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Understanding the political framework of biopharmaceutical development in Brazil: the case of monoclonal antibodies[1]

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Introduction

Over the last three decades, some industrialized countries have implemented a set of scientific, technological, and industrial policies to improve the economic landscape of the new emerging biopharmaceutical industry. Biopharmaceuticals generally refers to medicines developed using biotechnological methods (such as the culture of cells from mice and other mammals, cultivated under rigorous quality controls and best practices), as well as drugs produced using DNA technologies and genomic and proteomic techniques (Ecker et al., 2015).

Like many other biotechnology-based sectors (agri-food, plant genomics, veterinary medicine, new organic materials, etc.), the biopharmaceutical industry is now responsible for the highest profits in contemporary industry. Since 2000, more than 550 drugs have been approved by the US Food and Drug Administration to be commercialized all over the world. Furthermore, according to Tufts Center for Drug Development, every new compound (or new molecular entity, NME) requires an average of 12-14 years of research, development, clinical trials, tests and approval processes, a period which can cost about US $2.6 billion (Tufts, 2014).

This article aims to provide an introductory analysis of the political framework under implementation for the development and manufacturing of the so-called Monoclonal Antibodies (mAbs) in Brazil. We conducted a documental research on articles available in the Web of Science and reports and website information of federal governmental agencies. We also applied 28 interviews with the main stakeholders involved in the mAbs biopharmaceutical development agenda in Brazil (see details in Materials and Methods).

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Materials and Methods

This paper uses the qualitative research technique of document analysis to study the design and implementation of the Brazilian political framework for monoclonal antibodies development and manufacturing over the last two decades. In addition, to improve our understanding of the agenda and role of federal public policies in technological and manufacturing development in contemporary Brazil, we conducted 28 interviews (in person or by e-mail) in four states of the country (São Paulo, Minas Gerais, Rio de Janeiro and Parana) between June 2016 and July 2018.

We selected the main stakeholders involved with the governance regime for biopharmaceutical development: policymakers; managers of pharmaceutical companies; managers and manufacturing and engineering professionals from public and private (national and multinational) pharmaceutical companies established in Brazil; representatives of public and private pharmaceutical industry associations; experts on mAbs research and development (R&D); academic managers; and people from research institutions and universities (see Table 1 below).

We also searched the official database of the Brazilian federal government of imports of pharmaceutical goods, health policies and public-partnership partnerships (PPP) over the last twenty years. To illustrate the evolution of Brazilian imports of biopharmaceutical goods in recent decades, we selected some indicators from the System of Analysis of Foreign Trade Information – AliceWeb 2[2]. The information about health policies and PPP, we selected the reports and documents available in the website of the Brazilian Ministry of Health.

To present the framework of policies and initiatives for biopharmaceutical development over the last two decades in this conference paper, we have prepared a summarized presentation about two important characteristics of the design of the biopharmaceutical development agenda in Brazil: the objectives of the policies (and why biopharmaceuticals have emerged as a political agenda) and the current characteristics of the political framework with a focus on the Ministry of Health (MH) – mainly between the launching of the Secretariat of Science and Technology and Strategic Health Inputs (SCTIE) in 2002 and the National Program for Health Industrial Complex Development (PROCIS) in 2012. In this period, we focused on different initiatives that have been implemented regarding the manufacture of mAbs products in Brazil.

[2]AliceWeb 2 was developed by the Brazilian Ministry of Industry, Foreign Trade and Services and is available at <http://aliceweb.mdic.gov.br/>. AliceWeb 2 is updated monthly with data from the month most recently ended, and it is based on data from the Integrated Foreign Trade System.

