Science and Public Policy, 2023, **50**, 42–58
DOI: https://doi.org/10.1093/scipol/scac047
Advance Access Publication Date: 2 September 2022
Article

OXFORD

The industry of therapeutic monoclonal antibodies in Brazil: Public policies as instruments of technology upgrading

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Abstract

Therapeutic monoclonal antibodies (MAbs) are biopharmaceuticals prescribed in oncology, rheumatology, and for other chronic and autoimmune diseases. Over the last decade, the demand for MAbs grew significantly in developing countries like Brazil, concomitant to the restructuring of the global biopharmaceutical industry, opening windows of opportunities for catching-up economies. This paper aims to analyze the capacity of a public policy, the so-called Production Development Partnership Program (PDPP), to encourage the generation of national capabilities to the local biopharmaceutical industry and technological upgrading in the biopharmaceutical sector in Brazil. It is a case study supported by qualitative data from twenty-three interviews. By focusing on technology transfer processes rather than on more complex strategies of technological learning and upgrading in domestic agents, the impact of PDPP has been marginal. We draw insights from this empirical appraisal to outline some lessons and challenges involved in the implementation of technology-upgrading policies in developing countries.

Key words: public policy; technology upgrading; healthcare industry; developing countries; therapeutic monoclonal antibodies; Brazil.

1. Introduction

The emergence and reorganization of the biopharmaceutical industry in developing and low- and middle-income countries has been a relevant topic over the last decade. Biopharmaceuticals generally refer 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). This sector has been a flagship of institutional change, international management of high-tech services, manufacturing organization, financial and technological capabilities, and emerging strategic alliances to access global markets (Mittra 2016).

In catching-up economies, the strategies for biopharmaceutical development show strong differences in how stakeholders associate entrepreneurial behavior and governmental incentives to foster the local healthcare industry. Economists and social scientists have been analyzing the emergence of new political agendas to run feasible systems of technological learning and innovation (Torres and Hasenclever 2016; Ariffin and Figueiredo 2004). In turn, it may create opportunities for technology-upgrading processes to take place, allowing the productive structure to actively engage and evolve within global value chains (GVCs; Radosevic and Yoruk 2018).

Over the last decades, pharmaceutical companies based in low- and middle-income economies like India and Iran achieved cutting-edge capabilities for manufacturing biotechnology products and processes (Majidpour et al. 2021). In these countries, small knowledge-intensive firms became strategic to fostering research and development (R&D) activity in the healthcare industry internationally (Niosi 1999; Aharonson and Schilling 2016). By using their comparative advantages, these countries triggered pervasive levels of technological learning and productivity enhancement (Lin 2012). This is particularly critical, considering the budgetary burden imposed by the dependence of imports of biopharmaceuticals to health systems in catching-up economies (Gomes et al. 2016).

In countries like Brazil, Russia, and China, the healthcare industry has a strong government-led nature, with a varied mix of state-owned laboratories and public companies playing critical roles. These countries do not possess comparable levels of private R&D investments and liberal-oriented practices of entrepreneurship as in countries from Europe and North America. Thus, alternative paths toward technology upgrading have been explored with idiosyncratic governance arrangements. Analyses of the evolutionary trajectory of these catching-up economies contribute to the debate on the dynamics of regimes of technology upgrading and policies for strategic sectors. It shed light on the specificities of the

relationship among governmental initiatives, markets, and the technological environment embedded in middle-income traps. We are, then, particularly interested in the study of contemporary initiatives for developing and manufacturing therapeutic monoclonal antibodies (MAbs) in low- and middle-income economies. It illustrates the relevant aspects of the technological complexity of the healthcare industry and the dynamics of industry–government partnerships in the manufacturing of MAbs.

But what are MAbs? According to the National Cancer Institute (NCI), MAbs are 'a type of protein that is made in the laboratory and can bind to certain targets in the body, such as antigens on the surface of cancer cells' (NCI 2022). They are widely prescribed for treating commonly occurring chronic diseases, such as different types of cancers and immunodeficiencies like rheumatoid arthritis, psoriasis, Crohn's disease, and neurodegenerative disorders (Wang et al. 2014). According to Ecker et al. (2015), the technological history of MAbs can be traced back to the 1980s, when the first therapeutic product (Orthoclone OKT3) was approved in the USA in 1986. Since then, the approval of MAbs with therapeutic potential has grown significantly in those countries. Asher Mullard (2021) highlights that more than 100 MAbs have been approved by the US Food and Drug Administration (FDA) by 2021, and Kaplon et al. (2022) list about 155 MAbs that are now in the late stages of clinical studies according to 'The Antibody Society' (Mullard 2021; Kaplon et al. 2022).

Recently, the growth of local manufacturers of MAbs in Brazil has attracted attention from analysts and scholars interested in contemporary varieties of industrial policies and initiatives of technological learning in this sector in developing countries. Since early 2000s, the Brazilian Ministry of Health (MH) introduced new policies to improve local manufacturing and technological capabilities in the healthcare sector, responding to a rising demand for MAbs in Brazil in that period. Although the MAbs' technology dates to the late 1980s, only in 2013 a Brazilian company filed for a license to produce such a drug in the country. The first factory of MAbs was built in 2016 and the first MAb, Vivaxxia, was produced in September 2019 by the company Biotec Libbs, located in the São Paulo metropolitan area. Furthermore, despite having an annual pharmaceutical market growth potential of 7–10 per cent until 2020 (Afonso et al. 2015), it was only in 2018 that the first MAb biosimilar was produced in Brazil, as a direct result of the Production Development Partnership Program (PDPP), implemented by the Brazilian federal government in 2008, and the National Health Policy's demand for high-cost biopharmaceuticals.

Thus, this study discusses to what extent has the public policy (i.e. PDPP) contributed to spur technology-upgrading processes in Brazil? And what are the impacts in terms of developing domestic capabilities and establishing a biopharmaceutical industry in the country?

Hence, to advance the understanding of the role of productive development policies as instruments for technology upgrading in developing economies, this study aims to analyze the capacity of a public policy (PDPP) to encourage the generation of national capabilities to manufacture biopharmaceuticals (either in the public sector by public laboratories or in the private sector by national companies) and technological upgrading in the manufacture of MAbs in Brazil. A qualitative approach is applied, triangulating documentary research in official reports and twenty-three in-depth interviews with key stakeholders conducted between 2016 and 2017.

After this introduction, the remaining of the article is structured as follows: Section 2 'Technology upgrading in developing countries' provides an analytical framework based on technology-upgrading dynamics in catching-up economies. Section 3 'Methods' presents details of the adopted methodology details, and Section 4 'Trajectory of productive development policies in the Brazilian healthcare industry' brings its empirical findings. Section 5 'Discussion and implications' analyzes the results considering technology-upgrading processes, deriving key lessons from this case study, and addressing implications for research and policy. Section 6 concludes with final remarks and limitations of our assessment.

2. Technology upgrading in developing countries

The National Systems of Innovation (NSI) approach (Lundvall 1992; Freeman 1995) suggests that late-industrialized countries are those with significant gaps in knowledge-based infrastructures. Guided by this framework, a range of case studies presented successful initiatives of catching up in emerging economies, with special attention devoted to the emerging industrial hubs in Southeast Asia, such as China and South Korea (Malerba and Orsenigo 1993; Chang 2002). More recently, the dynamics of capability building toward innovation in catching-up economies has received increased attention from the literature on technology upgrading. Drawing from a systemic perspective, this line of research offers solid contributions to assess evolutionary trajectories.

Technology upgrading, a process involving learning mechanisms within the economic fabric, represents an essential aspect for countries to reach trajectories of economic development and catch up with its developed peers (Wang et al. 2019). Following Lin (2012), technological upgrading can be defined as a sustained process of industrial and technological evolution linked to countries' comparative advantages and productive endowments. Radosevic and Yoruk (2018) systematize these ideas around three comprehensive drivers that offer generic directions for Science, Technology, and Innovation (STI) policy:

(1) *Intensity of Technological Upgrading*: associated with current levels of technological capabilities and efforts available in domestic firms;
(2) *Breadth of Technological Upgrading*: related to the levels of diversification (in terms of technological knowledge) of the productive system, complementary infrastructure, and organizational capabilities of economic agents;
(3) *Interactions with the Global Economy*: international knowledge flows (inward and outward) representing the integration of the economic system with global connections taking place through trade, Foreign Direct Investment (FDI), and other forms of linkages.

