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Brazil's Role in the Biopharmaceutical Global Value Chain

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MIT-IPC Working Paper 16-004

June 2016

ACCELERATING INNOVATION in BRAZIL

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Abstract

Brazil's biopharmaceutical market has experienced dramatic changes since 2000, with improvements in the performance of local firms, as well as an expansion in consumer demand and productive capacity, which have made the country the sixth largest market in the world. While this rapid expansion has been driven by a burgeoning trade deficit, it has also created a space for the production of higher value-added products such as biologics. Currently, Brazil is at a crossroads in terms of its national biopharma strategy. Given the size of the healthcare market in the country and the increasing demand for access to new drugs, the country's strategy has historically prioritized access to approved 'imitator' drugs, first through generics and now through biosimilars. However, with significant assets in terms of scientific capabilities, potential medical applications from its biodiversity, and a large, growing domestic market, Brazil can be more than a fast follower. It has an opportunity to leverage its existing capabilities and assets to expand its embryonic biotech sector. Doing so will require a more global outlook on the industry and the ability to build born-global biotech firms, a few of which are already emerging in Brazil. While much has been achieved in terms of building Brazil's biopharma industry in a relatively short period of time, more investment in the 'innovation ecosystem', including capacity for clinical trials, IP protection, and talent is needed. There are also successful models for third-parties like SENAI to create shared facilities and training opportunities that could support the biopharma community more broadly.

This research was sponsored by SENAI. The IPC is grateful for their support.

Esta pesquisa foi patrocinada pelo SENAI. O IPC agradece pelo seu apoio.

Brazil's Role in the Biopharmaceutical Global Value Chain

1. Introduction

The global biopharmaceutical industry is both a product and driver of scientific advancement, as well as the source of innovative medicines that address a range of human health-related needs around the world. The term 'biopharmaceutical' reflects the evolution of the pharmaceutical industry, based in chemical production, which emerged in the late 1800s, to incorporate the more recent emergence of biotechnology, based on living cells and molecules, stemming from key innovations from the 1970s and 1980s. Today every major pharmaceutical company in the world is developing biotech-related drugs, thus the distinction between 'pharma' companies and 'biotech' companies is less meaningful than it was in the past, though the former is clearly a stand-alone industry. Biopharmaceuticals make up approximately 20 percent of the total pharmaceutical market and represent its highest-growth area, generating global revenues of over $190 billion in 2013 with over 8 percent annual growth, double that of traditional pharma (McKinsey, 2014).

Because of the complexity associated with their production, their efficacy with previously untreatable diseases, and their relative safety, biopharma drugs command high prices and thus present both a growth opportunity for established and emerging biopharma companies, as well as a challenge for health care systems in terms of cost control and accessibility to patients. The issue of affordability is especially pertinent in developing countries, where the cost of biologics overburdens what are often already overstretched public healthcare systems. For this reason, many countries that have traditionally played marginal roles in the biopharma industry have begun to seek more effective ways to engage as a way to bring new, effective treatments to patients at affordable costs.

Like many industries, the biopharma industry has been undergoing a process of globalization and fragmentation and the formation of global value chains (GVCs) is creating opportunities for developing countries and emerging markets. The prohibitive cost and uncertainty associated with science-based innovation has necessitated the development of risk-sharing strategic partnerships and collaborations, as well as outsourcing of lower value-added functions like manufacturing and clinical trials management.

Brazil is at a crossroads in terms of its biopharma strategy. Given the size of the healthcare market in the country and the increasing demand for access to new drugs, the country's strategy has historically prioritized access to approved 'imitator' drugs through the development of the

generic drug market. This strategy was followed for decades. However, beginning in the early 2000s, the strategy expanded to incentivize the development of a local biosimilars industry. Biosimilars, drugs that are 'bioequivalent' to approved biopharma drugs that go off-patent, offer countries like Brazil an opportunity to improve patient outcomes while keeping a lid on spiraling costs. In 2010, Brazil developed and implemented regulatory guidelines for these drugs, providing companies a clear pathway towards commercialization. This strategy helps provide Brazilians access to approved biotech drugs at a more reasonable cost (important given the increasing cost biotech drugs represent in the Brazilian health care market) and builds important internal capabilities within the country in terms of making biopharma drugs.

While Brazil has made significant strides in developing its biotech industry in a relatively short period of time, its strategy does little to advance the country's potential role as an innovator in the biopharma market. By focusing solely on biosimilars, Brazil risks falling further behind the rapidly expanding science-based innovation frontier. By the time a biosimilar has been developed for the Brazilian market, it is likely that a new drug will have replaced the old one. With significant assets in terms of scientific capabilities, potential medical applications from its biodiversity, and a large, growing domestic market, Brazil can be more than a fast follower. It has an opportunity to leverage its existing capabilities and assets to expand its embryonic biotech sector. Doing so will require the ability to build born-global biotech firms that are willing to venture beyond the relative safety of the Brazilian market.

