics (CMED, 2016) provides data concerning 214 national and multinational pharmaceutical companies[9] established in Brazil. The Association of Official Pharmaceutical Laboratories of Brazil (ALFOB, 2018) provides data on 21 associated laboratories. A prospective study has been conducted based on the list of industrial partners from the CNPq 2010 and the 2016 censuses database, concerning enterprises cataloged under The Brazilian National Classification of Economic Activities (CNAE) codes: Experimental Research and Development in the Physical and Natural Sciences (7210)[10] and Manufacture of Medicinal Products for Human Use

[5] Jointly conducted basic research; Jointly conducted applied research; Non-routine engineering activities including prototype development to industrial partner; Non-routine engineering activities concerning developments from partner to group; Software development from research group to industrial partner; Software development from industrial partner to research group; Technology transfer from group to partner; Technology transfer from partner to group; Technical consultancy; Input supply from group to partner; Input supply from partner to group; Human resources training (Companies training academic researchers); Human resources training (Research groups training corporate employees); Other types of relationships.

[6] Biophysics, General Biology, Biochemistry, Botany, Ecology, Pharmacology, Physiology, Genetics, Immunology, Microbiology, Morphology, Parasitology, Zoology, Biotechnology, Physical Education, Nursing, Pharmacy, Physical Therapy and Occupational Therapy, Speech Therapy, Medicine, Nutrition, Dentistry, Collective Health.

[7] For a comprehensive discussion on the methodological issues see: Britto et al. (2012); Vargas and Britto (2014).

[8] Alves (2017), The Brazilian Drug Market Regulation Chamber (CMED, 2016)[8] and The Association of Official Pharmaceutical Laboratories of Brazil (ALFOB[8], 2018)

[9] According to the CMED (2016), 103 companies are involved in production and development of new drugs, 64 are involved in biological drugs segment, 89 are related to generic drugs segment, 159 to biological similar drugs segment and 93 companies are involved in specific-targeted medicines. CMED (2016) does not provide the list of companies related to each market segment, thus all 214 companies were considered, except for 8 companies that were either distribution only companies or lacked basic corporate information such as CNPJ ID numbers.

[10] Bioscience and biotechnology firms may be catalogued under 28 different CNAE codes. Development in the Physical and Natural Sciences (7210) represented the most frequent used code to describe the segment (ALVES, 2017).

(2121). The sample was identified according to the Brazilian National Register of Legal Entities that provides an identification code for each organization established in Brazil (CNPJ ID numbers), enabling the comparison to the Census 2016 university-industry relationships CNPq microdata.

The network analysis is based on graph theory. A graph is a graphic diagrammatic abstract representation of an interconnected structure composed by a set of elements called nodes that are tied in pairs by one or more types of interdependency. The analysis is based on undirected and finite graphs; therefore, the edges have no specific orientation[11]. The networks are mostly bipartite due to data restrictions; thus, enterprises are able to connect to research groups but not to other enterprises. Interactions among research groups were also restricted. The metrics analyzed are: Number of nodes and ties; Centrality metrics indicating the importance of the nodes based on their connections; Betweenness centrality, measuring centrality based on vertices shortest paths; Degree metrics considering the number of ties to other actors in the network; Clustering coefficient, a measuring the degree to which nodes end to cluster together; Hyperlink-Induced Topic Search (HITS) metrics showing hubs and authority relations in the network; and Density that measurers proportion of ties in a network relative to the total number of possible interactions (WASSERMAN; FAUST, 1994). The networks are presented so that colors represent betweenness centrality metrics and node sizes represent hub measurements.

3. Theoretical Basis

Since the emergence of the biotechnology as a new technological paradigm in the late 1970's, the pharmaceutical innovation system has faced a large scale entry of new specialized biotechnology firms dedicated to exploring technological opportunities in very specific niches of knowledge, mostly generated within academic institutions (MCKELVEY; ORSENIGO, 2001). Despite the high and persistent entry rates, the entrants have not become fully integrated drug producers and were not able to reduce the market share of large pharmaceutical incumbent firms. The rising costs of the R,D&I chain; the scale and scope economies in R&D and marketing; the long and costly clinical trials phases; the regulatory affairs and drug approval requirements have favored the emergence of a dense network of collaborations and strategic alliances between heterogeneous organizations to access external knowledge sources and complementary assets that are critical to develop and delivery new drugs (ARORA; GAMBARDELLA, 1995. GRAVAGLIA et al, 2006. BALCONI; LORENZI, 2017. MALERBA; ORSENIGO, 2015).

In the last decades, the biopharmaceutical innovation systems have been marked by evolutionary changes and self-reinforcing dynamics concerning the search for more cost-effective models for drug development and efforts to reduce large companies' internal R&D structure, as well as an increasing tendency towards the global outsourcing of a broad set of technological services regarding drug discovery, clinical trials and production phases (BALCONI; LORENZI, 2017. MALERBA; ORSENIGO, 2015).

The alliances involving big pharmaceutical companies, biotechnology firms and, remarkably, academic institutions and public laboratories enable firms to benefit from governmental funding and increased flexibility (SCHUHMACHER et al, 2016. BALCONI; LORENZI, 2017). The biopharmaceutical innovation system is filled with a growing number of very specialized biotechnology firms with limited internal capabilities that rely constantly on the funding provided by large global biopharmaceutical companies and on specialized services provided by Contract Research Organizations (CROs) and Contract Manufacturing Organizations (CMOs). The industrial infrastructure composed by very specialized capabilities' carriers facilitates entry conditions and firm heterogeneity, alongside with a concentration tendency due to increased mergers and acquisitions operations. The biopharmaceutical R,D&I chain displays a tendency towards technological specialization and vertical disintegration, as it becomes increasingly advantageous to outsource specific technological task to highly specialized know-how intensive partners (BALCONI; LORENZI, 2017. SCHUHMACHER et al, 2016).

[11] The undirected graph choice is justified by the fact that the database classifies each established link up to three different types of interactions and 67% of total types of interactions are undirected edges. Thus, the analytic benefits of using directed graphs networks would be quite limited.

The vertical disintegration process has been accompanied by the geographic expansion of drug developmental stages and manufacturing activities enabling the incorporation of new participants from emerging countries. Large multinational pharmaceutical and biotechnology companies are increasingly focused in emerging markets, while biopharmaceutical companies from emerging markets target global markets in specific niches – such as generic and similar drugs – and integrate themselves in global value chains thought technological services provision (REZAIE; SINGER, 2010. REZAIE et al, 2012. BALCONI; LORENZI, 2017). Even though biopharmaceutical activities have been fostered in many countries by promoting technology transfer, academic entrepreneurship, venture capital provision and property rights regulations, attempts to replicate developed countries experiences have most often failed due to the multiple complex national idiosyncrasies of each System of Innovation (MALERBA; ORSENIGO, 2015).

Developing countries specialization patterns and potential virtuous insertion into global value chains reflects a specific combination of multiple complex aspects of national innovation systems regarding industrial capacity, skilled labor disposal, national institutional arrangements, universities and research institutes, knowledge spillovers and networks, country-specific resources, public provision of health services and medicines and other national economic, political, social, institutional and historical specifies (REZAIE; SINGER, 2010. REZAIE et al, 2012. BALCONI; LORENZI, 2017. MALERBA; ORSENIGO, 2015). Yet, excellence in academic research in a broad and interdisciplinary set of knowledge areas, the integration of highly developed scientific skills to all innovative process dimensions and public funding to biomedical research are crucial elements to develop biopharmaceutical activities (MALERBA; ORSENIGO, 2015).

Traditionally, health enterprises in developing countries – like China, India and Brazil – have focused their activities in low cost manufacturing, imitation and adaptation strategies of products originally developed in higher income countries, as a feasible way to offer quality products at affordable prices to attend domestic and global health needs. A common strategy has been to concentrate efforts in products that are financially and technically less demanding – enabling internal competence and capabilities building process in R&D, manufacturing and distribution, as well as revenues improvements – before venturing into more sophisticated initiatives. Over the past decades, many emerging market' firms have managed to leverage innovation processes and to reduce production costs, strengthening domestic industries and enabling firms to pursue riskier technological activities towards neglected diseases[12], noncommunicable chronic diseases, diagnosis and other therapeutic areas. However, few enterprises in developing countries are set to develop and deliver novel drugs to global markets, as they often lack the technical know-how and financial resources required to intake radical innovation processes and associated risks. Promising innovation leads in emerging countries are more likely to focus on specific pipelines or collaborative developments schemes with global established corporations (REZAIE; SINGER, 2010. REZAIE et al, 2012. BALCONI; LORENZI, 2017).