These dimensions put emphasis on national efforts to develop capabilities in key sectors—and complementary activities—and in establishing exchanges with foreign markets in such a way that knowledge flows can take place and be

absorbed. The engines of technology upgrading can then be set in motion, allowing countries to evolve in terms of innovative potential. Chuang and Hobday (2013) assess this trajectory in three phases: pre-entry, entry, and innovation and diversification. Figueiredo and Piana (2021) bring novel evidence on the development of technology-upgrading processes, highlighting the qualitative changes in learning processes occurring in catching-up economies. While pre-entry and entry stages are associated with 'doing, using and interacting', the innovation and diversification stage relies fundamentally in generating competitiveness in science and technology. This is in consonance with prior evidence on the evolutionary processes advancing from assimilation and diffusion toward the creation of indigenous R&D capabilities and knowledge-intensive entrepreneurship (Wong 2001).

However, while these commonalities can be observed, there is no blueprint for policy to trigger technology upgrading. In fact, Kergroach (2019) identifies significant trade-offs among initiatives targeted at generating technology-upgrading intensity, breadth, and global interactions. He terms dedicated policy mixes as 'polymorphs' that must take into account idiosyncrasies of nations' socioeconomic contexts. For instance, Brazil, Russia, India, China and South Africa (BRICS) economies have been associated with a lack of organizational and complementary capabilities to benefit effectively from foreign technology sources (Dominguez Lacasa et al. 2019), a point also raised by Kale (2019). Hence, it appears that to engage in the full extent of technology-upgrading dynamics, countries should first achieve a minimum threshold of internal competences. This is aligned with the assessment of microeconomic units, and capability-enhancing policies play a key role in this context (Qiu et al. 2013). In Brazil, the lack of technological capabilities in indigenous companies was also put forth as one of the possible results of ineffective industrial policies (Alves et al. 2021).

This pivotal position of policy in the dynamics of technology upgrading coincides with the criticality of the institutional dimension in shaping the conditions for catching up (Choung and Hwang 2019). The available set of regulatory, normative, and cognitive institutions largely affect how knowledge can diffuse among economic agents; in addition, it defines the sense of community in industrial systems, leveraging (or hampering) the formation of strategic networks (Breznitz 2005). In this vein, public institutions can be used as influential mechanisms to spark density in innovation systems. This seems to be particularly relevant for the case of public universities. For instance, in the 2000s, Taiwanese universities were responsible for substantially increasing the levels of R&D activity in the country, also acting as hubs for the generation and consolidation of high-tech ventures and fostering innovative potential by developing and transferring technologies to industry (Mathews and Hu 2007). Although more incipient, a similar pattern has also been observed in Brazil (Fischer et al. 2019). These features are even more relevant when dealing with contexts like the object of our research. Wang et al. (2019) identify the existence of a strong knowledge base as a key ingredient in driving competitiveness in science-based industries such as those involving biosciences.

On the other hand, the institutional environment can also be an important platform to drive connections between the NSI and other international players. India provides an interesting illustration for this case. After joining the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, the institutional environment for R&D in this country became more predictable, facilitating the insertion of local companies in GVCs (Kamiike 2020). In turn, this 'safer' environment and international interactions—together with the development of indigenous capabilities—promoted higher levels of technology transfer processes in the pharmaceutical industry and, ultimately, technology upgrading.

In fact, although moderated by the existing degrees of absorptive capacity in national players, international knowledge flows stand out as a critical feature for technology upgrading to navigate through its evolutionary stages and lead to the effective creation of innovative capabilities (Haakonsson and Slepniov 2018). (Lee et al. 2021b) echo this argument, adding the need for coordinated initiatives involving both state and nonstate actors embedded in innovation systems (national, regional, and sectoral). Internationalization modes affecting technology upgrading can vary, but literature has emphasized the role played by multinational companies (Kale 2019; Kergroach 2019; Ivarsson and Alvstam 2009), since these firms occupy leading positions in the dynamics of GVCs, also establishing their local presence in catching-up economies—a more effective way of exchanging knowledge than trade alone. Of course, these flows are moderated by the strategy of multinationals when establishing branches in these countries—whether they will develop linkages with indigenous actors—and on the absorptive capacity of local agents to internalize knowledge spillovers (Corredoira and Mcdermott 2014).

2.1 Productive development policies as instruments for technology upgrading

Based on the idea of effectiveness of public policies to upgrade capabilities in indigenous industries, literature has presented cases in which those initiatives have shifted the trajectory of innovation systems in developing and emerging economies (Khanna and Palepu 1999; Furtado and Freitas 2000; Fu et al. 2011; Malerba 1997). These studies offer important tools for understanding development in the contexts of unequal distribution of human, material, financial, technological, and political capital (Amankwah-Amoah et al. 2019).

In this vein, the notion of *Productive Development Policies* proposed by Sabel (2016) and Fernandéz-Arias et al. (2016) can be useful to provide a multilevel analysis of technology-upgrading processes in Latin America. According to Sabel (2016), this notion emerged from the weaknesses of old structuralist industrial policies. For the author 'deep changes in the organization of production have made industry—manufacturing—less central to industrial or productive development policy (…). Given the traditional ideas about economic development in Latin America, it is natural to cast these changes as a shift from (…) industrial policies centered on national business/government councils to industrial policies that encourage ongoing exchanges between higher level bodies (…) and ground level bodies addressing concrete problems, each correcting the shortcomings of the other' (Sabel 2016: 1).

Productive Development Policies can be understood as the set of public and private initiatives played by a heterogeneous and transversal group of stakeholders, coordinated by a dynamic intersectoral regime of governance flowing in a multilevel political landscape, aiming at qualitatively

enriching technology-based activities across different sectors (Hekkert et al. 2011; Kukk et al. 2016). Hence, Productive Development Policies can be understood as *de facto governance practices*, as proposed by Aukes et al. (2019). According to the authors, the study of *de facto governance practices* must account for the existence of informal and, sometimes, unpredictable democratic governance arrangements, which impact the institutional building of formal organizations: the legal framework, the rules of the game, tools of public and private policy, supra-governmental strategies, official guidelines, new and unexpected actors, etc. (Pestre 2008; Strasshein and Beck 2019). Thus, *de facto governance practices* constitute a mix of formal and informal procedures and behaviors by actors, which lie outside of formal governance arrangements (Aukes et al. 2019: 4) and contribute to the understanding of how actors shape new rules and institutions to pursue mutual interests to implement successful Productive Development Policies targeted at generating technology-upgrading processes.

3. Methods

Aiming at situating the PDPPs as a relevant political tool of the emerging Brazilian biopharmaceutical industry, this study adopted a combination of qualitative methods to make sense of primary and secondary data regarding the role of public polices to encourage the generation of national capabilities in the local public and private companies in the manufacture and technology upgrading of MAbs in Brazil.

A literature review collected updated evidence regarding the dynamics of technology upgrading in the global biopharmaceutical sector (Malerba and Orsenigo 2015), complemented by documentary research on the Brazilian public policies and application of semi-structured interviews with relevant stakeholders in the field. To understand aspects of R&D activity in MAbs and the organization of the Brazilian national health policies about public procurement and acquisition of biopharmaceutical goods and strategic inputs, three preliminary interviews were conducted in the city of São Paulo, Brazil: one with a specialist in molecular biology and two with former directors of the MH between February and March 2016. We reviewed nine official reports, two memoranda, and five meeting minutes of the so-called Executive Group of the Healthcare Industrial Complex (*Grupo Executivo do Complexo Industrial da Saúde*, GECIS), a key player of the PDPP. Additionally, directives issued by the Brazilian government between 1994 and 2019 were reviewed (available at the MH's databases and website, some referenced).

Data obtained to understand the role of public policies in the actual development of national capabilities of the emerging local biopharmaceutical industry in Brazil are based on open and semi-structured interviews carried out between 2016 and 2017 in person and by e-mail (two interviews of a policymaker from the National Bank for Economic and Social Development (BNDES) and a specialist from Brazilian Center for Research in Energy and Materials (CNPEM), see Table 1) with twenty-three professionals involved with policies and initiatives of R&D in MAbs. During this period, the paper's first author visited companies' offices and plants of private and public laboratories in Brazil as well as performed online meetings with stakeholders to expand our understanding about this field.

Then, sixteen interviews have been recorded and transcribed—five interviewees did not authorize recording. Participants were selected based on documentary research and due to their participation as speakers in GECIS decision-making forums and/or in strategic meetings of the PDPP. Consultants, professionals of R&D, and policymakers were selected by reading scientific articles, opinion pieces, and conference papers on the Brazilian biopharmaceutical industry. A search in the São Paulo Research Foundation's Virtual Library (BV FAPESP) informed our interviewee selection by listing grants and scholarships awarded to researchers working with MAbs in the state of São Paulo.[1] All of the interviewees hold senior/managerial roles in their organizations, and governmental boards and agencies i.e., CEOs/presidents of companies, directors and head of R&D departments in national and foreign biopharmaceutical companies; laboratory leaders and managers, in the case of public healthcare and medical research centers, and in innovation centers, in the case of private institutions; and full and associate professors and senior researchers employed by the top three universities and research institutes based on the number of publications on MAbs, i.e. University of São Paulo, Oswaldo Cruz Foundation, and Federal University of São Paulo. In total, nineteen institutions were visited between January 2016 and April 2019 in four Brazilian states (São Paulo, Minas Gerais, Rio de Janeiro, and Paraná). These involved primarily private and public pharmaceutical companies and individuals connected to federal government agencies. Information about the interviews is available in Table 1.