This paper provides an overview of the Brazilian biopharma market in terms of strengths, weaknesses and opportunities. The goals of the paper are four-fold. The first is to provide an overview of the structure and main trends of the global biopharmaceuticals industry, paying attention to key players and competitive dynamics, particularly around R&D management and the trend towards functional specialization. The second is to identify Brazil's current role in the biopharmaceuticals GVC, by providing trade data and an overview of the sector's ecosystem. The third focuses on understanding the institutional structures that have shaped Brazil's ecosystem and its idiosyncratic specialization in biopharmaceuticals. This is done through an examination of the specific factors, opportunities and bottlenecks that distinguish the country's experience from more "traditional" biopharmaceutical ecosystems. Finally, this paper aims to identify Brazil's biopharmaceutical strategy moving forward, including an overview of potential avenues for participation by third parties like the SENAI Institutes of Innovation (ISIs).

2. Main Features of the Biopharma Industry

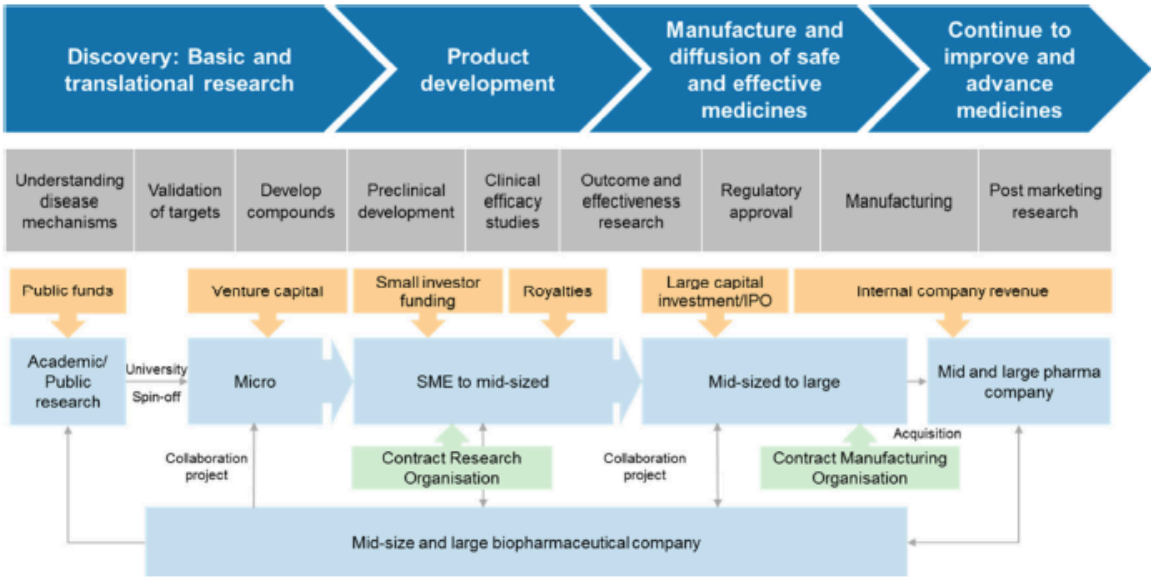
Defined as a collection of technologies that use and manipulate living cells and molecules to make products and solve systems, biotechnology has translated inventions in the biological sciences into products and technologies applied to human health, agricultural productivity, and other industries (Zechendorf, 1999; de Andrade, 2013). The focus of this paper is biotechnology

applied to the production of human medicines. Biotechnology-based medicines, here referred to as biopharmaceuticals, are more complex than traditional ones; the latter's active ingredients are made from chemical compounds based on small molecules, and have well-defined chemical structures that can be made by chemists in a lab, with predictable results. In contrast, biopharmaceutical medicines are made from large, complex molecules such as proteins. These require a more intricate and less predictable production process that relies on genetically modified microbes or cell lines. Further, in contrast to small molecule medicines that can be easily digested by the body if taken orally, the delivery systems of biotechnology-based products require that they be injected or infused into the body, adding an additional level of complexity to their production process and administration.

We can broadly identify and describe three general steps in the making of a biotechnology-based drug. The first is **discovery**, where scientists attempt to understand how a disease is caused, which cells are affected, and what genes (if the disease is caused by genetic factors) are turned on or off in the diseased cells, as well as what proteins are present in said cells when compared to healthy cells. This step requires a variety of tools such as growing cell cultures, cross-species studies, bioinformatics to organize the resulting data, biomarkers to measure biological functions, and proteomics to understand protein activity. This can be a years-long process that culminates with the selection of a target, or a specific molecule that a medicine should affect, followed by the identification of a drug candidate.

Once a promising drug has been identified, the second step is **product development**. In this step, the drug must undergo thorough testing for safety during preclinical trials before it can be tested in humans through clinical trials. In turn, clinical trials require three phases of increasingly large groups of patients to ensure safety and drug efficacy. On average, this process can take between ten and fifteen years. Once a drug has passed clinical testing, its maker can file for regulatory approval and begin the third phase, which is to **manufacture the drug** at commercial scale. This entails producing a master cell line containing the gene to make a particular protein, followed by growing large numbers of cells to produce the protein. Then, the protein must be isolated and undergo purification, before it is prepared for use by patients. Thus, from their initial process in a laboratory, cells must be sequentially transferred for scale-up in increasingly large bioreactors. In this process, any subtle change in environment can alter the quality of the drug and invalidate the final product. Thus, biomanufacturing is one of the more complicated and risky manufacturing processes in the world.