Overall, companies from emerging markets have expanded domestic and global population access to health products based on cost advantages models and increased products affordability, however these firms cannot eliminate health access gap and expand targeted markets on their own (ROEMER-MAHLER, 2014). While technology transfer through foreign direct investment, reverse engineering strategies, alliances, and cross-border partnerships have played key role to pharmaceutical sector growth in developing countries, indigenous innovation models and capabilities building processes have gained increased attention in countries like Brazil, South Africa, China and India (REZAIE; SINGER, 2010. REZAIE et al, 2012).

3.1 The Brazilian biopharmaceutical innovation system

The Brazilian biopharmaceutical innovation system is populated by different sets of interconnected companies and institutions. Health and S,T&I institutions, public policies, state procurement policies to attend the national health system demands, regulatory agencies, institutional arrangements, suppliers, hospitals engaged in clinical trials and other R,D&I activities, intermediary and final users are some of the

[12] Tropical neglected diseases and epidemies that affect mostly developing countries may represent an important window of opportunities for enhancing indigenous innovative capacity of domestic enterprises, as global pharmaceutical established corporations headquartered in high income countries tend not to develop drugs targeting diseases that are most common to affect only low income countries (REZAIE; SINGER, 2010).

key components that integrate and shape the Brazilian biopharmaceutical innovation system (VARGAS et al, 2013; VARGAS, 2017). Despite the acknowledged importance of the broad set of actors, linkages and context specificities, this study is mainly focused on industrial actors and their connections to S&T institutions, remarkably: i) biotechnology and bioscience firms operating in very specific niches of the biopharmaceutical R,D&I chain, ii) public laboratories, (iii) multinational pharmaceutical companies, (iv) national pharmaceutical companies and v) universities and research centers.

The Brazilian health biotech industry is populated by a growing number of young, small sized enterprises dedicated to performing R,D&I activities and to provide specialized technological services based on recent advances in life and health sciences. The companies are highly concentrated in the southeast region of Brazil. Most firms are still in the pre-operational phase; mainly controlled by national capital and strongly related to national academic institutions. There are approximately 300 bioscience firms and between 175 and 240 biotechnology firms in Brazil dedicated to many fields, such as human health, reagents, agriculture, animal health, bioenergy and environment. The companies dedicated to human health correspond to an average 40% of the total number of companies. A recent assessment of the Brazilian health biotech sector has identified and mapped 271 bioscience companies, 137 health bioscience companies and 96 health biotechnology companies (ALVES et al., 2018. ALVES, 2017).

Public research and production laboratories represent an important feature of Brazilian Health Industrial Complex[13]. The public infrastructure for research and production of vaccines and essential drugs dates to the beginning of the 20th century and regards the need to combat epidemics such as bubonic plague, yellow fever and cholera in Brazil (CHAVES et al, 2016). The first public institutes created in Brazil were Butantan Institute in 1899 and *Manguinhos* Serotherapies' Institute[14] in 1990. Nowadays, there are 22 public laboratories currently operating in Brazil that are responsible for attending about 80% of the Brazilian public demand for vaccines and 10% of the produced drugs amount in Brazil (GADELHA et al, 2012; REZAIE et al, 2012).

The large multinational pharmaceutical laboratories, established in Brazil since the 1950's, held around 51,49% of the Brazilian pharmaceutical market in 2018 (SINDUSFARMA, 2018). Historically, the multinational companies bring their production and distribution stages to Brazil but are most likely to keep their innovative efforts concentrated in their headquarters worldwide. Pharmaceutical world leaders tend to spend an average 20% of their sales revenues in R&D activities in their origin countries (PARANHOS et al., 2018). According to data retrieved from the Brazilian Innovation Survey, multinational companies invested only 0,38% to 1,4% of their sales revenues in R&D activities in Brazil from year 2000 to 2014, while the national pharmaceutical laboratories accounted for 0,71% to 5,1% invested sales revenues in the same period (SZAPIRO et al., 2017).

Even though pharmaceutical national companies' R&D expenditures are still limited compared to the pharmaceutical world leaders, the local production of generic drugs has significantly increased the share of national firms in the Brazilian pharmaceutical market and enabled critical technological learning processes. The national laboratories share in the Brazilian pharmaceutical market increased from 32% in 2003 (GADELHA et al., 2012), to 42,99 % in 2012 and 48,51% in 2018 (SINDUSFARMA, 2018). The innovation rate in pharmaceutical activities has increased from 46,8% in 1998-2000, to 63,7% in 2006-2008 and 52,2% in 2012-2014, overcoming the average industrial innovation rates in Brazil. And the amount of innovative expenditures destinated to internal and external R&D efforts increased from 26,1% in the year 2000 to 62% in 2014 according to data retrieved from the Brazilian Innovation Survey (SZAPIRO ET AL, 2017).

Brazilian pharmaceutical companies' strategies toward biological drugs production are mostly directed to biosimilars or bioequivalent market niche. Biosimilar drugs are defined as "near-duplicates" of patent-expired biopharmaceuticals. Due to the technological complexity involved in biotechnological processes,

[13] The Brazilian Health Industrial Complex (CEIS) is an analytical dimension of the Brazilian National System of Innovation in Health aimed to focus on productive components dedicated to the provision of health goods and services and involved in the dynamics of health innovation in Brazil. The adoption of the CEIS concept makes it possible to isolate components of the health complex in specific subsystems by identifying sectors of activity and technological paradigms, such as chemical, biotechnological, mechanical, electronic and materials (GADELHA ET AL., 2013).

[14] Which later became the Oswaldo Cruz Foundation (FIOCRUZ).

even the copying activities require amassing scientific and technological capabilities (VARGAS, 2017; GOMES, 2014).

The entrance into biological drugs' market involved, in some cases, the creation of pharmaceutical joint ventures. Bionovis and Orygen are two joint ventures in pre-operational phase created in 2012. Bionovis was created by the national pharmaceuticals Aché, EMS, Hypermarcas and União Química and has established technical collaboration agreements with the public laboratory Bio-Manguinhos – integrated in Oswaldo Cruz Foundation (FIOCRUZ) – and with two world market companies Janssen and Merck. Orygen was created by the national companies Biolab and Eurofarma and has collaboration agreements with EPIRUS and Pfizer. The joint ventures have jointly received 401 million Reais (approximately US$ 105 million) investments from the Brazilian National Economic and Social Development Bank (BNDES) for funding their industrial units and developing innovation, production and marketing activities. It is expected that Orygen launches five and Bionovis launches eight biosimilar products in the national market in the next few years (BNDES, 2016, EXAME, 2016).

Despite the focus in biosimilar drugs, some established companies within national market – like Cristália, Eurofarma and Aché Laboratories – are deploying efforts to incorporate biotechnological routes[15] in manufacturing large molecules and in innovative drugs discovery (VARGAS, 2017; REZAIE et al, 2012).

National biopharmaceutical innovative efforts have been strongly encouraged by public policies in Brazil due to its strategic importance to the Brazilian Health Industrial Complex sustainable growth and technological catch-up efforts. A systemic perspective of the industrial and the ST&I policies in the health sector has allowed the adoption of a wide range of instruments to support the development of biopharmaceutical activities in Brazil. Such instruments have involved not only direct promotion to R&D activities in national companies and public investments on S&T infrastructure, but also other strategies to support innovation, such as the review of the regulatory framework and the use of government purchasing power. The industrial policy mechanisms and S,T&I incentives are mostly aimed at supporting national pharmaceutical companies' innovative efforts and to broaden biopharmaceutical R,D&I chain in the country (VARGAS et al, 2013; VARGAS. BRITTO, 2014).

3.2. Scientific and technological capabilities in biopharmaceutical related knowledge areas in Brazil.

Although not directly involved in production activities, universities and research centers play a central role in the Brazilian Biopharmaceutical Innovation System. In addition to teaching and research activities, universities operate as a catalytic center for information flows from their own research and from interactions with companies, regulatory agencies, hospitals, clinics, medical centers and other actors that transmit new demands to the national pharmaceutical industry (ALBUQUERQUE; CASSIOLATO, 2002). The knowledge transfer between academic and productive spheres is particularly important to enable the development of products and services that are adequate to attend the specific phytosanitary standard requirements in Brazil. Strengthening collaborative relationships is also key to promote activities increasingly integrated to the Brazilian Health Industrial Complex and to strengthen innovation capacity (BRITTO et al, 2012).

Brazil has a wide range of academic institutions with consolidated research groups in biology and health sciences. The national share in internationally indexed publications grew at 9,6% average annual rate from 2000 to 2015, indicating the S&T infrastructure strengthening tendency (ALVES, 2017). The current stage of development of biotechnology in Brazil is largely due to the human resource training policy promoted by institutions such as the Higher Education Personnel Improvement Coordinator (CAPES) and CNPq. It is important to highlight that the industrial and S,T&I policies also incorporated instruments to stimulate the interactions between the industry and the universities and research centers. (BRITTO et al, 2012; VARGAS. BRITTO, 2014).