Primary questions posed to interviewees dealt with their relationship with the agenda of design and implementation of public–private partnership for MAbs' technology transfer and manufacturing over the last two decades, as well as other topics related to their:

(1) understanding about the role of interlocutors to interfere in the NSI in the biopharmaceutical sector internationally,
(2) involvement with decision-making processes and institutionalization of the PDPP,
(3) understanding about the role of R&D professionals, from universities, state research institutes, and businesses in the emerging biopharmaceutical sector in Brazil,
(4) relationship with pharmaceutical industry and the national healthcare systems,
(5) awareness about the lack of national capabilities of private companies and public laboratories to manufacture and deliver MAbs in local and global markets,
(6) participation in technology transfer and public procurement of health inputs in Brazil,
(7) comprehension about challenges of manufacturing process of biopharmaceuticals,
(8) perception about the lack of knowledge-intensive business service companies as intermediaries of R&D activity in MAbs' technological development,
(9) academic training and professional experience to localize and evaluate the impact of strategies of the Brazilian biopharmaceutical development,
(10) knowledge about the role of public laboratories as niche of industrial development,
(11) ideas about the future of the biopharmaceutical industry in Brazil, etc.

Table 1. Details of the interviews ($n = 23$).

Role	Institution	Interview day
Policymakers	Brazilian Ministry of Health—Department of Science and Technology DECIT	6 December 2016
	Ministry of Industry Development and Foreign Trade	5 December 2017
	Ministry of Science, Technology and Innovation (2008–2014)	9 August 2017
	National bank of Social and Economic Development BNDES	12 December 2016
Managers of public and private pharmaceutical companies	RECEPTA Biopharma	6 March 2017
	Brazilian Company of Pharmaceutical Biotechnology Bionovis S.A.	7 November 2016
	Merck Sharp and Dohme MERCK BRAZIL	5 July 2017
	Aché Laboratórios Farmacêuticos S.A.	10 November 2017
	Immunological Technology Institute BIO-MANGUINHOS	9 December 2016
	Ezequiel Dias Foundation FUNED	10 November 2016
	Paraná Institute of Technology TECPAR	18 May 2017
Representatives of industry associations	Association of the Pharmaceutical Research Industry INTERFARMA	31 January 2017
	Association of Official Brazilian Pharmaceutical Laboratories ALFOB	10 April 2017
	Associação Brasileira das Induústrias de Quiímica fina, biotecnologia e suas especialidades ABIFINA	3 May 2017
R&D specialists	University of São Paulo—Faculty of Medicine's Department of Radiology and Oncology	16 October 2017
	São Paulo Cancer Institute—Center for Translational Research in Oncology Lab	14 December 2017
	Instituto Butantan	21 November 2017
	RECEPTA Biopharma	24 August 2017
	Federal University of São Paulo—Faculty of Medicine's Department of Biophysics	16 August 2017
	Brazilian Center for Research in Energy and Materials CNPEM	12 May 2017
Consultants	Federal University of Rio de Janeiro—Institute of Economics	3 April 2017
	Oswaldo Cruz Foundation FIOCRUZ	18 April 2017
	Federal University of São Paulo—Vice-Dean	19 October 2017

Thematic interview guides have been constructed based in an extensive literature review about the characteristics of the biopharmaceutical industry internationally (Danzon and Nicholson 2012), as well as on articles, reports, and materials published by Brazilian experts on the so-called Health Economic-Industrial Complex (Gadelha et al. 2013), on the evolution of the public–private partnerships as instruments of the Brazilian National Health Policy (Torres and Hasenclever 2016), and on scientific and technological (Ecker et al. 2015) and political (Mittra 2016) specificities of the knowledge production and innovation in MAbs.

Additionally, since semi-structured interviews provide flexibility to adapt relevant topics during the research practice, several questions have been proposed from the experience of the first author during visitations in factories of private pharmaceutical companies and science labs of research institutes. For instance: under what conditions a biosimilar version of a branded medicine can be developed from scratch, practical aspects about how a team of engineers access and actually implement technology transfer processes, as well as questions about risk of those investments and potential conflicts of interest between state, public, and private national stakeholders and international companies that own the rights of licensing MAb technologies to be commercialized globally.

We then applied content analysis in the transcript results from the interviews over the course of 2019, as well as data from personal annotations during non-recorded interviews, visitations, and meetings of the New York University's Stern School of Business's symposiums and the New York Bio Pharma Networking Group (NYBPNG) events in 2018. Following Prasad (2008), content analysis is applied in our research as a method that 'falls in the interface of observation and document analysis' or 'a method of observation in the sense that instead of asking people to respond to questions', it 'takes the communications that people have produced and asks questions of communications', considered, then, 'as an unobtrusive or non-reactive method of social research' (Prasad 2008).

We remember that accessing data on decision-making of biopharmaceutical companies and governmental agencies was a challenge, since information about content of contracts, protocols, health technology assessment reports, and acquisition and technology transfer minutes are usually considered confidential, i.e. not easily turned public by leaders and directors of companies and public laboratories. It has complemented by informal meetings with professionals from the biopharmaceutical sector during the participation of the first author in events of NYBPNG from Fall 2018 to Winter 2019, while being visiting scholar in the New York University Stern School of Business' Department of Management and Organizations. This multi-method approach proved to be central to improve our comprehension of the global dynamics of technology in the biopharmaceutical sector.

Finally, methodology and preliminary results of the study were presented and discussed during the first author's participation in the Atlanta Conference on Science and Innovation Policy in 2016 and in the 23rd Conference on Science and Technology Indicators in Leiden, The Netherlands, in 2018. A final version of this paper and its conclusions has been presented in person in the Science, Knowledge, and Technology seminar series of the Department of Sociology of Columbia University in New York City in 2020 and remotely in the Forum of the International Sociological Association in 2021 in Porto Alegre, Brazil.

4. Trajectory of productive development policies in the Brazilian healthcare industry

Since mid-2000s, the implementation of productive development policies by the Brazilian federal government is a key

trend of the institutional change to set in motion technology-upgrading processes in the local healthcare industry—broadly affected by a reconfiguration of the global biopharmaceutical sector in the last two decades (Varrichio 2017). Those policies were primarily articulated as a State priority by the Brazilian National Health Policy (NHP) from 2004 afterward,[2] and the MH was the national authority responsible for the planning, design, implementation, and evaluation of productive development policies to the healthcare industry[3] (Ministério da Saúde 2016).

Historically, the MH has taken significant steps toward improving the interplay between agendas of healthcare inputs delivery and access and manufacturing development since late-1990s. One example of such agencies is the Department of Science and Technology (*Departamento de Ciência e Tecnologia*, or DECIT) created in 2000 to foster initiatives of science and technology as drivers of the healthcare sector. DECIT results of years of debates between policymakers and public health specialists involved the establishment of the Public Healthcare System (*Sistema Único de Saúde*, or SUS) by late 1980s, and it can be understood as a practical political tool of the National Policy on Science and Technology in Healthcare (*Política Nacional de Ciência e Tecnologia em Saúde*, or PNCTIS[4]) implemented years later in 1994 and led by the National Health Council (*Conselho Nacional de Saúde*, or CNS)[5] (Ministério da Saúde 1994: 36).

Despite the advances in the previous decade, it was only from 2002 that the MH explicitly positioned itself as a central player in the development of the national healthcare industry—integrating multiple state-driven industrial policies for economic development which lasts until the country's political crisis in 2015 (Doval and Actis 2016).[6] In 2004, the federal government created the National Secretariat of Science, Technology, and Strategic Inputs (*Secretaria de Ciência, Tecnologia e Insumos Estratégicos*, or SCTIE), incorporating DECIT in its institutional framework. The SCTIE represents an important step toward institutionalization of agendas of Science and Technology as a component of the NHP, created to reach the PNCTIS goals regarding medical inputs and manufacturing capabilities in healthcare (Ministério da Saúde 2016).

This new political framework became popular among pharmaceutical industry associations and led to higher participation of local and multinational companies with operations in Brazil in policymaking. Particularly noteworthy is the emergence of new alliances between the government and the drug manufacturing sector, composed of private domestic and foreign companies and the public pharmaceutical laboratories[7] (Interfarma 2012).