Figure 1: The Biopharmaceutical Value Chain



Source: CRA, 2014

The biopharmaceutical industry's unique, multidisciplinary and science-based structure makes it difficult to apply any one analytical framework when examining the actors that comprise it. Because we are interested in how Brazil fits into the global industry, and how it can upgrade its role, this paper uses the global value chain (GVC) framework to explore the industry's fragmentation and globalization. This approach focuses on the various actors that are critical to the industry, even those that fall outside the linear chain depicted in Figure 1. Nevertheless, the industry can be usefully depicted as a succession of activities, each of which requires collaboration on the part of various public and private actors. Simply stated, it takes a complex knowledge-based ecosystem to develop and bring a biopharma product to market. Because product cycles are so lengthy, the industry requires a supportive and stable institutional framework. For this reason, the biopharmaceutical industry has tended to flourish in countries and regions that can offer a solid enabling environment. Because science-based innovation requires the exchange of tacit knowledge, the industry has developed into regional clusters. To date, these clusters have tended to be located in industrialized countries with strong scientific capabilities and available risk capital, such as the United States, Germany, and Japan.

Figure 1 shows the networks of actors that comprise each step of the value chain. In addition to the range of capabilities and collaborations required at each stage, the figure illustrates the importance of public funds and venture capital to the success of an industry where profits, while sizeable, often take many years to materialize. A recent study estimated that the cost of developing a biotech drug today from initial research to market approval is $2.6 billion dollars (Tufts, 2014). The sector is highly dependent on lead firms' internal R&D efforts, their

coordination of knowledge networks that include experts from a variety of scientific disciplines, and their marketing and distribution capabilities. These features make it difficult to compare the industry with sectors where production processes are more easily and cleanly fragmented due to product-level modularity.

In this framework, the "traditional" breakdown of activities has tended to locate early stage production near R&D centers, with such activities conducted in-house to minimize problems related to transfers of partially tacit knowledge (Reynolds, 2010). This co-location in specialized clusters eases interactions with research institutions such as universities and hospitals. Thus, until relatively recently, most product development, and specifically pilot and clinical manufacturing were conducted exclusively near R&D centers in the U.S. and Western Europe. Meanwhile, the more standardized Phase III (within product development) and commercial manufacturing for high volume drugs have shifted to offshore locations, largely driven by tax advantages or proximity to consumer markets[1].

In terms of industry growth, the revenue and industry value-added of global biopharmaceutical activities have consistently outpaced world GDP growth. This trend is expected to continue, with a forecasted growth of 9.5% per year, on average, until 2020, in excess of annualized global GDP growth of 3.4% over the same period. A key factor in this growth is the increasing trade in biotechnology products. Currently, the European Union dominates biotechnology exports, with 66% of the world share. Germany is the largest exporter, with 14%, while the U.S. accounts for 13.3% of world biotech exports. In Asia, the top exporters are Japan (3% of the world share), China (2%), and Singapore (1%). An estimated 60-70% of all biotechnology patents developed in OECD countries are initially registered in the United States (IBIS, 2015). While new biotech players have started to emerge, with several countries investing heavily in their biotechnology industries, the U.S. market continues to produce the largest number of new biotech companies because of its intellectual property rights regime, its large market and its favorable reimbursement policies.

3. Competitive Environment and Key Private Sector Actors in the Biopharma GVC

As is the case in many GVCs, the industry is driven by *lead firms*, often large pharmaceutical or biopharmaceutical brands that orchestrate networks of university laboratories, biotechnology startups and global suppliers to push drugs into and through the clinical pipeline. These firms incur the brunt of the cost (and risk) associated with novel drug development. But while lead firms are often large, established companies, biotechnology firms are sometimes able to scale

1 Location decisions are determined by (1) wage levels; (2) corporate taxes; (3) market size and growth; (4) private sector development; (5) human capital (See Bevan and Estrin, 2004; Bellak and Leibretch, 2005; Perugini, Pompei, and Signorelli, 2005); and (6) intellectual property rights (See Malo and Norus, 2009).

without being acquired, growing instead through public research grants, successive rounds of venture capital funding and, in some cases, through initial public offering (IPO).

Innovation in science-based industries such as biopharma comes with a great deal of uncertainty, stemming from an inability to know the full range of potential outcomes associated with the decision to invest in a certain technology (Wong, 2011). This is why lead firms will often partner with, or acquire multiple *dedicated biotechnology firms (DBFs)*, where novel technologies can be drawn out of university laboratories and go through the initial tests of technical and commercial viability. Furthermore, once a drug is ready to begin the long and arduous clinical trials process, a firm will likely engage with a specialized *contract research organization (CRO)*. As one biopharmaceutical R&D director puts it, his firm likes to "keep things as turn-key as possible" when it comes to clinical trials management. Finally, given the high cost associated with maintaining a global manufacturing footprint, many biopharmaceutical firms will rely on *contract manufacturing organizations (CMO)* at both early clinical stages and later scale up stages during the commercial phase.