[15] Pharmaceutical chemical and biotechnological routes are complementary. Amassing capabilities in chemical procedures are often required to enable the adopting of biotechnology in pharmaceutical R&D and production activities (ALVES, 2017).

The data collected from the CNPq directory from 2000 to 2016, shows a significant growth in the number of research groups, research lines and number of researchers dedicated to knowledge fields in biological and health sciences. Table 1 shows that the number of research groups in critical knowledge areas grew (13%, average) during 2000-2016 period, as well as the number of research lines (17%) and the number of researchers (21%). The thirteen critical knowledge areas selected for the analysis represented an average 15% of total research groups in the CNPq directory, while biological and health correspond to 12% and 16% respectively. The data points to an average growth of selected areas that is overlapped by the average growth of health sciences and the entire set of CNPq areas. As a result, the share of selected areas research groups in comparison to CNPq is decreasing over the years, going from 17% in the 2000 to 12% in 2016 regarding research groups; from 18% to 13% regarding research lines and from 15% to 12% regarding the number of researchers in the analyzed period.

Table 1 - Number of research groups, research lines and researchers in Biological and Health Sciences

Year / Knowledge grand areas		2000	2002	2004	2006	2008	2010	2014	2016	Total Growth	Average Growth
Research Groups	Biological sciences	1720	2126	2561	2624	2696	3108	3650	3668	113%	12%
	Health sciences	1832	2513	3371	3610	3961	4573	5609	5877	221%	19%
	Selected Areas	2055	2599	3276	3358	3503	3894	4565	4589	123%	13%
	CNPq Total	11760	15158	19470	21024	22797	27523	35424	37640	220%	18%
Research Lines	Biological sciences	5726	7727	10167	11184	12010	14585	17086	17265	202%	18%
	Health sciences	5984	8107	11208	12610	14382	16728	21196	22263	272%	21%
	Selected Areas	6743	9209	12401	13446	14821	16953	20453	19649	191%	17%
	CNPq Total	38126	50473	67903	76719	86075	106715	139154	147392	287%	22%
Researchers	Biological sciences	8731	11133	14911	16787	18790	23390	31462	32948	277%	21%
	Health sciences	10607	13498	20424	24323	28159	34375	47069	50854	379%	26%
	Selected Areas	10144	12700	18064	20589	23493	28007	37694	37348	268%	21%
	CNPq Total	66786	83850	119205	138278	159948	205445	293991	321797	382%	26%

Source: Elaborated by the authors based on the data published by CNPq directory (2018)

The existing gap between national scientific output in strategic knowledge areas and the technological applications is one of the main bottlenecks for national industry's innovative capacity building. Despite the strong scientific research capacity in the country, the research community is strongly oriented to pure academic activities and has an uneven development according to the area of activity (CHIARINI et al., 2013).

The number of research groups that reported active relationships with the productive sector grew 72% on average in selected areas from the year 2002 to 2016, overlapping in great amount the 54% average growth rate experienced by CNPq total interactions (Table 2). However, the growth in biological sciences (82%) is more prominent than the selected areas growth in the same period. The proportion of selected areas in CNPq collaborative groups grew from 11% in 2002 to 15% in 2016.

Table 2 – Number of research groups engaged in university-industry collaborative relationships (2002-2016)

Year / Knowledge areas		2002	2004	2006	2008	2010	2014	2016	Total Growth	Average Growth
Biologica l sciences	Interactive Groups	119	224	244	276	352	1461	2045	1618%	82%
	% Total	6%	9%	9%	10%	11%	26%	35%	522%	
	% CNPq	9%	1%	10%	10%	10%	16%	16%	73%	
Health sciences	Interactive Groups	116	236	275	332	430	1350	1721	1384%	69%
	% Total	5%	7%	8%	8%	9%	37%	47%	916%	
	% CNPq	9%	1%	11%	12%	12%	14%	14%	50%	
Selected Areas	Interactive Groups	145	249	279	313	397	1512	1956	1249%	72%
	% Total	6%	13%	8%	9%	10%	33%	43%	663%	
	% CNPq	11%	2%	11%	11%	11%	16%	15%	35%	
CNPq Total	Interactive Groups	1279	2151	2509	2726	3506	9348	12681	891%	54%

Source: Elaborated by the authors based on the data published by CNPq directory (2018)

The academic laboratories' lack of good practices certification and delays in admirative procedures constrain university-industry knowledge transfers. Challenges also arise from structural problems in the Brazilian innovation system. S&T institutions often act as technological service providers due to the absence of private companies in some critical stages of pharmaceutical R&D value chain. Historically, the low innovative patterns of generic-based Brazilian pharmaceuticals impact the quality and the duration of university-industry relationships. Many university-industry interactions in Brazil arise from national private companies' need to solve specific problem in R&D stages, however these problems are often low complex and easily solved based on existing knowledge. Despite the existence of highly qualified personnel in the industry, only 11% of full time scientist located in pharmaceuticals companies' R&D laboratories in 2014 in Brazil had post-graduation degrees. Hiring graduate degree students could improve national pharmaceutical absorption capacity and ease the access to external sources of knowledge, as graduates may act as knowledge gate keepers building bridges with academic research groups. However, the issue is mostly associated with limited private companies' strategies towards innovation rather than to failures in the Brazilian academic system (PARANHOS et al., 2018; CHIARINI et al., 2013; BRITTO et al, 2012).

4. Collaborative relationships between research groups and the industrial sphere: A Knowledge Network analysis

According to the proposed methodology, were identified 385 productive actors: 102 small and medium sized health bioscience firms, 148 Brazilian pharmaceutical companies[16], 23 Brazilian Public Laboratories[17] and 112 multinational pharma companies established in the country. Most of the companies and public laboratories identified in the sample are in Brazilian southeast region[18], especially in São Paulo (52%) and Rio de Janeiro (16%).

A low percentage (27%) of the 385 sampled actors established interactions with academic research groups according to CNPq 2016 data: 243 university-industry relationships were established between 103 industrial partners and 63 Brazilian S&T institutions. There are no available patterns to evaluate the university-industry frequency, but the results are considered rather lower than expected considering knowledge-based activities.

As many Public Laboratories operate both drugs and vaccines producers and as S&T institutions, some interactions may regard strictly inter-academic relationships[19].

Table 3 shows the obtained results. Public Laboratories concentrate most of the interactions, as 12 laboratories represent 38% of total interactions. National laboratories represented 84% of total interactions and accounted for 78.6% of all laboratories engaged in university-industry relationships. National pharmaceutical companies also established a higher indicator of interaction per interactive partners (1.9) compared to multinational pharmaceutical companies (1.7).

---

[16] Including 3 Brazilian pharmaceutical joint-ventures: Bionovis, Orygen and Supera Pharma.

[17] The biotechnology state owned companie Biobrás was incorporated in the public laboratories list.

[18] Many companies are established in more than one location. Were identified 439 geographical coordinates referred to the 385 sample.

[19] Interactions established by 3 Public laboratories were not considered because they have shared Universities' CNPJ IDs: CERTBIO, IPEFARM and NUPLAM. FIOCRUZ interactions not identified as BIOMANGUINHOS or FARMANGUINHOS were discarded to avoid university-university interactions counting issues. Table 3 indicators consider only 20 Publics Laboratories and 382 sample size. The 27% interactive indicator was only marginally affected.

Table 3 - Identified productive elements and interactions with CNPq research groups					
	Bioscience firms	Brazilian pharmaceutical companies	Public labs	Multinational Pharmaceutical companies	Total
Number	102	148	23	112	385
Number of interactions	50	63	92	38	243
Number of interactive partners	35	34	12	22	103
% interactive partners/number of actors	34%	23%	60%	20%	27%
% Total interactions	21%	26%	38%	16%	100%
% interaction per actor	1.4	1.9	7.7	1.7	2.4

Source: Elaborated by the authors based on the presented methodology and the data published by CNPq directory (2018)

Most relevant knowledge areas in university-industry relationships were pharmacy (24%), medicine (18%), biochemistry (14%) and microbiology (9%). Pharmacy was highly relevant for bioscience firms (20%) and Brazilian pharmaceutical companies (55%) . Biochemistry, genetics and microbiology were relevant areas for bioscience firms (48%) and public laboratories (36%). Medicine was critical to the multinational pharmaceutical companies (53%), and to a lesser extent to public laboratories (20%). While interactions in pharmacy, biochemistry, genetics and microbiology may be related to the conduction of R&D activities in new compounds, interactions in medicine were probably related to the importance of clinical trials and product adequacy procedures. Further empirical inquiries are suggested to verify these assumptions. Biotechnology itself has only been introduced as a CNPq discipline in the year 2016, thus it is not yet significant.