Table 1 – Interviews

Group name	Institution	Job title	Type of interview
Policymakers	MINISTRY OF HEALTH	Ex-ministry of State	e-mail
		Ex-director of the Department of Science and Technology	in person
	MINISTRY OF INDUSTRY DEVELOPMENT AND FOREIGN TRADE*	Ex-president of ABDI	in person
	MINISTRY OF SCIENCE TECHNOLOGY AND INNOVATION	Ex-president of FINEP	in person
	BNDES	Ex- secretary of Science, Technology and strategic inputs	e-mail
Managers of public and private pharmaceutical companies	BIONOVIS	Medical-Scientific director	in person
	RECEPTA BIOPHARMA	President/CEO	in person
	MERCK BRAZIL	President	in person
	ACHE	Manager of R&D	in person
	CRISTALIA	Manager of R&D	e-mail
	BIOCAD	Director of Manufacturing	e-mail
	BUTANTAN	Ex-president	in person*
	BIOMANGUINHOS	Director of biotechnology division	e-mail
	FUNED	President	in person
		Director of Manufacturing	in person
	LIBBS	Director of external communication	e-mail
	TECPAR	President	e-mail
Representatives of industry associations	ALFOB	President	e-mail
	INTERFARMA	President	in person
	ABIFINA	President	e-mail
Experts on R&D and academic managers	UNIVERSITY OF SAO PAULO	Full professor of the Faculty of Medicine and Scientific director of Sao Paulo Cancer Institute	e-mail
	BUTANTAN	Senior researcher and coordinator of GSK/FAPESP biologics center	in person
	RECEPTA BIOPHARMA	Ex-director of R&D	in person
	CNPEM	Researcher	in person
	FEDERAL UNVERSITY OF SAO PAULO	Senior researcher	in person
Consultants from research institutions and universities	FEDERAL UNIVERSITY OF RIO DE JANEIRO	Full professor of the Faculty of Economics	in person
	FIOCRUZ	Full professor of Public Health	e-mail
	FEDERAL UNIVERSITY OF SAO PAULO	President of R&D of UNFESP Foundation	in person
		Total	**28**

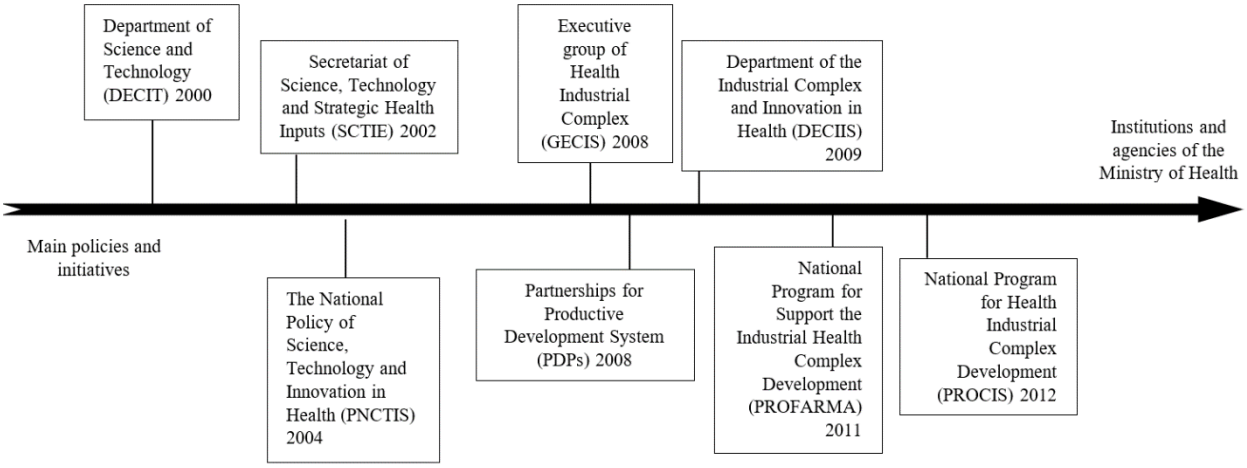
Source: Elaborated by the authors, 2018.

Results

The MH has implemented different policy initiatives and instruments to improve the health science, technology and manufacturing activity in Brazil. This policy was made explicit by two significant actions taken by the federal government: first, as previously mentioned, the creation of SCTIE, and second, the launch of the National Policy for Science, Technology and Innovation in Health (*Política Nacional de Ciência, Technologia e Inovação em Saúde*, PNCTIS) in 2004. According to interviewees, MH played a relevant role as a governmental body between 2002 and 2013 in promoting a set of transversal public policies capable of impacting different public and private agendas, meeting the demands of different groups involved in the so-called "health economic-industrial complex" (HEIC) (Costa et al, 2016).