In 2006, discussions arose within the MH about the need to implement a set of productive development policies to meet NHP's needs (Costa et al. 2015). In 2008, the Executive Group of the Healthcare Industrial Complex (GECIS) has been created under the SCTIE structure, responsible for conducting meetings, decision-making, and deliberations regarding technology-upgrading policies and improvement of Science and Technology (S&T) in the healthcare sector.[8] GECIS aimed to facilitate the governance of a heterogeneous set of public–private stakeholders bringing solutions to MH instances, and by 2010 the federal government authorized a new package of official initiatives to compose the so-called 'Plano Brasil Maior', a National Industrial Policy Strategy launched in August of 2011 that selected Healthcare as an strategic sector, with implications to the fiscal sustainability of ongoing agendas of productive development policies (Silva and Novaes 2017).

4.1 The Production Development Partnership Program (2012)

According to Gadelha and Temporão (2018), technology-transfer-oriented productive development policies were the preferred political approach adopted by the MH for improving the Public Healthcare System, and it would contribute to the creation of new jobs and investments in the local healthcare industry. To achieve these goals, a systemic articulation among different agents was promoted to foster technological learning and upgrading in domestic agents (Varrichio 2017). It has been followed by ordinary policies of the MH, like the management of public procurements of pharmaceutical goods and inputs, and initiatives to lower prices of high-cost biological medicines purchased by the Public Healthcare System (Gadelha and Temporão 2018). Regarding public procurement of high-cost biopharmaceuticals, initiatives were geared toward purchasing cheaper *biosimilars*.[9] Aiming at reducing governmental expenditures with drug purchase and acquisition and by dealing with NHP's directions, the so-called PDPP has been officially registered under Directive No. 837 on 18 April 2012, three years after its first partnership in 2009 (Silva and Elias 2019: 221).

PDPP is a Brazilian public policy designed to create business partnerships to create or strengthen technology/manufacturing capabilities of local producers of health inputs like diagnostic tests, reagents, personal protective equipment, pharmaceutical goods, high-cost biopharmaceuticals like vaccines, serums, proteins, and immunomodulators, and other technologies (Ministério da Saúde 2016). The program incentivizes public pharmaceutical laboratories and private firms (domestic or foreign), in which the federal government agrees to purchase the manufactured products resulting from partnerships, to guarantee a steady supply of strategic drugs and healthcare inputs for the proper functioning of SUS. The main goals of the PDPP are described in Table 2.

The PDPP is centralized in three decision-making bodies: the Technical Evaluation Committee, the Deliberative Committee, and the Technical Regulatory Committee. The partnerships fall into one of four categories—PHASE I: Evaluation and decision; PHASE II: Technology absorption and transfer; PHASE III: Technology absorption and transfer with acquisition; and PHASE IV: Technology internalization, as presented in Fig. 1.

Since manufacturing capabilities are strategic to a successful technology transfer entrepreneurship, the program invested financial resources in the building of new biopharmaceutical factories or to expand already-existing biotechnology facilities. Long-term loans came from BNDES through the Program to Support Healthcare Industrial Complex Development, launched in 2013 and considered a key associated policy of PDPP (Costa et al. 2015).

When the PDPP was fully implemented by 27 June 2013, partnerships were contracted involving seventeen national and foreign private companies and eight national public laboratories. About a year later, proposals for additional 104 partnerships were submitted, involving fifty-seven private and nineteen public laboratories. These agreements called for

Table 2. Priority areas of the *PDPP*.

Priority areas	Description
Public procurement in health	To optimize the use of the public procurement through selective centralization of expenditures in public health, with the goal of lowering SUS' purchasing costs and facilitating the production of innovative products in the country, focusing on improving the public's access to strategic products
Technological development	To promote joint technological development and exchange of knowledge in the interest of innovation by public and private Brazilian manufacturers, building a solid base that allows them to be competitive and prepared to compete globally in a context of constant technological change
Manufacturing development	To focus on local manufacturing of high-cost products which are deemed strategic for SUS and/or which have significant health and social impacts, ensuring full availability and thus reducing SUS' vulnerability
Reducing prices of health technologies	To negotiate significant and progressive price reductions as technology is transferred and developed, in accordance with SUS' strategy, which might reduce the governmental expenditures with health products and inputs

Source: elaborated by the authors, based on official data of the MH (2017).

establishing partnerships to develop 101 products of interest to Brazilian public health—among them are seventy-three drugs and biological products (about six MAbs in 2019) and twenty-eight additional healthcare products. According to data from the Department of the Healthcare Innovation and Industrial Complex 100 partnerships were active as of March 2019, involving thirty-eight private and fourteen public companies (Ministério da Saúde 2018).

4.2 Dynamics of technological upgrading in the public–private partnerships for biosimilar monoclonal antibodies

The rise of expenditures with healthcare has been a cause for concern around the world. In Europe and USA, those costs are primarily incurred by families and health insurance plans, but in countries with Universal Public Healthcare System like Brazil, most of it has been covered by the governments. According to Osorio-de-Castro et al. (2014), in 2014, despite representing just 4 per cent of the list of products delivered by the Public Healthcare System, 51 per cent of the governmental funding addressed to buy health medicines and inputs has been directed to the acquisition of biological medicines and other biopharmaceutical products (Osorio-de-Castro et al. 2014).

As a result, purchasing MAbs is at the center of the health policy planning international debate since the last decade (Danzon and Nicholson 2012). Given the high demand and cost for those biopharmaceuticals in Brazil over the last 20 years, MAbs were a priority in the PDPP. According to one policymaker interviewed: 'To reduce the governmental healthcare expenditures is the main goal of the political framework' (Policymaker).

Since accessing MAbs is expensive and technologically complex, this is considered a great challenge for the Brazilian healthcare planning (Silva and Novaes 2017). Thus, the aim of the PDPP is well-known by its stakeholders, i.e. 'to train the industry, whether public or private, to produce medicines that burden the National Public Health System. It was an interesting solution, it is a 5-year process in which technology transfers gradually and, at the end of 5 years, you would have this qualification' (Policymaker).

The fiscal impact of this sector in the Brazilian market is clear. Brazil figures as the main country in volume of imports of pharmaceutical goods in Latin America, registering more than 7.3 US$ billion in its international trade balance (Statista 2022) (Fig. 2).[10] The Brazilian biopharmaceutical market is strongly supplied by imported products, and according to SISCOMEX more than 56 per cent of biopharmaceutical profits come from the trade of few MAbs (Gomes et al. 2016). Luz et al. (2017) showed that the MH witnessed an accelerating increase in expenses with two types of biopharmaceuticals—immunomodulators and antineoplastic (MAbs, fusion proteins like etanercept, and other biological preparations) (Luz et al. 2017).

A central aspect of the PDPP is its focus on the manufacturing of biosimilar versions of branded MAbs for which patents have already expired, established by partnerships that allowed local companies to produce MAbs commercially. Thus, the products and technologies that are being transferred to Brazilian companies and public laboratories are not necessarily new

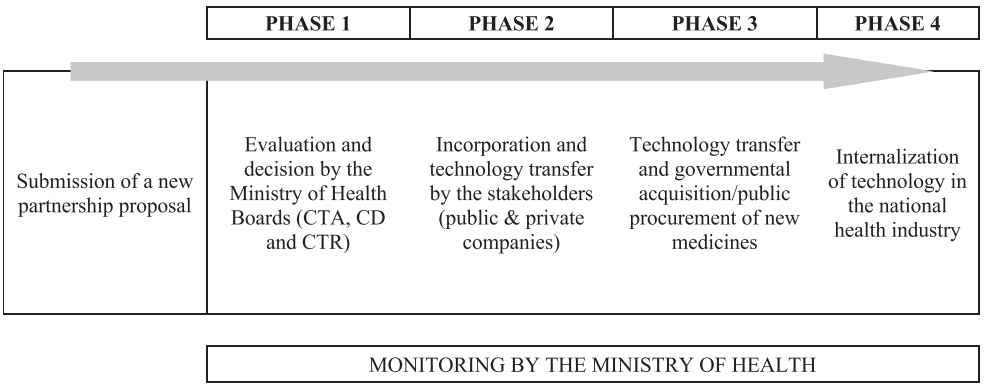

Figure 1. Phases of the PDPP.