The thirteen selected knowledge areas represent 92% of total interactions, as shown in Table 4. Thus, the selected areas represent a good proxy for knowledge areas that are critical to biopharmaceutical activities.

Table 4 - Interactions per knowledge areas and groups of actors					
Knowledge areas	Bioscience firms	Brazilian pharmaceutical companies	Public labs	Multinational Pharmaceutical companies	Total
Biophysics	1		2		3
General biology	1				1
Biochemistry	15	4	14	2	35
Biotechnology			1		1
Botany				1	1
Ecology			1	1	2
Pharmacy	10	35	12	2	59
Pharmacology	2	11	7		20
Physiology	2				2
Physiotherapy				1	1
Genetics	6		8	3	17
Immunology	2	4	3		9
Medicine	4	2	18	20	44
Microbiology	3	3	11	5	22
Morphology	1		4		5
Nutrition		2			2
Odontology	2	1		2	5
Parasitology			5	1	6
Collective health	1	1	4		6
Zoology			2		2
Total interactions	50	63	92	38	243
Selected knowledge areas	47	59	85	33	224
% Selected areas	94%	94%	92%	87%	92%

Source: Elaborated by the authors based on the data published by CNPq directory (2018)

The university-industry relationships took place involving mostly industrial partners located in São Paulo (42%), Rio de Janeiro (16%), Minas Gerais (15%) and Paraná (12%) and S&T Institutions located in Rio de Janeiro (26%) and São Paulo (24%).

There were 98 interactions involving industrial partners and S&T institutions located in different federal units and 145 interactions within the same federal units. Most frequently S&T institutions involved in inter-state interactions were the Oswaldo Cruz Foundation – FIOCRUZ (16), the Federal University of

Pernambuco – UFPE (8), the Federal University of Rio de Janeiro – UFRJ (7), Federal University of Minas Gerais – UFMG (5) and the Brazilian National Commission of Nuclear Energy – CNEN (5). Inter-state interactions are potentially correlated with research quality and academic excellence.

Table 5 shows university-industry interactions classified by types if relationship, considering three possible types for each interaction established. During 2014-2016 period, 382 types of relationships were reported in the database. Basic and applied research were the most frequent types of interactions (58% of total types of interactions). Basic research was more frequent among public laboratories (55) and multinational pharmaceutical companies (20), while applied research occurred more often within bioscience firms (25), national pharmaceutical companies (40) and public laboratories (37).

Technology transfer from group to partner and input supply from partner to group were also significant. However, knowledge must flow in both ways (from group to partner and from partner to group) to enable effective technological transfers. There were low evidences of both ways' technological transfers (only 8 pairs of tied nodes).

Table 5 - Types of Interactions per groups of actors

	Bioscience firms	Brazilian pharmaceutical companies	Public Labs	Multinational Pharmaceutical Companies	Total
Technical consultancy	3	4	1	5	13
Non-routine engineering to group	0	0	0	1	1
Input supply from group to partner	1	1	1	0	3
Input supply from partner to group	5	14	9	11	39
Other types of relationships	10	3	6	1	20
Applied research	25	40	37	13	115
Basic research	15	17	55	20	107
Technology transfer - group to partner	13	18	14	3	48
Technology transfer - partner to group	5	5	3	1	14
Human resources training – researchers	2	4	2	1	9
Human resources training - employees	4	1	8	0	13
Total types of relationships	83	107	136	56	382

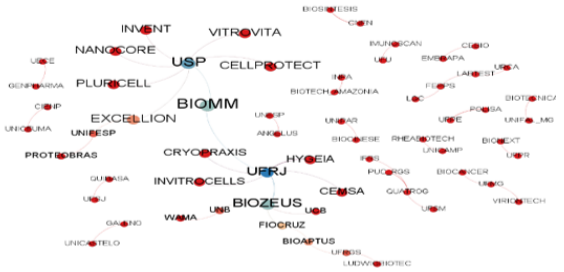
Source: Elaborated by the authors based on the data published by CNPq directory (2018)

The knowledge networks are composed by multiple interactions between enterprises, public laboratories and S&T institutions. The analysis held considered subgraphs for each type of industrial partner, enabling the evaluation of different patterns among them. The main network statistics are summarized in Table 6.

The subgraph composed by interconnected bioscience firms and S&T Institutions is shown in Figure 1. The network main hubs were the companies Biomm (0.418) and Biozeus (0.318), besides the S&T Institutions: USP (0.362); UFRJ (0.289). Most important nodes according to betweenness centrality measures were UFRJ (158.0); USP (137.0); Biozeus (119.0); BIOMM (117.9) and, to a lesser extent, FIOCRUZ (57.0). When weakly connected components are excluded from the network (Figure 1.1), it is possible to identify: the importance of Biomm in connecting indirectly USP to UFRJ; the star structure formation around Biozeus, UFRJ and USP. The star structures around central nodes and the absence of clear cluster structures are a direct consequence of the database limitations regarding the bipartite networks.

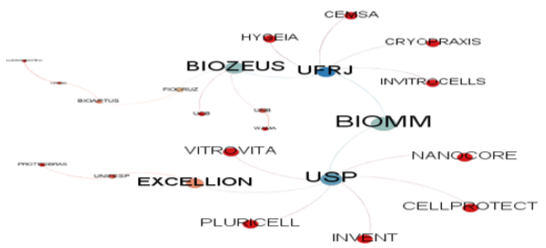
Figure 2 shows the Brazilian pharmaceutical companies and S&T Institutions subgraph. The network main hub was the pharmaceutical company Cristália (0.565). Other important hubs are UFPE (0.391), USP (0.256) and BUTANTAN (0.254) – which operates as both public laboratory and research center. It is possible to identify a star structure configured around the Federal University of Rio Grande do Sul (UFRGS), even though this structure is completely disconnected from the graph main tree. When weakly connected components are excluded (Figure 2.1), it becomes easier to identify: the multiple undirected connections between Cristália, USP and Butantan; and the direct connections between Cristália and the star UFPE.

Figure 1 – Bioscience SME Firms and S&T institutions network



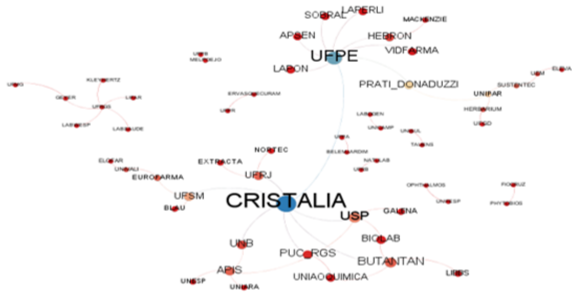
Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 1.1 – Bioscience SME Firms and S&T institutions network (weakly connected components excluded)



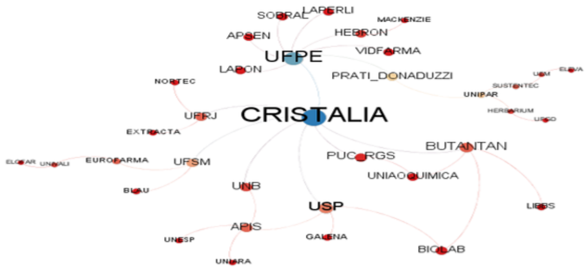
Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 2 – Brazilian pharmaceutical companies and S&T institutions network



Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 2.1 – Brazilian pharmaceutical companies and S&T institutions network (weakly connected components excluded)



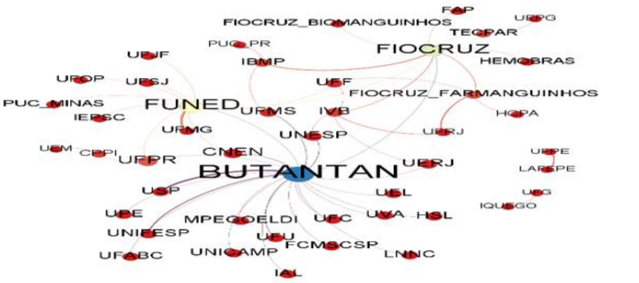
Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 3 shows Brazilian Public Laboratories and S&T institutions subgraph. It is important to remark that some laboratories also operate as research institute and even as teaching facilities. The interactions shown in Figure 4 were selected to avoid strictly academic linkages. It is, however, difficult to isolate productive activities from research and academic ones. The main hubs were BUTANTAN (0.604), Ezequiel Dias Foundation – FUNED (0.351), FIOCRUZ (0.294), the Federal University of Paraná – UFPR (0.193) and CNEN (0.186). The average clustering coefficient of the network is 0,095 and it presents total 3 triangles, reflecting a more complex network than all the other subgraphs[20], which displayed null average clustering coefficient. Most relevant institutions based on clustering coefficient metrics were CNEN (1.0), UFPR (0.333), FUNED (0.054), FIOCRUZ (0.027), BUTANTAN (0.014). When weakly connected components are excluded (Figure 3.1), it becomes clear the importance of CNEN and UFPR for connecting the stars BUTANTAN and FUNED; the role played by UNESP, IBMP, IVB, UFRJ, UFMS and UERJ in indirectly connecting BUTANTAN to FIOCRUZ; and also the importance of UFF acting as a bridge between FUNED and FIOCRUZ.