This was a special moment for the birth of new institutions and initiatives designed to serve at least three general goals. The first was to provide new institutions and executive boards to the MH, directed at developing and implementing new initiatives to support health science, technology, and innovation agendas in tune with the aims and social and economic demands of the Brazilian public health system (*Sistema Único de Saúde, SUS*). To strength the role of public health system as promoter of science, technology and innovation was launched as the main goal of the PNCTIS in 2004. The second goal was to improve the efficiency of the SUS as the main importer and buyer of pharmaceutical goods, medical devices and R&D-intensive biopharmaceutical products, prioritizing stakeholders of the HEIC, which was launched as the main goal of the Partnerships for Productive Development Systems (*Parcerias para o Desenvolvimento Produtivo, PDPs*). Finally, the third goal was to improve manufacturing capacity via technology transfer (TT) contracts for Brazilian public and private laboratories to produce off-patent biopharmaceuticals after 2012, to supply the SUS and to control drug prices for high-cost biologicals (mainly for mAbs and vaccines) (Torres & Hasenclever, 2016). A summary of those policies and initiatives is provided in Figure 1 and Table 2 below.

Figure 1: Main policies and initiatives developed by the Brazilian MH, 2000-2012.



Source: Prepared by the authors based on document research and interviews, 2018.

Table 2: Institutions and initiatives for the HEIC development in Brazil.

Federal Authorities	Abbrev.	Year	Agencies, policies and initiatives	Main recent activities related with HEIC development	Transversal policies		
					2004	2008	2012
Ministry of Industry, Foreign trade and Services	BNDES	1952	National Bank of Social and Economic Development	Financing of two large biotechnology industrial enterprises in the State of Sao Paulo (BIONOVIS and ORYGEN plants). Value: US$ 100 million (Final investments projection: US$ 252 million*). PROFARMA 2011		PDPs: Partnerships for Productive Development Systems, PDPs.	PROCIS: National Program for Health Industrial Complex Development.
	ABDI	2004	Brazilian Agency of Industrial Development	Prepared studies and policy reports about the technological and production capacity of new emerging biopharmaceutical companies			
Ministry of Health	DECIT	2000	Department of Science and Technology	First explicit MH agency created to develop and implement strategies for STI in health in public and private stakeholders of the health sector.	PNCTIS: The National Policy of Science, Technology and Innovation in Health.		
	SCTIE	2002	Secretariat of Science, Technology and Strategic Health Inputs	The main board of the Brazilian MH directed to propose transversal policies and coordinate initiatives of public health services and goods, STI policies, medical devices and pharmaceutical manufacturing groups, regulatory boards and other stakeholders.			
	GECIS	2008	Executive group of Health Industrial Complex	Board composed of experts and people from academia, industry, government and civil society, engaged in verifying and approving new actions related with to the Brazilian HEIC			
	DECIIS	2009	Department of the Industrial Complex and Innovation in Health	First MH agency explicitly created to develop strategies for the HEIC demands and policies.			
Ministry of Science, Technology, Innovation and Communications	PCT	1961	Science and Technology Policy	Plays the traditional S&TP role supporting new research projects, grants and funding for R&D in mAbs via the National Council for Scientific and Technological Development (CNPq).			
	FINEP	1967	Funding Authority for Studies and Projects, FINEP	Supports R&D activity in small and big companies of biotechnology and biopharmaceutical projects.			

Source: Prepared by the authors based on document research and interviews, 2018.

"Biopharmaceutical dependence" and the monoclonal antibodies

In Brazil, the importance of national biopharmaceutical industry development had emerged as a political agenda by 2005. The main issue in the government setting its agenda was the rising public health expenditures on the importation of biopharmaceutical goods, mainly caused by the impact of the high prices of therapeutic biopharmaceuticals. Data available from the Ministry of Health's 2009 report show that biopharmaceuticals represented 2% of the amount of drug acquisition, but around 40% of the Ministry's total expenditures in value (Gadelha et. al., 2012).

Furthermore, a recent article by Luz et al. (2017) shows that since 2010 the Brazilian federal government has been experiencing a rapid increase of expenditures in the acquisition of two categories of biopharmaceuticals, immunomodulating and antineoplastic, which are considered essential health supplies for the SUS. The main type of biopharmaceuticals for these two categories are m*onoclonal antibodies* (mAbs)[3].