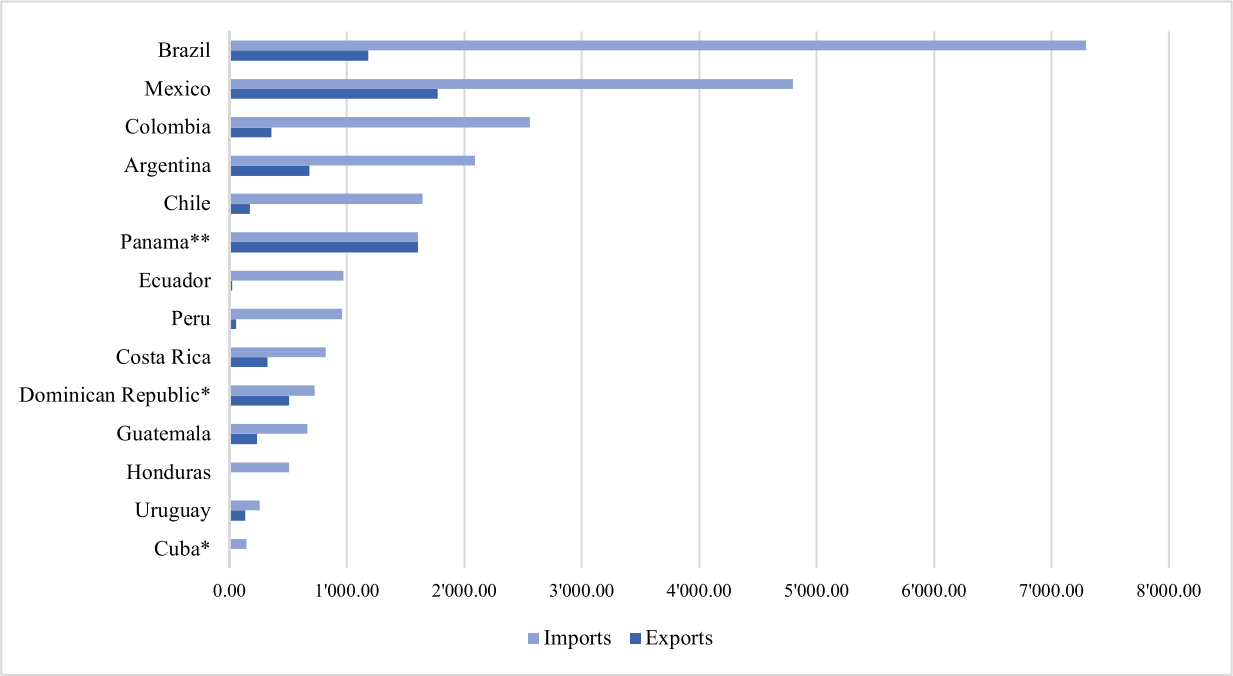

Figure 2. Pharmaceutical imports and exports of major Latin American countries in 2019 (US$ million).

molecules and are part of the multinationals' portfolio of expiring patents of the global pharma businesses. It has been discussed in the interviews: [the PDPP's partnerships focus on] 'products whose patent has already expired or is about to expire. Or, even if the patent has not expired, there is already another product behind it that will surely replace it' (Policy-maker). For example, the six MAbs chosen to be produced by the Brazilian company Bionovis S.A. have patents that expired in 2012.

Infliximab was the first MAb produced in the PDPP scheme. The partnership was implemented in 2015 between Janssen-Cilag, the Brazilian joint venture Bionovis S.A.,[11] and the public company Bio-Manguinhos. According to IPEA (2018), the branded product of *infliximab* Remicade® is in the Brazilian market since 1998, but since 2015 more than 80 per cent of all vials of biosimilar *infliximab* acquired by the MH were produced through PDPP. It represents approximately 180,000 vials at a total cost of $175 million of Brazilian Reais (BRL) (approx. US$33 million) (IPEA 2018: 45).

Other partnerships include *adalimumab* and *rituximab*, established between multinational companies and public and private local companies. Three partnerships for *adalimumab* were established, one of them by foreign companies Alteogen, Mabxience, and PharmaPraxis, the joint venture Orygen Biotecnologia,[12] the private local company Libbs, and the two public companies—Instituto Vital Brasil IVB and Bio-Manguinhos.[13] For *rituximab*, a partnership among Pfizer, Orygen Biotecnologia, and the public company Bahiafarma was implemented, but terminated in 2019 due to technical and political issues in the technology transfer process.

Lastly, in 2016 a partnership for *bevacizumab*—an internationally well-known MAb for cancer treatment—was signed. This partnership was executed among a group of private companies (Biocad, Libbs, Mabxience, Orygen, Alteogen, and Bionovis) and Bio-Manguinhos (Ministério da Saúde 2018). By the end of 2019, twelve partnerships for seven MAbs have been established as part of the PDPP as we can see in Table 3.

4.2.1 Intensity of technological upgrading

These examples illustrate and provide empirical support for the discussion of the PDPP's partnerships from the perspective of technology upgrading. Regarding the *Intensity of Technological Upgrading* dimension, associated with current levels of technological capabilities and efforts available in domestic firms, Brazilian biopharmaceutical companies involved in the partnerships (i.e. mainly emerging joint venture of private companies and public pharmaceutical laboratories) work more with biosimilars than with innovation specifically: 'In our way to understand, biosimilars are not innovation' (Specialist in R&D). It is about developing new processes and products for the company and not exploring innovations for the sector to be competitive in global markets as stated by one interviewee: '[…] all those policies [of PDPP] have no component of radical innovation' (Consultant). In addition, the partnerships do not discuss issues related to access to raw materials, that is, to the pharmaceutical ingredient. In this regard, the country will continue to be dependent on the foreign market for frontier knowledge production, placing the PDPP policy as an initiative that addresses pre-entry and entry stages of technology upgrading, but falling short in spurring the innovation phase in domestic agents.

An outlier in this context is Recepta Biopharma (ReceptaBio). Cited in different interviews as a company focused on MAbs' R&D activities, ReceptaBio sought to develop its technological capabilities through the consolidation of an internal center of excellence and the development of a research network with scientists from national institutions like the University of São Paulo, Instituto Butantan, Federal University of São Paulo, and Oswaldo Cruz Foundation, among other

Table 3. Details of the Brazilian productive development partnerships (2008–2019). Obs.: Several partnerships might have been withdrawn or discontinued after 2019, as well as new contracts of partnerships for MAbs can be included in the PDPP scheme from 2019 onward. Changes in ongoing partnerships or new PDPP contracts established from 2019 might have been changed the configuration presented in the table.

Details of the Brazilian productive development partnerships for MAbs in Brazil (2008–2019)								PDPP Stakeholders (2008–2019)		
MAb product (name)	Brand name	Technology holder or licensed by	Country	Approval date FDA EMA	Patent/Exclusivity expiry dates in the USA and Europe	Process number and date of first registry at ANVISA	Partnership approved in the PDPP scheme at	Public pharmaceutical companies/Official labs	Brazilian private companies	Foreign/ Multinational companies
Adalimumab	Humira®	AbbVie	USA	Dec 2002 Jun 2003	Dec 2016 Oct 2018	105,530,294 April 2003	2013	Bio-Manguinhos; Instituto Vital Brasil; Bahiafarma	Orygen;Libbs	Alteogen; PharmaPraxis; Mabxience
							2015	Fundação Ezquiel Dias	Bionovis	Merck Serono
							2018	Instituto Butantan	Libbs	–
Rituximab	Rituxan®; MabThera®	Biogen	USA	Nov 1997 Jun 1998	Sep 2016 Nov 2013	101,000,548 Jun 1998	2013	Bio-Manguinhos; Instituto Vital Brasil; Instituto Butantan	Bionovis;Libbs	Mabxience
							2015	Bahiafarma	Orygen	Pfizer
							2015	Instituto Butantan	Libbs	–
Certolizumab; Pegol	Cimzia®	UCB Pharma	Belgium	Apr 2008 Oct 2009	Feb 2024 Jul 2021	116,180,239 May 2011	2013	Bio-Manguinhos	–	UCB Pharma; Meizler
							2018	Bio-Manguinhos	Bionovis	–
Trastuzumab	Herceptin®	Genentech; Roche	USA;Switzerland	Sep 1998 Aug 2000	Jun 2019 Jul 2014	101,000,552 Sept 1999	2013	Bio-Manguinhos; Instituto Vital Brasil; Bahiafarma	Orygen;Libbs	Alteogen/ PharmaPraxis/ Mabxience
Infliximab	Remicade®	Centocor; Janssen Biologics; Janssen Biotech Inc.	Netherlands; USA	Ago 1998 Ago 1999	Sep 2018 Feb 2015	100,930,208 Dec 2000	2013	Bio-Manguinhos	Bionovis	Jansen-Cilag
Cetuximab	Erbitux®	Eli Lily and Company	USA	Feb 2004 Jun 2004	Feb 2016 Jun 2014	100,890,335 Oct 2006	2013	Bio-Manguinhos; Instituto Vital Brasil; Instituto Butantan	Bionovis/Libbs	Mabxience
Bevacizumab	Avastin®	Genentech; Roche	USA;Switzerland	Feb 2004 Jan 2005	Jul 2010 Jan 2022	101,000,637 May 2005	2013	Bio-Manguinhos; Instituto Vital Brasil; Instituto Butantan; TECPAR	Bionovis;Libbs; Orygen	Mabxience; Biocad; Alteogen

Source: elaborated by the authors with data from Ministério da Saúde (2016), Varrichio (2017), IPEA (2018), and Pimentel (2018) and from the interviews.

international collaborations, like Ludwig Institute for Cancer Research, Mabxience, and Merck Serono. However, according to some interviewees (consultants and specialists in R&D), ReceptaBio outsourced a series of internal activities upon the entry of new investors, relying on the established competence of its partners. This movement allowed the company to exchange skills and not depend on internal infrastructure, in addition to minimizing delays. On the other hand, it resulted in communication and flexibility difficulties due to the absence of face-to-face interactions and limited the scientific publication of the company's research results—an aspect that hindered further connections of the firm with the academic community. As one interviewee from ReceptaBio stated, because of challenges associated with coordination with partners, 'an internal scientific team would be able to generate more [scientific] publications'.