Figure 4 shows the multinational pharmaceutical companies established in Brazil and national S&T institutions subgraph. The main hubs were GlaxoSmithKline (0.465) and USP (0.367), followed by the companies Merck Sharp and Dohme (0.252), Elli Lilly (0.222), AtraZeneca (0.222), Abott (0.222) Merk (0.216) and the universities USP (0.367), UFRJ (0.366), The Federal University of São Paulo – UNIFESP (0.181) and UFMG (0.166). Figure 4.1 display the reduced network. The structure analysis highlights the importance of AstraZeneca, Elli Lilly, Abott and UNIFESP in connecting the stars USP to UFRJ; and the role played by MSD and MERK working as bridges between UFMG and USP.

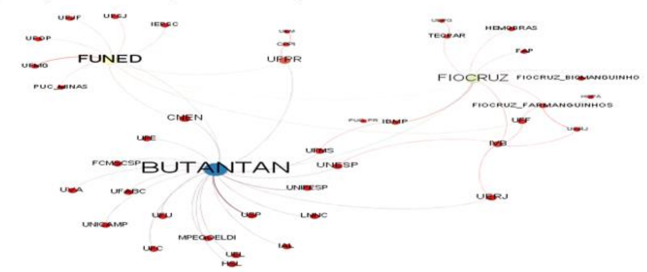
[20] The positive clustering coefficient is a consequence of the fact that Public Laboratories may operate as both S&T institutions and productive actors. So that Network 3 is not necessarily bipartite.

Figure 3 – Public laboratories and other S&T institutions network



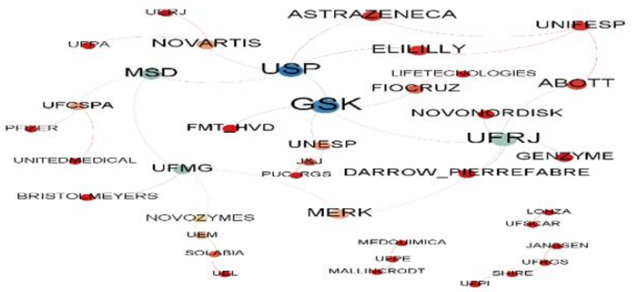
Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 3.1 – Public laboratories and other S&T institutions network (weakly connected components excluded)



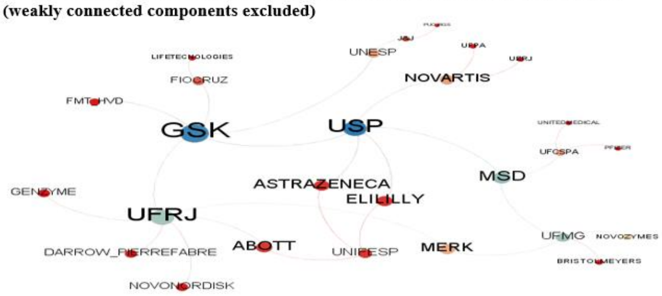
Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 4 – Multinational pharmaceuticals and national S&T institutions network



Source: Elaborated by the authors based on the data published by CNPq directory (2018)

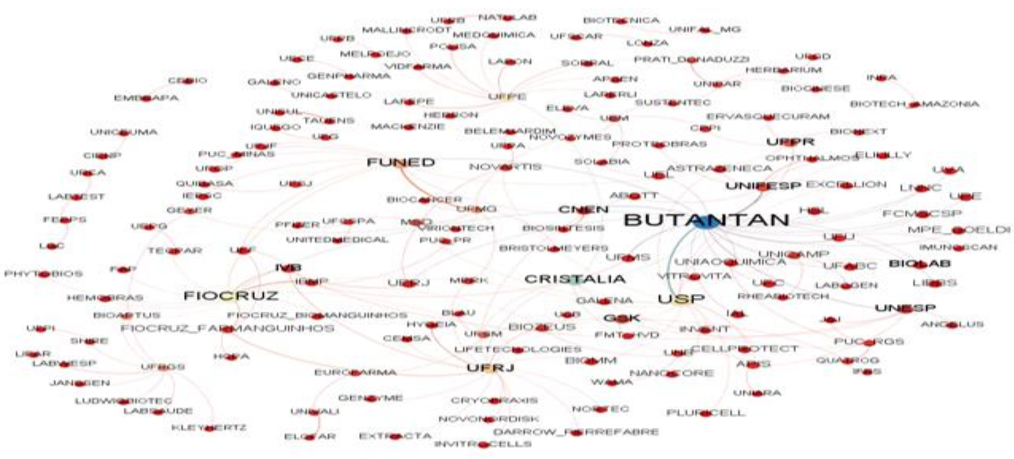
Figure 4.1 Multinational pharmaceuticals and national S&T institutions network (weakly connected components excluded)



Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 5 displays the complete graph considering the five previously presented subgraphs. The network gathered 164 nodes and 185 ties. The average clustering coefficient was 0.026 and there were 5 triangles. The main hubs in the knowledge network became even more visible: BUTANTAN (0.527), USP (0.310), FIOCRUZ (0.265), FUNED (0.230), UFRJ (0.188) and UNESP (0.161). The national pharmaceutical company Cristália (0.205) and the multinational GlaxoSmithKline (0.157) appear as highly important hubs. The betweenness centrality measures also indicated the importance of UFPE (1932.95), UFMG (1082.45) and UFGRS (1071.46), aside from BUTANTAN (4403.61), Cristália (3166.38), FIOCRUZ (2315.15), USP (1980.58), UFPE (1932.95), UFRJ (1647.46) and FUNED (1348.78). Considering the clustering coefficient, the national pharmaceutical companies Biolab (1.0) and Cristália (0.047), alongside with CNEN (0.33), UFPR (0.1), FUNED (0.054), BUTANTAN (0.016), USP (0.014) and FIOCRUZ (0.010) were highly important nodes for connecting two or more important hubs in the network.

Figure 5 – Biopharmaceutical enterprises and national S&T institutions network



Source: Elaborated by the authors based on the data published by CNPq directory (2018)

The interactive S&T institutions also interacted with other universities and research centers. Figure 6 shows the previous network including strictly academic relationships between Brazilian S&T institutions in biological and health sciences[21]. The extended graph gathered 401 nodes and 1686 ties. The average clustering coefficient was 0.667 associated with 4637 total triangles. Biopharmaceutical industrial actors

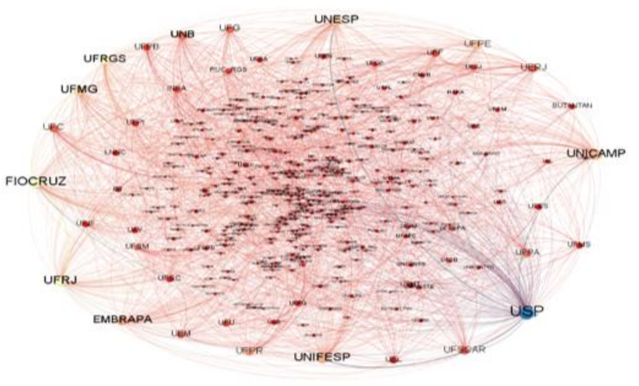
[21] Were considered only relationships in which identified S&T institutions engaged as partners with other S&T institutions.

are, thus, indirectly connected to a broader and much more complex knowledge network in national S&T sphere. Some S&T institutions – such as USP, FIOCRUZ, UFRJ, The State University of Campinas – UNICAMP, UNESP, UNIFESP, UFMG and UFRGS – operate as knowledge gatekeepers, connecting many knowledge sources around them. Betweenness centrality measures highlighted the critical role of USP (16934.29), FIOCRUZ (9090.22), UFRJ (8768.23), UFRGS (8302.08) and UFMG (6933.07).

Strictly academic linkages were also identified within international context. Figure 7 includes interactions established between interactive Brazilian S&T institutions and foreign partners in biological and health sciences. The network is composed by 725 nodes and 1049 ties. The average clustering coefficient: 0.006 and there are 6 triangles. Brazilian S&T institutions – such as USP, FIOCRUZ, UFRJ and BUTANTAN – operate as critical gatekeepers integrating the national S&T infrastructure to foreign external sources of knowledge, and indirectly linking the Brazilian Biopharmaceutical Innovation System to the knowledge created within highly respected S&T institutions abroad[22].