While the biopharmaceutical industry is not characterized by the same level of modularity as say, the electronics industry, there are certain points along the value chain that lend themselves to outsourcing. Hence, there has been increasing reliance on global partners. Collaboration with DBFs and universities is common in the early stages of drug development due to the inherent uncertainty associated with discovery and the basic science involved in the research. Outsourcing becomes common during the later stages of drug development, when drugs enter the clinical pipeline. At this stage, global suppliers become critical GVC actors. This section describes some of the key private sector actors that comprise the biopharmaceutical GVC, focusing on the lead firms, DBFs, CROs and CMOs that collectively bring novel drugs from bench to market.

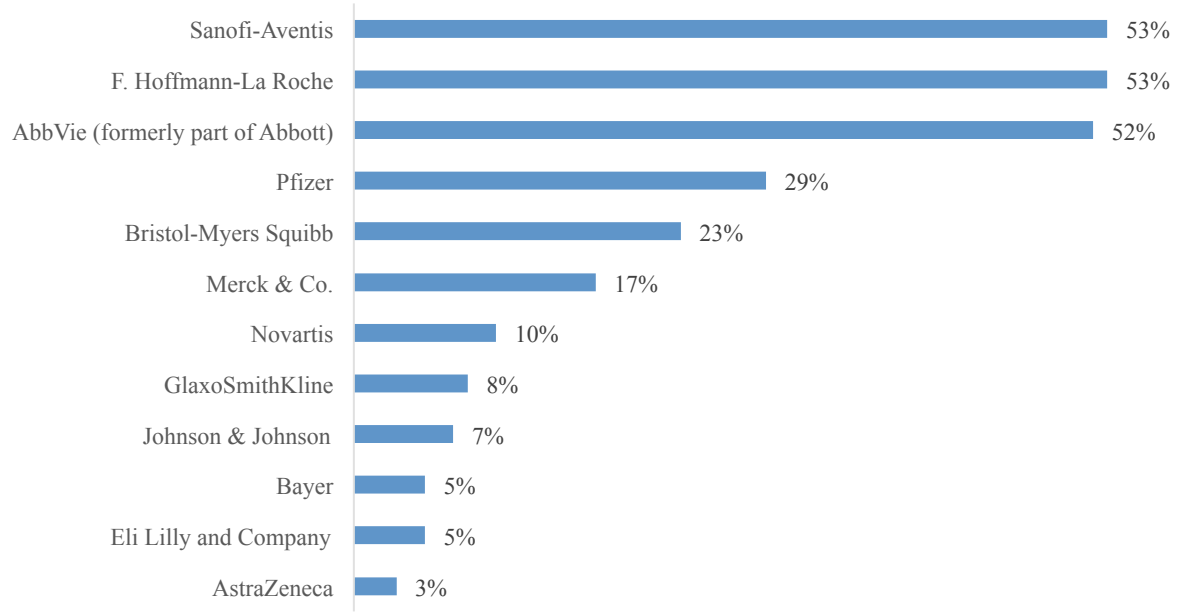
Lead Firms

Lead firms in the biopharmaceutical industry are either converts from the pharmaceutical industry or DBFs that have managed to grow through successive funding cycles without being acquired outright. Global industry concentration is low. This is largely because lead firms often diversify to produce drugs for a variety of clinical indications, allowing them to build core competences in different industry niches. Novartis was the largest pharmaceutical company in the world in 2014 with $47 billion in aggregate revenue. Revenues were 23 percent higher than the fifth largest firm, Merck. If instead of focusing on aggregate market share, we focus on market share in specific therapeutic categories, market concentration becomes more evident. For example, Roche is the clear market leader in oncology, with $25.2 billion in revenues generated through the sale of oncology drugs. This is 86 percent more than the fifth largest firm in the oncology space, Bristol-Myers Squibb (PMLive, 2016).

Pharmaceutical firms have shifted towards biologics to varying degrees, as

Figure 2 demonstrates. Two of the world's leading biopharmaceutical firms, Sanofi and Pfizer, have redirected their strategic focus towards biologics in a very short time. Between 2010 and 2012, their revenue from biopharmaceutical drug sales grew by 53 and 29 percent, respectively, relative to revenue from small molecule pharmaceutical drugs. Others like AstraZeneca have shifted more slowly, depending on their small molecule drugs to drive growth.

Figure 2: Change in % Revenue from Biologics vs. Small Molecule Drugs, 2010-2012



Source: EvaluatePharma, from Otto et al., 2014

While the largest lead firms are pharmaceutical firms that have shifted into large molecule production, some important players have always focused on biologics. These firms tend to be younger, as the field of biotechnology emerged and began to grow in earnest in the 1980s. Gilead and Amgen are among the largest biopharmaceutical companies in the world, with market capitalizations of $118 billion and $120 billion respectively as of June, 2016. They both started out as small DBFs over 30 years ago. But while the path these firms have taken is possible in large, industrialized markets like the U.S. and Europe, the path is not so clear in emerging markets. Below, we discuss the challenges associated with attracting the funding necessary to grow from a small, university-based startup to a global lead firm.