4.2.2 Breadth of technological upgrading

In the second dimension, *Breadth of Technological Upgrading*, related to the levels of diversification of the productive system, complementary infrastructure, and organizational capabilities of economic agents, our study indicates scarce capabilities in universities and research institutes in their involvement with R&D activities on MAbs. This perception is not unique and exclusive to companies. Interviewees from research institutes mention that, despite having equipment that could be offered as facilities for the industry, these platforms are not accredited for production. Research made in these units needs to be replicated and validated externally. Specialists in R&D from the private sector confirm this difficulty. According to one interviewee, academic research lacks the rigor demanded by the industry in terms of dynamic range, reproducibility, and test validation. Despite the existence of testing equipment, university laboratories do not have the human resources to operate the equipment in accordance with the guidelines of good practice in the pharmaceutical industry. Furthermore, universities face an organizational challenge regarding Technology Transfer Offices, with professionals with low level of previous business experience, thus affecting the fluidity of technology transfer processes. The following sentence confirms these challenges: 'S&T is important to the sector, but in Brazil the academic sector is to slow and have no technical competence to respond to the market time and demands' (Pharmaceutical Companies).

We understand this dimension as one of the most problematic in Brazil's technology-upgrading process in the emerging biopharmaceutical industry of MAbs. According to managers from multinational pharmaceutical companies, Brazil's health industry does not have the competences for the development and production of a monoclonal for therapeutic purposes, but only for diagnostic kits or intermediary products. Indigenous agents do not have the specific knowledge, human resources, financial resources, routinized R&D activity, and adequate manufacturing infrastructure that allow for an increase in the Breadth of Technological Upgrading between PDPP's stakeholders. The interviewee from a national pharmaceutical company highlights that the partnerships will not solve the problems related to these aspects. For him and for the industrial associations, the recipients of technologies, in this case the research institutes, do not have the necessary capabilities to absorb the transferred technologies: 'The national system of S&T is basically academic and not oriented to the challenges of the industrial sector' (Consultants).

Additionally, it is observed that PDPP in Brazil pays little attention to start-ups and knowledge-intensive business services (Lafuente et al. 2017), which are relevant players in the biopharmaceutical industry internationally. After years of analyzing this policy, the debate on the potential role of knowledge-based start-ups as intermediaries in MAbs' manufacturing projects is marginal or even inexistent in its official documents and policy reports. According to interviewees, start-ups working with the discovery of drugs and biotechnological products in Brazil exist in a limited number, signaling a lack of maturity in this specific sectoral system, considering that entrepreneurial activity grants dynamism to innovative endeavors. Particular attention should be paid to academic entrepreneurs with a strong scientific base. Instituto Butantan and Orygen Biotecnologia, for example, have implemented initiatives in this sense, expanding partnerships with the São Paulo Research Foundation and research institutes in São Paulo State and Rio de Janeiro and seeking to encourage its researchers to create start-ups, given that technology transfer to the market and even the development of medicines are not viable alternatives. However, this is not articulated with the political tools of PDPP or part of a more coherent national strategy to improve the biopharmaceutical development.

4.2.3 Interactions with the global economy

In the third and final dimension, which concerns *Interactions with the Global Economy*, it is recognized that the PDPP collaborated to improve a positive interaction between national and multinational companies/institutes globally. Interaction and knowledge flows are evident in the case of infliximab Remicade®, the partnership among Janssen-Cilag, Bionovis S.A., and Bio-Manguinhos, and rituximab, the partnership between Libbs and Mabxience. Regarding the last, in 2019 Libbs launched Vivaxxia, being the first biosimilar MAb fully manufactured in the country, i.e. a direct result of the PDPP about a decade after registering of the first list of MAb partnerships. Examples of interactions with the global economy were reported by managers of ReceptaBio, with the production of an antibody in the Netherlands and the performance of animal tests in North Carolina and cell assays in England. The interviewees acknowledge the benefits of collaborating with international partners: 'we run projects of innovation with partners abroad. We have an offer of companies that are more competent to attend our demands, since we have to do things very fast' (Pharmaceutical Companies).

In addition, interlocutors affirm that PDPP fostered a change in the place of Brazilian pharmaceutical companies in the global sectoral network. Even companies that do not have partnerships for technology transfer within the scope of the program have sought to establish more complex partnerships. Aché Laboratórios Farmacêuticos S.A., for example, joined the Structural Genomics Consortium to 'gain experience, accelerate projects and even develop a network of people in Brazil who can work with drug discovery' (Pharmaceutical Companies).

Notwithstanding, interlocutors consider that PDPP contributed little to the creation of sustainable and endogenous innovative capabilities in the national pharmaceutical industry. According to an interviewee from one of the industry associations, Brazilian companies producing MAbs are not

'receiving a technology from today's molecule of monoclonal, but one from a few years ago. So, 5 years from now, when they control the technology, they will have gone back 15 years'. Specialists in R&D and consultants share the same view. For specialists in R&D, 'We are always making copies and transferring old technologies in health, that is why we have no international competitive sector of pharmaceutical products', while for consultants 'It is not possible to speak that we are creating a competitive industry for international standards'.

Further interviews corroborate this perception and agree that PDPPs promote the development of productive capabilities—but not technological ones—by offering access to the Brazilian market. PDPPs are still 'a somewhat short-sighted policy from the point of view that local manufacturing and production does not mean a technological advance of the country on its own. The production of biological medicines, even with advanced technology, if it does not generate enough knowledge to allow the research and development of new biological compounds, will quickly become obsolete' (Pharmaceutical Companies).

5. Discussions and implications

Our findings highlight the controversial role and outcomes of the policies for the biopharmaceutical development in Brazil. On the one hand, the implementation of a new institutional regime of policies and initiatives improved the local businesses to respond to the governmental agenda. On the other hand, this state-centered agenda, sustained by technology transfer contracts of obsolete technologies, hindered a more effective insertion of Brazilian biopharmaceutical companies in GVCs. This happened as a function of the lack of strategies targeting the development of innovative capabilities in indigenous agents. In this regard, the PDPP policy seemed to be oriented at triggering pre-entry/entry stages, but it lacks an approach to build on these and reach the innovation stage of technology upgrading.

As a result, limits for technological evolution have negatively affected learning processes, thus failing to generate competitiveness improvement. This carries relevant lessons for a wide array of STI policies in developing countries, with relevant implications for the development of biomedical knowledge worldwide (Costa and Silva 2019). Of course, recommendations derived from our analysis are based on the Brazilian case, and implications of our analysis do not necessarily reflect the heterogeneous reality of other catching-up economies. Nonetheless, we believe that some key insights from our assessment can shed light on processes of policy formulation toward technology upgrading beyond the Brazilian context.

In this regard, policymakers ought to consider that differences in pre-entry/entry and innovation stages require distinct approaches in order to lead to capabilities associated with knowledge creation (Wong 2001). This seems to be the next step in the technology-upgrading ladder for MAbs in Brazil, a lesson that resonates with experiences in other countries and sectors across the Global South. In this section, we dig further into the implications of our assessment for these dynamics.

5.1 Technology upgrading and institutional context

The study of technology upgrading processes of the biopharmaceutical industry in Brazil shows how sectoral stakeholders merge different *institutional rationales* to implement new governing frames to foster manufacturing capabilities of local companies of the healthcare sector. According to Kukk et al. (2016), institutional change is a crucial component of implementing sustainable technological upgrading, and PDPP can create a favorable environment to technological development, learning, and creation of collaborative networks. Governance approaches adopted by scholars suggest that policy designs dedicated to foster technology upgrading are constantly seeking to advance interests relating to filling technology gaps in economic sectors and that this agenda advances the relationship among conventional governmental agencies, businesses, and civil society (Marks et al. 1996; Silva and Costa 2012; Radosevic and Yoruk 2018).