Relationships involve 560 Foreign Institutions, such as: Université Laval (8), Escola Superior de Enfermagem de Coimbra (7), Karolinska Institutet (7), University of British Columbia (7), University of Oxford(7), Harvard Medical School (6), McGill University (6), Universidad Autónoma de Madrid (6), Università di Bologna (6), University of Groningen (6), Johns Hopkins Bloomberg School of Public Health (5), Kings College - Strand Campus (5), Maastricht University (5), National Institutes of Health - USA (5), Universidad de Buenos Aires (5), Universidad de Chile (5), Universidade de Évora (5), Universidade do Minho (5), Université Claude Bernarde Lyon 1 (5), University of Cambridge (5), University of Southern California (5), Yale University (5), Administración Nacional de Laboratorios e Institutos de Salud (4), Centers for Disease Control and Prevention (4), Harvard School of Public Health (4), Harvard University (4), Institut Pasteur (4), Instituto de Salud Carlos III (4), Johns Hopkins School of Medicine (4), National Cancer Institute - USA (4), Pan American Health Organization (4), The University of Sydney (4), Universidad de la Republica Uruguay (4), Universidad de Zaragoza (4), Universidad Nacional de Córdoba - Argentina (4), Universidade Nova de Lisboa (4), Universita degli Studi di Napoli Federico II (4), Université de Montreal (4), University College (4), University of Florida (4), University of Liverpool (4), University of Münster (4), University of Pittsburgh (4), University of York (4), Vanderbilt University (4), Washington University School of Medicine (4), World Health Organization (4).

Figure 6 – Biopharmaceutical enterprises and national S&T institutions network (interactions between S&T national institutions considered)



Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Figure 7 – Brazilian biopharmaceutical enterprises and national S&T institutions network, considering interactions with Foreign institutions

Source: Elaborated by the authors based on the data published by CNPq directory (2018)

5. Main findings

Brazil has a consolidated S&T infrastructure characterized by a growing number of research groups, research lines and researchers during the period 2000-2016. A major challenge is the current misalignment

[22] These institutions also operate as central nodes according to betweenness centrality measures.

between S&T research indicators and technological applications in innovative efforts regarding activities considered strategic by policy makers and policy goals, as well as an uneven advance in soft sciences[23] and hard sciences[24] (CHIARINI et al, 2013). The decrease in the ratio of the thirteen selected knowledge areas in health and biological sciences considered critical to foster biopharmaceutical R,D&I value chain activities compared to the total CNPq knowledge areas in 2000-2016 period corroborates the misalignment argument. Despite the loss in terms National S&T indicators share, the overall increase in university-industry relationships points to an indigenous capability building process undertaken in knowledge areas that are critical to support Biopharmaceutical developments in Brazil.

The analysis held is based on a 385 sized sample of industrial actors allegedly involved in biopharmaceutical activities in Brazil, composed mainly by bioscience firms (26%), Brazilian pharmaceutical companies (38%) and multinational companies established in the country (29%). Most of the sampled companies and public laboratories are established in the Brazilian southeast region, mainly in São Paulo and Rio de Janeiro.

According to CNPq 2016 database, 103 biopharmaceutical industrial partners established 243 interactions with 63 universities and research centers in Brazil during the period 2014-2016. The considerable low university-industry interaction rate (27%) may reflect either a gap between S&T output and Industrial technological applications – due to a low innovative pattern associated to several pharmaceutical companies –; a university bias towards strictly academic activities or a consequence of the CNPq Directory understatement pattern. Further studies are suggested to evaluate the impacts of self-declaration model in the CNPq interaction database.

Most interactions were established within pharmacy (24%), medicine (18%), biochemistry (14%) and microbiology (9%) knowledge areas. While bioscience firms, Brazilian pharmaceutical companies and public laboratories interacted mostly with research groups from pharmacy, biochemistry, genetics and microbiology areas, multinational companies interacted mostly with groups involved in medicine knowledge area. The first indicates active R&D activities in new biopharmaceutical compounds being conducted by Brazilian companies and public laboratories, while the latter indicates potential multinational involvements in clinical trials and product adequacy procedures. Further empirical studies are suggested to verify the correlation between knowledge areas and possible technological applications in industrial sphere.

The geographic dispersion of interactions followed the patterns of concentration displayed by sampled companies, mainly located in the Brazilian southeast region. Industrial partners were mostly located in São Paulo (42%), Rio de Janeiro (16%), Minas Gerais (15%) and Paraná (12%), while interactive S&T Institutions were often based in Rio de Janeiro (26%) and São Paulo (24%). Locational proximity plays a distinguished role in the university-industry relationships as 60% of interactions have been established within the limits of the most prominent Federal Units. The 40% inter federal unit interactions indicates the importance of high quality centers such as FIOCRUZ and UFRJ.

Concerning the types of interaction, 58% of total relationships regarded jointly conducted basic and applied research, indicating good quality relationships in terms of capacity to generate possible commercial applications. Applied research occurred more often involving public laboratories, bioscience firms and Brazilian pharmaceutical companies, indicating innovative efforts held by the national laboratories. Basic research involved mainly multinationals and public laboratories, indicating the involvement of both segments in more complex, riskier and longer term R&D activities, as well as a bigger absorptive capacity developed by these companies and public laboratories. It is possible that multinational companies' activities involving clinical trials' procedures may have been declared as research without immediate application due to research groups' self-declaration data collection bias. Further studies using clinical trials database and interviews are suggested to investigate such possibility. A major concern regards the limited occurrence of

[23] Law, Finance, Literature and social applied knowledge areas (CHIARINI et al, 2013)

[24] Mathematics, engineering and most of the knowledge areas that are considered strategic to Brazilian industrial development, such as Software, Pharmaceuticals, Biotechnology, Nanotechnology, semiconductors, capital goods and bioenergy (CHIARINI et al, 2013).

bilateral types of interactions – such as technological transfers from group to partner and from partner to group – jeopardizing effective knowledge flows.

According to the network metrics summarized in Table 6 below, despite the bioscience firms' network displayed the highest number of nodes in comparison to other industrial segments (62), the network density is rather low (0,023), and a high number of weakly connecting nodes is perceived (18). The result compatible with the presence of several academic spinoffs that integrate such segment – new companies that are still building basic competences and capabilities – which tend to be linked only to their origin university.

Only a few percentage (23%) of the identified Brazilian Pharmaceutical companies interacted with Brazilian S&T Institutions. The reduced rate of interactive partners among identified companies is probably associated with the average low innovative performance of many Brazilian pharmaceutical enterprises. However, the firms engaged in university-industry relationships were more likely to stablish linkages with more than one S&T Institution, that was the case of União Química, Biolab, Geyer, Prati Donaduzzi and Cristália. Another highlight is the overall importance of the company Cristália in terms of centrality in the network formation. However, the percentage 23% percentage is higher than the analogous 20% of identified multinational pharmaceutical companies that established university-industry relationships in Brazil. Also, Brazilian pharmaceutical companies accounted for 26% of total interactions while multinational companies engaged only in 16% of total university industry interactions. Thus, based on the empirical evidence, it is possible to state that Brazilian pharmaceutical companies interact more with Brazilian universities than multinational pharmaceutical companies do.

The Brazilian pharmaceutical companies' subgraph, despite having a higher number of nodes (58), present a relatively lower density (0,031) accompanied by a higher number of weakly connected nodes (10), when compared to the multinational companies' subgraph indicators (39; 0.051 and 4, respectively). The average path length of the Brazilian pharmaceutical companies' graph (3.929) is also higher than the multinationals' subgraph (3.883) as the Brazilian companies are connected to a higher number of S&T Institutions (34 versus 22), resulting in a relative lower node proximity.

The public laboratories' subgraph involved a distinguished specificity concerning the possibility that these laboratories operate as both National S&T Institutions and productive agents. Even though the effort to consider only those interactions in which the laboratories were involved as industrial actors, it is quite difficult to completely isolate university-industry relationships from academic only interactions. The network presented the highest number of ties (52), reflecting average degree of 2.261 and only 3 weakly connected nodes that together indicates a great level of proximity between the public laboratories and Brazilian universities. The proximity may also be inferred from the diminished diameter (6), considered the elevated number of nodes (46). Most public laboratories were connected to more than one university and some of them are directly connected to other public laboratories. Many universities were also connected to more than one public laboratory. The positive and non-null average clustering coefficient (0,095), corroborates the higher complexity of the network structure. Institutions such as CNEN, UFPR, FUNED, FIOCRUZ and BUTANTAN proved to be highly important due to their clustering effects.