Dedicated Biotechnology Firms (DBFs)

It has long been recognized that internal R&D capabilities are important but alone insufficient means of developing new technologies (Mowery, 1983; Mowery and Rosenberg, 1993). Firms must be able to access, acquire, assimilate and exploit external knowledge to develop and sustain competitive advantage, especially in fast-moving industries (Cohen and Levinthal, 1990; Zahra and George, 2002). "Many firms are no longer structured like medieval kingdoms, walled off

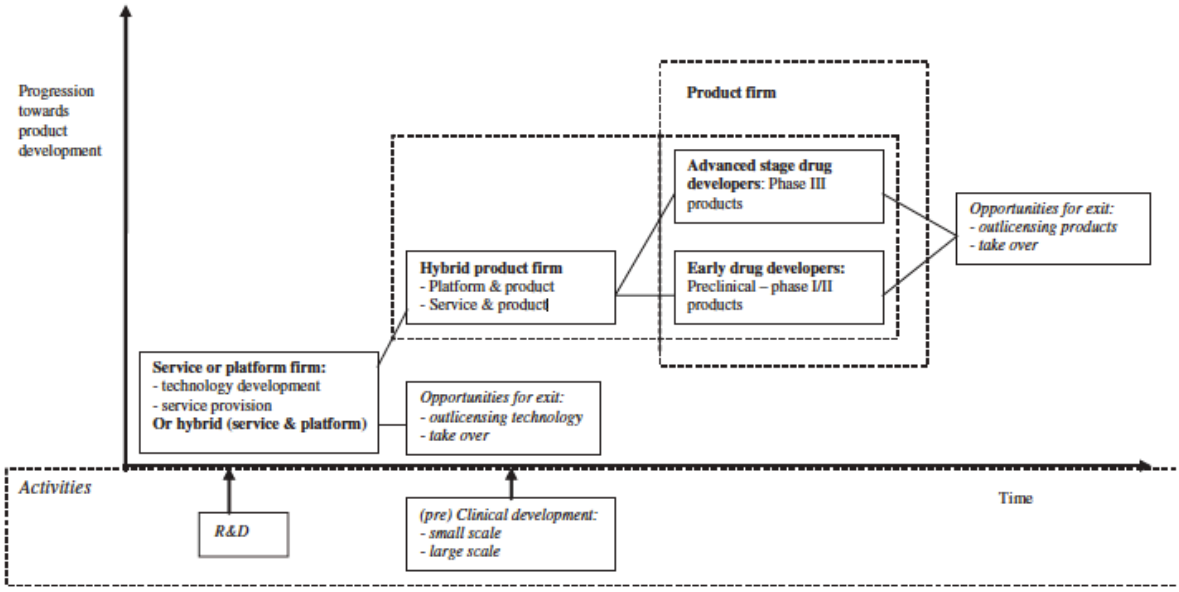
and protected from hostile outside forces. Instead, we find companies involved in an intricate latticework of collaborative ventures with other firms, most of whom are ostensibly competitors" (Powell, 1990, pp. 301). Networks aid in the transmission of tacit and highly complex knowledge across firm boundaries, where vertical integration is inefficient and knowledge cannot be easily priced. Networks are especially important in the early stages of drug development, when the high likelihood of failure makes investing in any single technology problematic.

DBFs often begin as startups created by university-affiliated researchers, built around a specific proprietary technology or product. They are rooted in learning networks that provide them with access to knowledge and resources that would otherwise be unavailable. The range of skills required to bring a product to market typically includes basic research, applied research, clinical testing, marketing, distribution and regulatory engagement. These business functions are too broad and complex to be contained in one firm (Powell et al., 1996). Consequently, DBFs rely on ties to competitors, universities and hospitals, domestic and foreign suppliers, public and private research organizations, patent offices, state and federal government funding bodies and regulatory agencies to acquire knowledge and develop new technologies (Blumenthal el al., 1986). Indeed, DBFs tend to cluster around the public research institutions on which they depend for labor and novel scientific ideas (Owen-Smith and Powell, 2004).

If they are able to demonstrate early stage drug efficacy, these firms are often presented with two potential growth trajectories. One involves growth on the basis of dilutive funding, through successive VC rounds, and eventually through IPO, and the other involves acquisition by a large biopharmaceutical firm, or a pharmaceutical firm shifting into biologics. Again, the high rate of failure in the early stages all but ensures that it is the small DBFs that bear the risk associated with drug development. It is only after a certain level of initial success that these firms can hope to grow rapidly through the VC cycle or through acquisition. However, this model is not universal, as research on biopharmaceutical firms in Western Europe indicates, due to the fact that the capital market features of the United States are difficult to emulate, even in European countries that have sophisticated knowledge ecosystems. Instead, biopharmaceutical firms may evolve through hybrid business models to compensate for the difficulties in acquiring capital.