On the other hand, this should not be confused with institutional *uncertainty*, an outcome of significant changes in the PDPP policy that changed the rules of the game for ongoing projects (Varrichio 2017). Hence, while PDPP does require experimentation and adequations—since it is an institutional innovation in its own merit—it must also be met by long-term stability in order to promote systemic shifts in the technological capabilities of public and private agents (Roca et al. 2021; Yu et al. 2020; Choung and Hwang 2019). Technology upgrading is a long-term process surrounded by technological and market uncertainties. Accordingly, it requires an institutional environment that allows agents to evolve and develop adequate capabilities. Constant shifts in policy will reduce the propensity of agents to engage in effective technology upgrading, but institutional rigidity can also have deleterious effects in these dynamics. Based on this discussion, the first recommendation from our research can be outlined:

> ***Takeaway #1—The implementation of effective technology-upgrading policies requires a delicate balance between change and stability in the institutional context.***

5.2 Technological capabilities and prioritization

Historically, technology transfer has been the preferred instrument of technology upgrading of catching-up economies, when trying to overcome technology gaps of the national economy. This phenomenon occurs for different reasons and may be related to the high risk to innovate (Fu et al. 2011), to the existence of ineffective public policies incentivizing industry and R&D-based services (Guimarães 1989), to high overhead costs for businesses engaged in that kind of activity in developing countries (Furtado and Freitas 2000), to the low demand for knowledge in the businesses operating in those countries (Chan and Daim 2011), or to a global expansion in the supply of R&D available internationally, facilitated by the diffusion of information technologies as a result of the globalization (Barnett 1994).

However, as demonstrated in our assessment, technology transfer per se does not necessarily lead to the internalization of technologies and to the generation of innovative capabilities in indigenous agents. As argued by Lacasa et al. (2019), the paths toward effective technology upgrading are myriad and they involve complex decisions by policymakers and economic agents. Importantly, this notion is attached to the formulation of policy mixes—rather than standalone initiatives. They can assume different configurations—which must fit the local socioeconomic characteristics—but will demand a combination of mechanisms that can leverage technological

capabilities in firms (Kergroach 2019). Such perspectives did not seem to be included as part of the PDPP rationale. Instead, a focus on price reduction appeared to overshadow interests in triggering technology upgrading. This is problematic in that it may create an industry oriented solely to the domestic market and that it can only be cost-competitive under the umbrella of trade restrictions. In this case, the surplus of users of the healthcare system will be diminished. Such background leads to our second and third takeaways:

> **Takeaway #2—The implementation of effective technology-upgrading policies requires considering the existing levels of agents' technological capabilities and relatedness levels with other technological domains. Such features are key not only to promote more efficient knowledge absorption, but also to reach the innovation stage of technology upgrading processes and generate valuable spillovers for other activities.**

> **Takeaway #3—While the focus on social challenges is a legitimate platform to inform technology-upgrading policies, it must be integrated with contextual features of the innovation system involving aspects related to productive specialization and existing capabilities in domestic agents.**

In addition, prior literature recommends that countries facing middle-income traps should focus on short-cycle technologies as a more efficient way of generating faster technological and economic progress (Lee 2013). Biopharmaceuticals are not part of this group of technologies. Hence, its potential to leverage technological progress and spillovers is *limited*. propose that only after the country enters the high-income status it should orient its innovation system toward long-cycle technologies with higher entry barriers. Accordingly, our fourth corollary follows:

> **Takeaway #4—The implementation of effective technology-upgrading policies should consider the technological cycle of target technologies. Effects of specific knowledge domains on economic development and growth shall vary, and prioritization strategies need to incorporate this perspective.**

5.3 Systemic engagement

Knowledge generation and diffusion in health industries is highly dependent on a systemic perspective, thus involving myriad agents (Tatsch et al. 2022). Our analysis revealed that universities, agents that have been identified as critical for technology upgrading in the Brazilian context (Tatsch et al. 2022; Fischer et al. 2019), had marginal contributions for PDPP projects (Pimentel 2018; Varrichio 2017). These dynamics represents a core weakness of the sub-systems responsible for generating technological upgrading in the country. In fact, firms are only weakly connected to research networks in the country (Tatsch et al. 2022). As a result, scant technological development takes place in the Brazilian health sector as a whole.

As Tatsch et al. (2022) propose, this appears to be a function of the heavy reliance on multinational corporations (which focus on technological development in their home countries) and the lack of innovative capabilities in Brazilian firms to engage in the production of MAbs (which makes them less prone to establish collaborations with academic partners). In turn, public laboratories play a central role as agents of knowledge acquisition and technological development (Varrichio 2017). However, as our findings suggest, such an approach of state-led technology upgrading falls short in creating the condition for systemic evolution.

On a related subject, the promotion of knowledge-intensive entrepreneurship and supportive ecosystems is key to nurture the evolution of technological and innovative capabilities (Lin 2017). Unfortunately, this does not seem to be the case in Brazil, where the incipient scene for biotech start-ups demonstrates lack of venture capital and lack of collaborations between these nascent ventures and large incumbents (Torres and Hasenclever (2016)). Such background leads to our fifth takeaway:

> **Takeaway #5—The implementation of effective technology-upgrading policies should promote and be based on systemic engagement. While fostering specific networks of agents for concrete objectives can be a good starting point, technology upgrading requires broader interactions that go beyond centralized governance.**

5.4 Global connectedness

Guennif and Ramani (2012) offer an interesting approach to the experience of the pharmaceutical sector in developing countries, focusing specifically on India and Brazil. By analyzing their experiences and trajectories, the authors show that the two countries faced asymmetric levels of access to global R&D networks (Guennif and Ramani 2012: 434). In our analysis, the policy frameworks considered solely a unidirectional process of technology transfer as a pillar for systemic upgrading in biopharmaceuticals. The co-creation of knowledge has not been part of the agenda, leaving domestic players still in a position of dependence and struggling with the challenge to translate the results to public needs—as shown by the recent coronavirus disease-19 crisis and lack of vaccine knowledge, manufacturing, and innovation capabilities in Brazil (da Silva et al. 2021).

While PDPP has been able to reduce imports of inputs and technologies related to biopharmaceuticals, it did little more than offer access for foreign pharmaceutical companies (technology holders) to the Brazilian healthcare system. According to consultants and associations of Brazilian pharmaceutical companies, it relegates national companies to a marginal position in the international market access and technological collaboration networks for MAbs, as shown by Ecker et al. (2015), Kong et al. (2017), and Lai et al. (2018). In turn, our sixth and final takeaway is offered:

> **Takeaway #6—The implementation of effective technology upgrading requires the comprehension of global connectedness as a bidirectional component. Solely including international partners as sources of resources and capabilities is a way of overlooking the true potential of productive integration in GVCs. The internal market may matter as a first step, but innovative endeavors require deeper embeddedness in international networks.**

6. Concluding remarks

This study presents an interdisciplinary inquiry toward understanding the current development of manufacturing capabilities and technology upgrading of the biopharmaceutical industry in a developing country. In Global South economies, the dynamics of knowledge and innovation in healthcare brings new theoretical and methodological challenges to the analysis of how public policies for industry, health access, and science, technology, and innovation can be understood as interrelated systems of governance of productive development.

Sustained by interviews with key players of the PDPP's partnerships, we discuss the rise of a new policy framework in Brazil in response to rapid organizational change in the global biopharmaceutical industry, as well as to solve the poor access to technologies and services needed to internalize manufacturing capabilities in the local emerging biopharmaceutical sector. As demonstrated, there is no straightforward way to overcome technology gaps in economic sectors in developing countries. Rather, it is a very complex task and involves a set of heterogeneous actors, which is permanently building and shaping new institutional rationales conditioned by cultural, historical, and political contexts.

In this article we presented the role of a public policy, the PDPP, to encourage the generation of national capabilities to manufacture biosimilar MAbs and to foster agendas of technology upgrading in emerging biopharmaceutical markets. In particular, our attention resided in assessing a specific sectoral and public–private oriented-political arrangement established by different public and private stakeholders—but centralized under the sphere of the federal government. The PDPP illustrates how public policies can be relevant for stimulating emerging stakeholders and biopharma projects. It also shows the responsibility such policies have when offering artificial advantages to economic actors, supported by a robust system of public procurement.

Our study, however, admit several challenges and limitations, mainly regarding

(1) the lack of transparency about key information about PDPP's partnerships, i.e. restricted access to contracts of technology transfer between private companies and public laboratories—for what semi-structured interviews aimed at overcoming the existence of 'grey zones' between MH, public and private stakeholders, and the public;
(2) the academic bias in the selection of interviewees. People involved with the university system and public research institutes were those most willing to collaborate with the research. However, it added an additional issue as *partisan politization* of discourses about the PDPP outcomes, which had to be considered in the content analysis, and
(3) the research timeline and access to data faced important challenges throughout the political turbulences in Brazil from 2015. It was a period marked by a traumatic impeachment of the former president Rousseff, followed by two presidents navigating in a context of deep political and economic instability that represented the interruption of national programs of infrastructure and public investments.