All subgraphs have been merged into a broader network which represents the university-industry relationships established within the boundaries of the Brazilian biopharmaceutical innovation system. The number of ties was exactly the sum of subgraphs' ties (185), however the number of nodes (164) was lower than the analogous sum of subgraphs' nodes (211) reflecting the existence of 47 nodes that were double counted due to S&T Institutions operating in more than one subgraph. Therefore, the average degree of the complete graph (2.256) is higher than most subgraphs except for the public laboratories' (2.261), corroborating the relative importance of BUTANTAN, FIOCRUZ and FUNED as graph's main hubs.

The average clustering coefficient (0.026) also highlighted the importance of public laboratories such as CNEN, FUNED, BUTANTAN, FIOCRUZ, alongside Brazilian pharmaceutical companies Biolab and Cristália, and some universities like UFPR and USP, due to their clustering effect in the knowledge network.

The graph's density (0.014) decreased when all the subgraphs were merged in comparison to each subgraph previous density. The diameter did not decrease in comparison to bioscience firms', national and multinational pharmaceuticals' subgraphs and the number of weakly connected nodes remained high. Results indicate the existence of specific patterns that characterize each subgraph that do not perfectly blend in when the main graph is constructed. Furthermore, there are S&T Institutions that are more specialized in interacting with specific industrial components.

Table 6 – Network results

	Nodes	Ties	Average degree	Weakly connected nodes	Avg. Path Length	Density	Diameter
Bioscience firms	62	44	1.419	18	3.621	0.023	10
Brazilian Pharmaceutical companies	58	51	1.759	10	3.929	0.031	10
Public laboratories	46	52	2.261	3	2.723	0.050	6
Multinational pharmaceutical companies	39	38	1.949	4	3.883	0.051	10
Total	164	185	2.256	13	4.146	0.014	10
Total with BR S&T Institutions	401	1686	8.409	1	2.661	0.021	5
Total with foreign S&T Institutions	725	1049	2.894	6	3.916	0.004	12

Source: Elaborated by the authors based on the data published by CNPq directory (2018)

Table 7 consolidates the subgraphs' and merged graphs' main hubs. Some S&T Institutions, such as USP and UFRJ, were central nodes for many subgraphs. Public Laboratories such as BUTANTAN and FIOCRUZ also appeared as relevant hubs for the merged graph and many subgraphs, either operating as productive actors or as Research Institutes. However, some S&T institutions were more likely to establish interactions within determined subgraphs. That was the case of UFPR for Pubic Laboratories, UFPE and UFSM for national pharmaceutical companies. Institutions like UNICAMP, UNIFESP, UFMG, UFRGS and UNB showed strong potential to enhance proximity in the networks and to be more intensive in university-industry relationships but were still oriented towards more strictly academic activities and interactions. Regarding relations with foreign knowledge sources, UFRJ, USP and FIOCRUZ worked as bridges integrating national and international research institutes.

Table 7 – Network's main Hubs

	Productive partners	S&T institutions
Bioscience firms	BIOMM, BIOZEUS	USP, UFRJ
Brazilian Pharmaceutical companies	CRISTALIA	UFPE, BUTANTAN, USP, UFSM, UFRGS
Public laboratories	BUTANTAN, FUNED, FIOCRUZ, CNEN	UFPR
Multinational pharmaceutical companies	MSD, GSK	USP , UFRJ
Total	BUTANTAN, FIOCRUZ, FUNED	USP, UFRJ, UNESP
Total with BR S&T Institutions	FIOCRUZ	USP, UFRJ, UNICAMP, UNESP, UNIFESP, UFMG, UFRGS, UNB
Total with foreign S&T Institutions	FIOCRUZ	USP, UFRJ

Source: Elaborated by the authors based on the data published by CNPq directory (2018)

6. Conclusions

This paper provides an initial assessment of the Biopharmaceutical System of Innovation in Brazil, firstly, by identifying a heterogeneous sample of 385 public and private producers that integrate such system. The sample was classified according to four different categories: 102 bioscience knowledge intensive entrepreneurships with applications in human health, 148 Brazilian pharmaceutical companies, 23 public laboratories and 112 multinational pharmaceutical companies established in Brazil. The sample identification according to enterprises' Brazilian National Register of Legal Entities (CNPJ ID numbers) is a major contribution to academic research for enabling the cross use of several different databases based on CNPJ codes and by approximating the diverse universe of producers that integrate the Biopharmaceutical System of Innovation in Brazil.

In doing so, the study also contributes to the academic literature specialized in pharmaceutical studies by analyzing the importance and nature of the university-industry relationships in crucial areas to the biopharmaceutical research and, foremost, by highlighting the different patterns of interaction according to the specifies of each productive base partition. Approximately 27% of the identified sampled engaged in 243 linkages with 63 Brazilian S&T Institutions in health and biological sciences in 2014-2016 period. Interactions were mostly nurtured in pharmacy (24%), medicine (18%), biochemistry (14%) and microbiology (9%) knowledge areas. Brazilian public and private laboratories accounted for 84% of total interactions. The number of Brazilian pharmaceutical companies engaged in university-industry relationships overlaps both the number and the frequency of multinational pharmaceutical companies interacting with Brazilian universities and research centers. The result corroborates the theoretical hypothesis that multinational pharmaceutical companies tend to keep most of their innovative efforts concentrated in their origin headquarters abroad. While national public and private laboratories interacted mostly with research groups from pharmacy, biochemistry, genetics and microbiology knowledge areas, multinational companies were more intensive in relationships in medicine knowledge area. Approximately 58% of university-industry relationships concerned jointly conducted research with or without immediate application of results. While applied research activities involved mostly national public and private laboratories, basic research efforts occurred more often among multinational companies and national public laboratories. The limited frequency of bilateral types of interactions is a major concern identified in the study.

The social networks approach applied to study university-industry collaborations also contributes to identifying both S&T Institutions and companies that are central to knowledge networks formation and organizations that operate as structural bridges or knowledge gate keepers connecting originally disconnected networks structures. Due to the characteristic of the Biopharmaceutical knowledge-based activities, the capacity to access directly or indirectly external sources of knowledge – such as universities and research centers, other enterprises, users, producers, hospitals engaged in clinical trial procedures, political and regulatory bodies and other System of Innovation components – are considered critical to firms' innovative capacity. It is feasible to suppose that the firms currently engaged in relationships with academia that played central roles in knowledge networks formation are those more likely to have built internal capabilities, knowledge skills and the ones who have undertaken considerable innovative efforts. Also, the institutions that are more able to connect with many different types of firms and to operate as structural bridges are those more likely to support and enhance systemic integration within the Biopharmaceutical System of Innovation in Brazil. These results hold critical potential implications to support future technical and normative vertical actions oriented to nurture Biopharmaceutical activities in Brazil.

The knowledge network analysis indicated that public laboratories, such as FIOCRUZ, BUTANTAN and FUNED, stand out as bridges and have structural roles connecting originally disconnected nodes while operating as both industrial and S&T institutions. Other highly central S&T Institutions were USP and UFRJ. The Brazilian pharmaceutical company Cristália arose as an important hub in the network, considering both centrality and prestige measurements, indicating significant technological efforts being undertaken by the firm. The Brazilian bioscience firms Biomm and Biozeus and the multinationals MSD and GSK were, also, key hubs in their respective subgraphs. Other S&T Institutions – such as CNEN, UFPR and UFPE – stood out when clustering measurements and specific subgraphs were considered. Highly relevant universities in the Brazilian S&T context – such as UNICAMP, UNESP, UNIFESP, UFMG, UFRGS, UNB – could have embraced a more active role in biopharmaceutical university-industry relationships, though data indicated a bias towards pure academic partnerships.

7. References

ALBUQUERQUE, E. CASSIOLATO, J. E. As especificidades do sistema de inovação do setor saúde. *Revista de Economia Política, v. 22, nº 4 (88). Oct - Dec 2002.*

ALVES, N. Um estudo prospectivo das empresas de biotecnologia em saúde humana no Brasil. Master Thesis in Economics. Faculdade de Economia. **Universidade Federal Fluminense**. Niterói. 2017.

ALVES, N. VARGAS, M.A. BRITTO, J. Interações universidade-empresa: um estudo exploratório sobre as empresas de biotecnologia em saúde. **Econômica,** Niterói, v. 20, n. 1, p. 31–60. June, 2018.

ARORA, A. GAMBARDELA, A. The division of innovative labor in biotechnology. In: ROSEMBERG, N. et al (orgs). **Sources of Medical Technology:** Universities and Industry. Washington, DC: National Academy Press. p.188-208, 1995.

BAHIA, L. COSTA, L. GADELHA, C. VARGAS, M. Compras governamentais: as mãos invisíveis do Estado para a inovação. In: COSTA, L. BAHIA, L. GADELHA, C.A.G. org. **Saúde, Desenvolvimento e Inovação**. Rio de Janeiro.: CEPESC Ed. v.2, 2015.