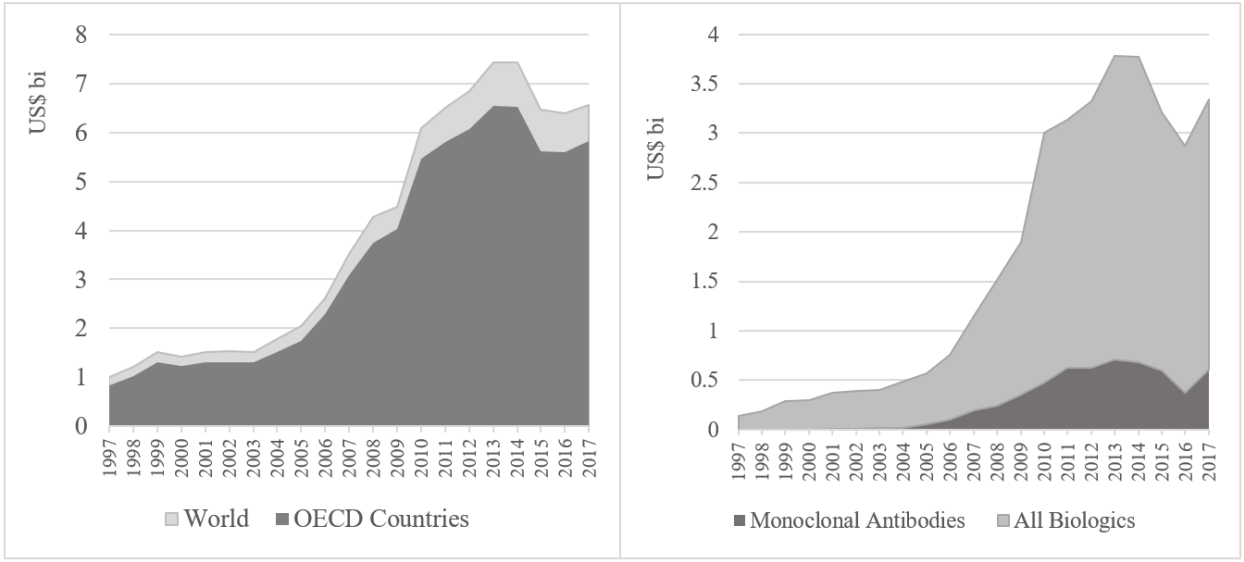
Therapeutic mAbs are the top-selling biopharmaceuticals globally and considered important for the treatment of common chronic diseases, such as different types of cancer (mainly breast and lung), immunodeficiencies, rheumatoid arthritis, and neurodegenerative pathologies[4]. In Brazil, these diseases no longer affect specific social classes, but rather occur in populations of low to average income, mainly in large and populated urban areas (Wang et. al., 2014). It has posed a challenge to Brazilian health planning, since treatment for such diseases requires high-cost biopharmaceuticals.

To solve this problem, policies for biopharmaceutical development and manufacturing in Brazil emerged in 2008 with the creation of GECIS and coordinated formally by DECIIS in 2009. According to members of these agencies, the creation of policies for biopharmaceuticals was based on the realization of the huge dependence of Brazil on imports of pharmaceutical and biopharmaceutical goods from OECD countries, as well as a rise of Brazilian imports from BRICS countries (as shown in Figures 3 and 4). Both trends were generating a rise of public health expenditures, with a strong impact on Brazil's trade balance. Additionally, the fast rise in spending on development associated with biologics (generally) and mAbs (specifically) was considered strategic to mitigate the dependence on imports of biopharmaceutical goods from companies abroad.

[3] According to the Collins English Dictionary, mAbs are copies of "an antibody, produced by a single clone of cells grown in culture, that is both pure and specific and is capable of proliferating indefinitely to produce unlimited quantities of identical antibodies: used in diagnosis, therapy, and biotechnology" (Collins Dictionary, 2018).