For example, a study of medical biotechnology firms in the Netherlands suggests three types of business models portrayed in Figure 3: "service companies," "small research companies," and "integrated companies," with firms falling into the categories of service firms, hybrids, early stage drug developers, and advanced stage drug developers. More importantly, the business models of young firms can and do change over time, in a sequence shaped by the limited resources available to them (Willemstein et al., 2007). Similar business models and sequences have been found to prevail among, for example, German firms (Ernst & Young, 2003).

Figure 3: Variety of Business Models Among DBFs



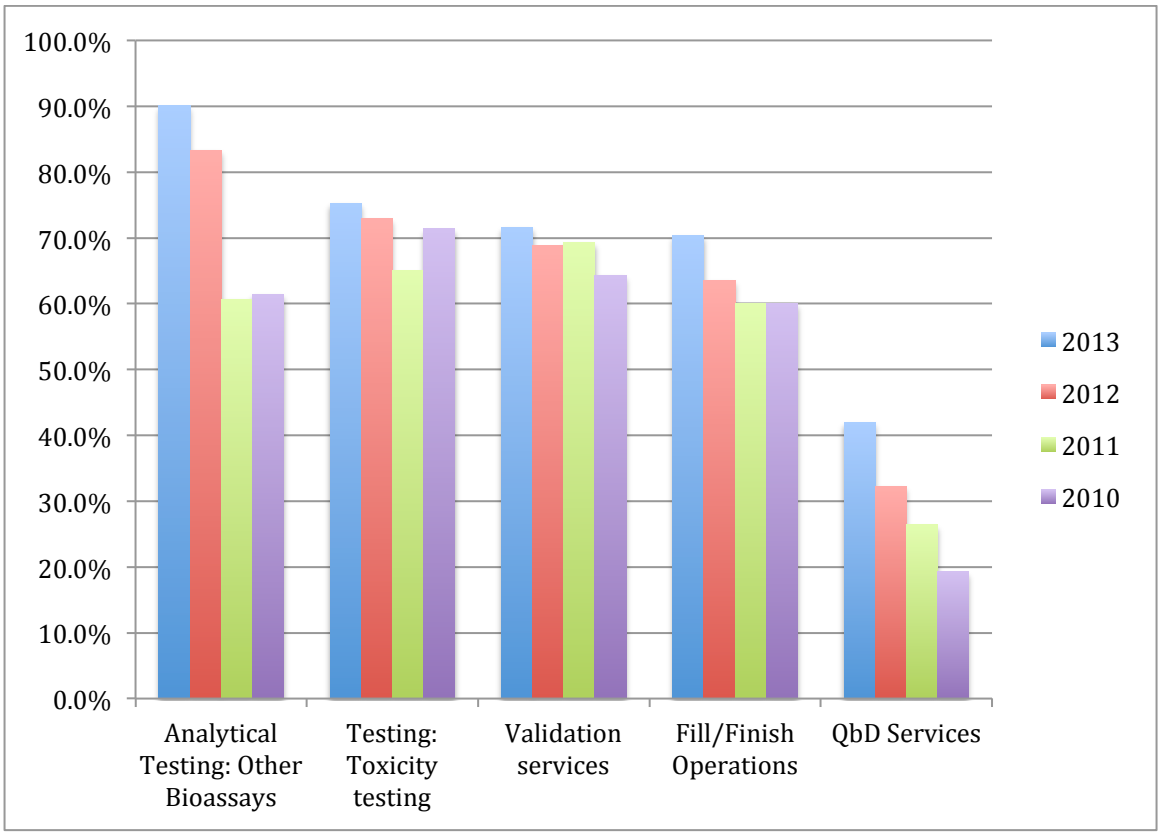
Source: Willemstein et al, 2007

Contract Manufacturing Organizations (CMOs)

Outsourcing has become a common feature of the biopharmaceutical industry, with lead firms outsourcing testing and validation services, clinical trials management and manufacturing operations to an increasingly global supply base (see Figure 4 and Langer, 2013). Outsourcing of upstream (12.2% in 2013, up from 7.6% in 2010) and downstream (11.7% in 2013 versus 9.1% in 2010) production operations is still relatively modest, but increasing. Similarly, process development areas that have long constituted core in-house activities are seeing small increases in outsourcing (9.4% of upstream process development activities in 2013, versus 4.2% in 2010, and 7.7% of downstream process development in 2013, versus 5.5% in 2010).

Lead firms have increasingly relied upon global suppliers to manufacture at scale as their skills and capacity to do so have increased in recent years. Biopharmaceutical lead firms often leverage the globally distributed manufacturing capacity that CMOs offer to produce drugs throughout the development process while avoiding the need to make capital-intensive investments in internal production capacity. The geographic distribution of biomanufacturing has seen some recent changes, in part due to innovations in single-use equipment and manufacturing technologies that make biomanufacturing possible at smaller scales, as well as cheaper and more modular. In addition, capacity is being added in the rapidly growing markets of some developing and transitioning countries such as Singapore, South Korea, India and China. Moreover, governments' efforts to attract biologics production have played a part in these developments, as is the case with some countries requiring vaccine manufacturers to produce locally, often through joint venture or local companies.