BALCONI, M. LORENZI, V. The increasing role of contract research organizations in the evolution of the biopharmaceutical industry. **African Journal of Business Management**, v. 11(18), pp. 478-490, Sep 28, 2017.

BANCO NACIONAL DE DESENVOLVIMENTO ECONÔMICO E SOCIAL (BNDES). BNDES aprova R$ 401 milhões para produção de remédios biotecnológicos contra câncer e doenças autoimunes. 2015. Retrieved Feb 21, 2016, from: <http://www.bndes.gov.br/SiteBNDES/bndes/bndes_pt/Institucional/Sala_de_Imprensa/Noticias/2016/Todas/20160204_farmaceutica.html>.

BRITTO, J.; VARGAS, M.A.; GADELHA, C.A.G. COSTA, L.S. Health-related scientific and technological capabilities and university-industry research collaboration. In: Rev. **Saúde Pública** [online], v. 46, pp.41-50. 2012.

CÂMARA DE REGULAÇÃO DE MEDICAMENTOS (CMED). Anuário Estatístico do Mercado Farmacêutico 2016. Retrieved Jan 15, 2018, from: <http:// http://portal.anvisa.gov.br/ cmed>.

CHAVES, G. HASENCLEVER, L. OLIVEIRA, M.A. Conexões entre as políticas de desenvolvimento industrial no setor farmacêutico e a política de saúde no Brasil: Um percurso das décadas de 1930 a 2000. In: HASENCLEVER, L. et al (org.). **Desafios de operação e desenvolvimento do Complexo Industrial da Saúde**. E-Papers Ed., p.47-98. Rio de Janeiro. 2016.

CHIARINI, T. RAPINI, M. VIEIRA, K. Produção de novos conhecimentos nas universidades federais e as políticas públicas brasileiras recentes de CT&I. In: **Conferência Internacional LALICS 2013 "Sistemas Nacionais de Inovação e Políticas de CTI para um Desenvolvimento Inclusivo e Sustentável".** Rio de Janeiro. Nov 2013.

CORIAT, B.; ORSI, F.; WEINSTEIN, O. Does biotech reflect a new science-based innovation regime? In: **Industry and Innovation**, v.10, p.231-253. 2003.

DOSI, G. MAZZUCATO, M. Introduction. In: DOSI, G. MAZZUCATO, M (orgs). **Knowledge Accumulation and industry evolution. The case of Pharma-Biotech**. Cambridge University Press, p.1-19. 2006.

ELIASSON, G. ELIASSON, A. The Biotechnology Block of Competences. In: **Revue de Economie Industrielle**, v.2 , p. 7 - 26. 1996.

EXAME. Cade aprova joint venture de Pfizer e Orygen Biotecnologia. Editora Abril. 2013. Retrieved 20 Feb, 2016, from: <http://exame.abril.com.br/negocios/noticias/cadeaprovajointventureentrepfizereorygenbiotecnologia>.

GADELHA, C.A.G. MALDONADO, J.M. VARGAS, M.A. BARBOSA, P. COSTA, L. **A dinâmica do sistema produtivo da saúde: inovação e complexo econômico industrial.** Rio de Janeiro: Ed. Fiocruz, 221p. 2012.

GADELHA, C.A.G. VARGAS, M.A. MALDONADO, J.M.; BARBOSA, P. O Complexo Econômico-Industrial da Saúde no Brasil: dinâmica de inovação e implicações para o Sistema Nacional de Inovação em saúde. In: **Revista Brasileira de Inovação**, v. 12 (2), p. 251-282. Campinas, 2013.

GOMES, E. Clusters e biotecnologia para a superação da imitação: estudo de caso da indústria farmacêutica brasileira. 391f. Doctoral Thesis in Public Policies, Strategies and Development. Instituto de Economia, **Universidade Federal do Rio de Janeiro**. Rio de Janeiro, 2014.

GRAVAGLIA, C. MALERBA, F. ORSENIG, L. Entry, market structure and innovation in a "history friendly" model of the evolution of the pharmaceutical industry. In: DOSI, G. MAZZUCATO, M. (Orgs) **Knowledge Accumulation and industry evolution. The case of Pharma-Biotech.** Cambridge University Press, p.234-266. 2006.

MALERBA. F. MCKELVEY, M. Conceptualizing knowledge based entrepreneurship: Definition and model. In: MALERBA, F. et al (orgs). **Dynamics of Knowledge-Intensive Entrepreneurship: Business strategy and public policy.** Routledge Taylor & Francis Group, p.19-48. 2016.

MALERBA, F. OSENIGO, L. The evolution of the pharmaceutical industry. In: **Business History, 2015.**

MCKELVEY, M. ORSENIGO, L. Pharmaceuticals as a Sectoral Innovation System. In: **ESSY Project. European Sectoral Systems of Innovation**. 2001

MIGLIOLI, J. Biotecnologia na região de Ribeirão Preto: um estudo sobre aglomeração de empresas. Master Thesis. Faculdade de Medicina de Ribeirão Preto. **Universidade de São Paulo**. Ribeirão Preto. 2015.

MOWERY, D. SAMPAT, B. Universities in National Innovations Systems. In: FAGERBERG, J. et al. (orgs). **The Handbook of innovation**. Oxford University press, 2005.

PARANHOS, J. STEINER, F. CATALDO, B. MOREIRA, T. Potenciais e vulnerabilidades da interação empresa e instituições científicas e tecnológicas no setor farmacêutico: a visão dos atores. In: HASENCLEVER, L. et al (orgs). **Vulnerabilidades do Complexo Industrial da Saúde: Reflexos das políticas industrial e tecnológica na produção local e assistência farmacêutica**. Ed. Contraponto, p. 25-52, 2018.

PAVITT, K. Sectoral patterns of technical change: Towards a taxonomy and a theory. In: **Research Policy**, v. 13, p. 343 - 372. 1984.

REZAIE, R. MCGAHAN, A. FREW, S. ABDALLAH S DAAR, A. SINGER, P. Emergence of biopharmaceutical innovators in China, India, Brazil, and South Africa as global competitors and collaborators. Health Research Policy and Systems, 2012.

REZAIE, R. SINGER, P. Global health or global wealth? In: Nature Biotecnology, v.28, n. 9, p. 907-909. 2010.

SCHUMACHER, A. GASSMANN, O. HINDER, M. Changing R&D models in research-based pharmaceutical companies. In: **Journal of Translational Medicine**, v.14 n.1. 2016.

SINDUSFARMA. Relatório Anual de Atividades 2018. Retrieved july, 18, 2019 from: <http://sindusfarma.org.br/cadastro/public/uploads/publicacoes/arquivos/133/RAA_Sindusfarma_2018.pdf>.

SZAPIRO, M. H. S.; CASSIOLATO, J. E.; LASTRES, H. "Panorama das Políticas de Desenvolvimento Produtivo no Brasil no Período 2003-2015". Relatório de Pesquisa desenvolvido no âmbito do Projeto "Estudios sobre Políticas de Desarrollo Productivo en Brasil" da Organização Internacional do Trabalho (OIT), 2017.

VARGAS, M. A. GADELHA, C.A.G. MALDONADO, J.M.S.V. COSTA, L. Innovation in pharmaceutical and health biotechnology industries: challenges for a virtuous agenda. In: **Revista de Saúde Pública**, v. 46. p. 37-40. 2012.

VARGAS, M. A.; BRITTO, J. Innovation, and competence building in the pharmaceutical and biopharmaceutical industry in Brazil. In: 12th Globelics Conference - Partnerships for innovation-based development, 2014, Addis Ababa, Ethiopia. 2014.

VARGAS, M.A. Base Biotecnológica no Brasil: desafios e nichos estratégicos. In: GADELHA, C.A; GADELHA, P; NORONHA, J. PEREIRA, T. (Org.). **Brasil Saúde Amanhã: complexo econômico-industrial da saúde**. 1ed.Rio de Janeiro: Editora Fiocruz, v. 1, p. 61-87. 2017.

VARGAS, M.A. GADELHA, C.A.G. MALDONADO, J.M. COSTA, L. QUENTAL, C. Indústria de base química e biotecnologia voltadas para a saúde no Brasil: panorama atual e perspectiva para 2030. In: FIOCRUZ; IPEA, MINISTÉRIO DA SAÚDE; SECRETARIA DE ASSUNTOS ESTRATÉGICOS DA PRESIDÊNCIA DA REPÚBLICA (Org.). **A saúde no Brasil em 2030: prospecção estratégica do sistema de saúde brasileiro: desenvolvimento produtivo e complexo da saúde**. 22 ed. Rio de Janeiro: Editora Fiocruz, v. 05, p. 29- 78. 2013.

WASSERMAN, S. FAUST, K. **Social Network Analysis: Methods and Applications**. Cambridge University Press, 430p.1994.