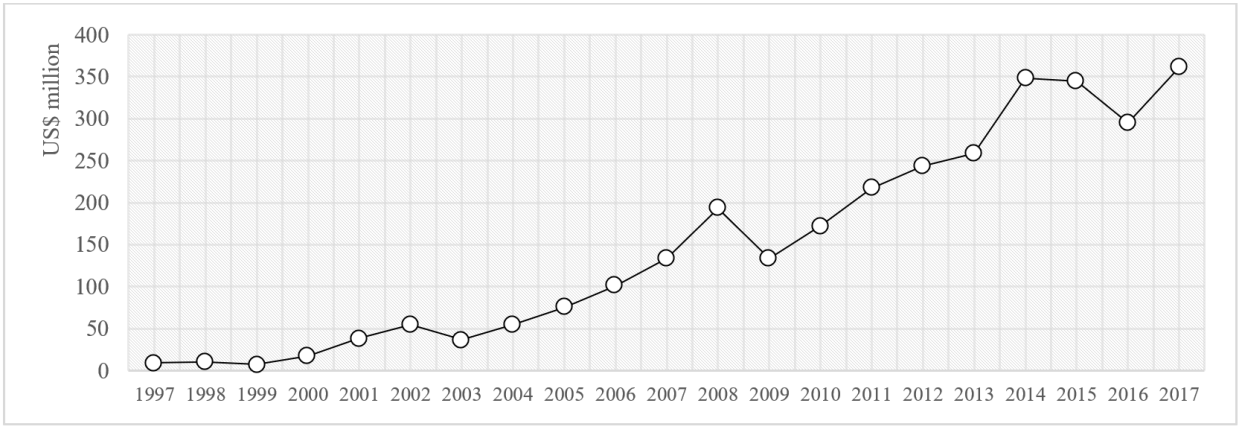
[4] According to Ecker and colleagues (2015), "The commercial development of therapeutic monoclonal antibodies commenced in the early 1980s, and by 1986 the first therapeutic monoclonal antibody, Orthoclone OKT3, was approved for prevention of kidney transplant rejection. Since the approval of OKT3, therapeutic monoclonal antibodies and antibody-related products (…) (collectively referred to hereafter as monoclonal antibody products) have grown to become the dominant product class within the biopharmaceutical market. (Ecker et al., 2015, p. 9).

Figure 2: Brazilian imports of pharmaceutical (total) and biopharmaceuticals (only bio-) goods, total and from OECD countries in US$ bi, 1997-2017.



Source: Prepared by the authors with data from the AliceWeb 2.0 database

Figure 3: Brazilian imports of pharmaceutical goods from BRICS, in US$ millions, 1997-2017.



Source: Prepared by the authors with data from the AliceWeb 2.0 database

The PDP system is considered one of the main policies of implementation of technology transfer for mAbs manufacturing. According to the policymakers and people from industry that we interviewed, the TT strategy was designed and began to be implemented in 2009 as a shortcut to improving technological capacity for the pharmaceutical companies in Brazil. For mAbs, eight companies with plants in the country were selected to produce five mAbs products and Etanercept. According to the MH, once fully implemented the PDP's TT, the government will save around US$ 1.3 billion with the mAbs acquisition (Ministério da Saúde, 2013).

Figure 4: Companies and mAbs products participating in PDPs System, 2018.

COMPANIES	
ORYGEN	Private Brazilian
BIONOVIS	Private, Brazilian
BIOMANGUINHOS	Public, Brazilian
BUTANTAN	Public, Brazilian
LIBBS	Private, Brazilian
CRISTALIA	Private, Brazilian
AXIS BIOTECH	Private, Brazilian
BIOCAD	Private, Russian

mAbs PRODUCTS
ADALIMUMAB
BEVACIZUMAB
INFLIXIMAB
RITUXIMAB
TRASTUZUMAB
*ETANERCEPT

Source: Prepared by the authors, according to the PDPs System platform on the Ministry of Health's website.

Discussion

The global biopharmaceutical industry has rapidly evolved over the last two decades, representing a challenge for social scientists, policymakers and professionals. Science and Technology Studies (STS) has been tasked with explaining the impact of the industry's technological change on social issues (knowledge production, ethics, knowledge control regimes, intellectual property, economic growth, sustainability, etc.). Also, it is already clear for social scientists that the biopharmaceutical sector is being constructed under a new regime of governance in which new knowledge, manufacturing platforms and regulatory systems are emerging quickly. For this reason, it is very important to understand the role of groups and interests and how they are shaping the political agenda for the life sciences in the 21st century (Hilgartner, 2017).

Conclusion

Changes in the international markets for new biopharmaceuticals are reconfiguring the literature about national systems of innovation and healthcare technologies in developing countries. Since the beginning of the 21st century, countries like China, South Korea, Singapore and Brazil have secured high level of investments from national and multinational pharmaceutical companies in the emerging life sciences sector, bolstered by favorable governmental policies (Mittra, 2016).

The building of the Brazilian policies for manufacture of mAbs presenting itself as controversial. We selected (at least) three main characteristics of the political agenda for mAbs development and manufacturing in the country. First, the competitiveness of the national emerging biopharmaceutical companies is based in to produce similar copies of mAbs molecules (biosimilars) developed by foreign companies, governmental market reserve and contracts of inputs supply to SUS; secondly, the manufacturing initiatives and the science and technology policies were set as parallel agendas and, third, the framework of policies did no relevant

incentives or funding support instruments for new emerging companies and start-ups of biotechnology.

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