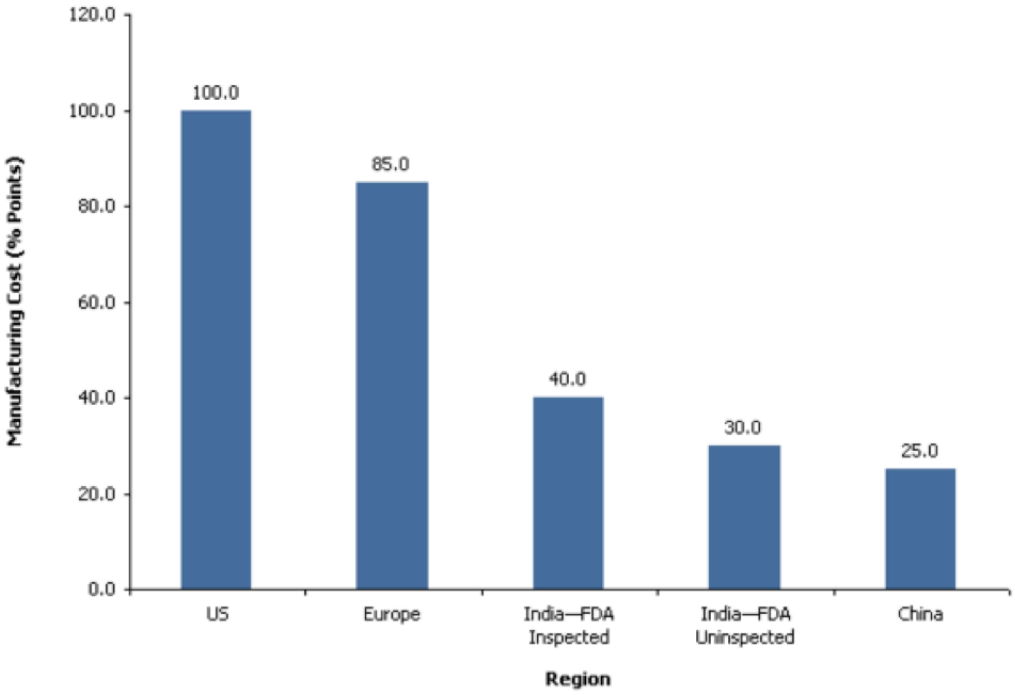
Figure 4: Percent of Biomanufacturers Outsourcing at Least Some Activity, 2010-2013



Source: Langer, 2013

South Korea for example, made a strategic decision to enter the biotech industry from downstream. The country invested in building biomanufacturing capabilities and now has two of the largest CMOs in the world, Celltrion (with 230K liters of mammalian capacity) and Samsung Biologics (which will have 360K liters and 1,700 workers by 2018). At the same time, earlier predictions that countries like India and China would become important players in outsourcing through the Contract Manufacturing Organization (CMO) segment have not materialized so far, despite their significant cost advantages (see Figure 5). In fact, both countries have recently begun to drop positions as preferred outsourcing destinations in favor of Germany, Singapore, South Korea, the U.K., Ireland, and Austria. The reason, according to the same 2013 outsourcing survey, is that biomanufacturers' priorities in choosing a CMO have shifted, with respondents becoming much more concerned with issues of regulatory compliance than simply cost (Langer, 2013).

Figure 5: Pharmaceutical Contract Manufacturing Market: Comparison of Manufacturing Cost in Different Regions, Benchmarked to the U.S., 2012