Nonetheless, our analysis highlighted the problems that the adoption of a technology transfer strategy, along with its governance by the state, can produce. By not articulating this approach with other elements of the Brazilian National System of Innovation, the PDPP only marginally created incentives and conditions for Brazilian firms to engage in knowledge production, conditioned to a contextual political configuration in the federal level. Additionally, and sustained by the interviewees, the combination of a weak (and anti-global) strategy for science, technology, and innovation in healthcare, the continuous interference of organized groups in the federal and state bureaucracies, and the lack of initiatives to provide sustainability to local private and emerging companies of biotechnology to compete independently in the global biopharmaceutical market, combined, fall short in the three pillars of technological upgrading processes, namely: establishing technological intensity in domestic agents, diversifying and complexifying indigenous technological knowledge, and establishing knowledge-driven ties with global networks. Instead, the data presented in the paper suggest policies focused on qualifying national players in manufacturing copies (biosimilar) versions of MAbs through technology transfer of expired patents of MAbs, as well as driven by contracts of national market reserve in partnerships with multinational pharmaceutical companies (owners of the technology licenses). It reflects an immediate solution strategy with little vision for the future, seeking mainly to solve a State's fiscal problem instead of boosting a sustainable agenda for STI to the local biopharmaceutical industry. The implemented PDPP paid little attention to knowledge-intensive entrepreneurial firms, neglecting their role as relevant global players in the biopharmaceutical industry as suggested by the cases in Singapore and China (Chan and Daim 2011).

On the flip side, since State and business rationales are not easy to match, the PDPP shows how public policy might improve national capabilities toward the renewal of knowledge-driven business sectors and/or the creation of it from scratch. The novelty of new joint ventures built in Brazil in this period to improve the biopharmaceutical sector, taken by a Head of Production/Innovation from a joint venture company: 'To make a MAb biotech facility is, with no doubt, a great challenge to be solved and, for sure, the biggest one of my career' (Pharmaceutical Company). Additionally, the building of a national public narrative that allies the principles of the Public Health System with aims of the national pharmaceutical industry is quite positive, considering that Brazil is a recent western Democracy and low- and middle-income economy.

In this sense, future research on strategies of biopharmaceutical development in emerging economies like Brazil is needed and could significantly update the debate about the current interfaces between public policies and technology upgrading in Global South. New case studies about public policies for manufacturing capabilities and technology upgrading in MAbs should be done through an international comparative perspective. It can place in context other developing economies that had been well-successful in this matter, i.e. India and South Korea, or those ones that have accessed global markets for biosimilar MAbs as Russia and Argentina, or contexts of rise of intermediary companies of knowledge-intensive business services, fundamental for

sectoral technology upgrading, as the case of Singapore and China.

The inquiry of international experiences of public policies for the biopharmaceutical development and the emergence of new regimes of governance of technology upgrading in MAbs can clarify strategies and paths that developing countries could adopt to improve, sustainably, manufacturing/technology knowledge and collaborations. Also, it improves our understanding about the asymmetries in the flows of manufacturing technologies, intellectual property, and healthcare research and innovation as key trends of the contemporary global biopharmaceutical industry. To generate pervasive effects in economic systems, such policies require a robust integration with broader features of the innovation system that affect the dynamics of technological learning and development of indigenous agents. Such conditions enhance our perception of the multidimensional nature of technology-upgrading process, in which State, governments, business alliances, and organizational rationales of public and private players of biopharmaceutical industry should be culturally and carefully analyzed.

Funding

This work was supported by São Paulo Research Foundation (Grants FAPESP 2015/24133-5 and 2017/18500-0) and the National Institute of Science and Technology on Health Technology Assessment (Grant INCT—MCTI/CNPq/CAPES/FAPs 16/2014 n. 88887.373046/2019-00). Bruno Fischer's contributions to this article received financial support from the Basic Research Program of the National Research University Higher School of Economics and by the Russian Academic Excellence Project '5-100'. Paola Schaeffer's contributions were supported by financial resources received from the National Council for Scientific and Technological Development (CNPq).

Conflict of interest statement. None declared.

Acknowledgements

The authors acknowledge the Department of Preventive Medicine of the Faculty of Medicine of the University of São Paulo for all the institutional support to make this work possible. Also, the authors acknowledge the members of the Science, Knowledge and Technology Workshop for the kind comments on the manuscript offered to [i.e., Renan da Silva] during his visiting scholar internship in the Department of Sociology at Columbia University in the City of New York in 2020, gladly hosted by Diane Vaughan and Gil Eyal. They also acknowledge New York University, in the name of Melissa Schilling, for hosting [the first author] in the Department of Management and Organizations of the New York University's Stern School of Business between February 2018 and January 2019, when most of the tools and inspirations for this article were built.

Notes

1. BV FAPESP contains specific information about researchers in the State of São Paulo, where more than 45% of MAb research takes place in the country, according to Da Silva and Novaes (2018). For this state, a search for the keywords 'anticorpo monoclonal OR anticorpos monoclonais OR anticorpo monoclonal terapeutico OR anticorpos monoclonais terapeuticos' returned a list of 775 results—288 grants and 467 awards/scholarships as of 19 February 2022. BV FAPESP may be accessed through the following links: http://www.lattes.cnpq.br and http://www.bv.fapesp.br, respectively.
2. NHP is based in a robust political–institutional framework such as the public health system, private health insurance, pharmaceutical assistance, pharmacovigilance, and regulation. It is the set of actors which provide healthcare products or services in the country.
3. MH counts with a strong political and fiscal capacity. According to the Federal Transparency Database, the MH's 2019 budget was $122.6 billion BRL, which is approximately 1.8% of Brazil's GDP (Portal da Transparência 2019). Additionally, healthcare expenditures in Brazil reached $546 billion BRL in 2015, which is more than 9% of the country's gross domestic product (GDP).
4. In practice, the PNCTIS served as a manual of directives to guide S&T policy in the MH's decision-making. The document stakes out an important political stance for S&T at the level of the federal government, which explicitly expresses the concern of government regarding a greater diversification of the actors involved in the healthcare technology development agenda, but which also lays the foundation for it to concentrate its governance under the umbrella of the State through the institution of the MH.
5. The CNS is a body of the MH, which serves as the final decision-making authority for all matters related to the National Policy on Science and Technology in Healthcare (PNCTIS).
6. The role of regulatory policies is also relevant for the analysis of knowledge control regimes. In 1999, the Brazilian Health Regulatory Agency (ANVISA) was created, and it constituted a new state-run legal apparatus to regulate health technology produced, distributed, and/or sold in Brazil (Gama and Andreoli 2013).
7. Public/Official pharmaceutical laboratories is the name given to facilities which manufacture medical supplies, drugs, and other pharmaceutical products which are maintained by the State, either through the federal or state governments, and which specialize in manufacturing products considered strategic to SUS's proper functioning. It is crucial to recognize that these centers were particularly important in the production development policies presented in the current study, since they were the intended recipients of the MAb technology transfer initiatives.
8. Apart from the GECIS, the Department of the Healthcare Industrial Complex (*Departamento do Complexo Industrial da Saúde*, or DECIS) was created in 2008 as part of the SCTIE and became part of the public policy framework of interest to the so-called 'Complexo Econômico-Industrial da Saúde'. Although it has been important in the general framework, we have decided to focus more on the GECIS, which is the decision-making board of the federal government that aims at implementing decisions related to the agenda of healthcare inputs. For more information and details about the role of the DECIS, see Ministério da Saúde (2016).
9. According to a report by the Applied Economics Research Institute (IPEA), 'Biosimilars are defined as biologic products registered through development by comparability, which is the regulatory method used for a biologic product (…) is proven in terms of quality, efficacy, and safety, between the biosimilar and the biologic product of reference' (IPEA 2018).
10. According to Statista, 'In 2019, Mexico was the Latin American country that showed the highest value of pharmaceutical exports, with more than 1.77 billion U.S. dollars. Meanwhile, Brazil was the country with the highest value of pharma imports that year, with nearly 7.3 billion U.S. dollars. The South American nation's 2019 trade balance of pharmaceutical products amounted to a deficit of 6.11 billion U.S. dollars' (Statista 2022).
11. This company is a joint venture among the laboratories Aché, EMS, Hypera Pharma, and União Química Farmacêutica Nacional S.A, in a facility under construction in the city of Valinhos, in the State of São Paulo. The creation of this joint venture had the main

objective of minimizing and sharing the risks between the different shareholders involved in the business.

12. Orygen Biotecnologia is a private company created through a joint venture between the Brazilian companies Eurofarma and Biolab. Its manufacturing facility is under construction in São Carlos, also in the State of São Paulo.
13. Bio-Manguinhos is formally known as the Immunology Technology Institute of the Oswaldo Cruz Foundation, and it is located on the FIOCRUZ campus in the city of Rio de Janeiro.

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