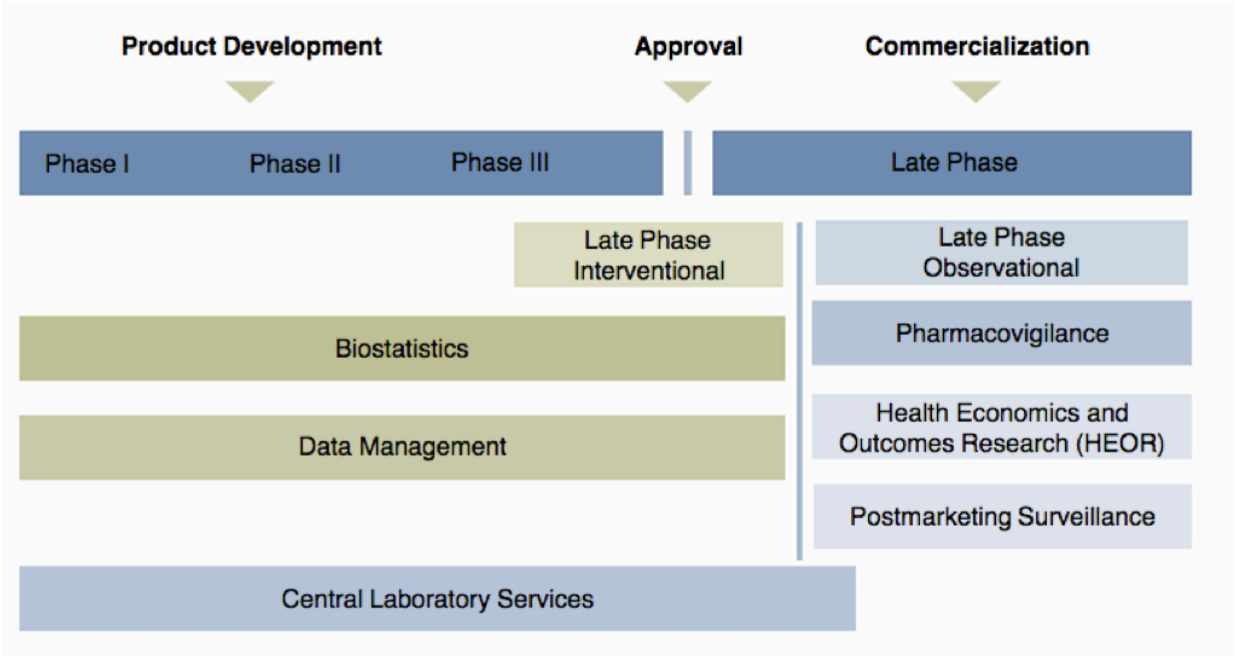


Source: Frost & Sullivan, 2012

Contract Research Organizations (CROs)

Many biopharmaceutical firms outsource to Contract Research Organizations (CROs), which engage in bioassay development, preclinical and clinical research, clinical trials management and pharmacovigilance (drug safety testing) among other activities (see Figure 6). The importance of having a global supplier for activities such as clinical trials management cannot be understated. The regulatory pathway for large molecule drugs is complex, and varies from one country to the next. CROs support lead firms by ensuring that multisite clinical trials are executed in accordance with each country' regulatory framework. They manage the patient recruitment process, identify key opinion leaders in the medical community to support trials and act as principal investigators (PI) and collect and manage data from all sites under management. One pharma executive remarks that it is difficult to have enough in-house capacity to deal with a geographically dispersed clinical trial. A phase III trial can take you up to 100 sites and anywhere between 400 and 600 patients. The cost and complexity associated with clinical trials management is perhaps the chief driver of industry outsourcing.

Figure 6: CRO Activities by Stage of Clinical Development



Source: Frost & Sullivan, 2014

As this summary suggests, the biopharmaceutical industry is evolving. The once vertically integrated industry is progressively becoming de-verticalized with the rise of CMOs and CROs. These global suppliers are increasingly global actors based in both industrialized countries and emerging markets. Furthermore, the technical and financial challenges associated with developing biotech drugs have led to the creation of multiple business models for emerging DBFs. In the US, some of these firms grow through successive rounds of funding to become large biopharmaceutical lead firms in their own right. Others are acquired by biopharmaceutical firms seeking to broaden their pipeline of biologics. But while the US has been relatively successful in terms of supporting DBFs, the enabling environment necessary to support their growth is often lacking in other countries, including Brazil.

4. Brazil's Current Role in the Biopharmaceutical GVC

Brazil's biopharmaceutical market has experienced dramatic changes since 2000, with improvements in the performance of local firms, as well as an expansion in consumer demand and productive capacity that have made the country the sixth largest market in the world. While this rapid expansion has driven a burgeoning trade deficit (mostly in semi-finished medicines and APIs based on mature small molecule products), it has also created a space for the production of higher value-added products such as biologics, allowing Brazil to carve out a spot in the human health biomanufacturing global value chain.

While hardly any commercial production of biopharmaceuticals took place locally prior to 2008, the availability of public funding programs (including purchases by the national health system) and large local pharmaceutical firms venturing into these products have contributed to an expansion of biomanufacturing and R&D activities over the last decade. The local content of these operations needs to be better understood; currently, an estimated 86% of companies have to use imported products or services. Upon closer examination, the trade statistics confirm what our research team learned through various interviews with industry stakeholders. For this project, we developed a sector definition on the basis of secondary materials. The definition is based on the 2007 Harmonized System (HS) classification. The six-digit, product-level HS codes have been aggregated into sub-sectors that include raw materials, laboratory biotools and instruments and consumable final goods. UN Comtrade data was used to construct Brazil's trade profile.

Brazil's biopharmaceutical industry is increasingly dependent on imports, especially for raw materials, including active pharmaceutical ingredients (APIs). Between 2010 and 2014, Brazil's trade deficit in raw materials grew by 13 percent a year (see Table 1). In the past, import substitution policies attempted to develop a local API industry in pharmaceuticals. However, the policy focus changed from 2003 onwards. In 2014, the country imported $8.5 billion worth of biopharmaceutical goods, ranking it 15th in the world in terms of imports. While the country's trade deficit is large in laboratory biotools and instruments and consumable final goods as well, it is not growing at the same rate as it is for raw materials. This may have to do with the fact that Brazil has increased its generic drug manufacturing capacity significantly in recent years. Local drug production now satisfies a significant portion of aggregate domestic demand. Very little of what is produced in Brazil is exported. While Brazil did export $1.7 billion worth of biopharmaceutical goods in 2014, it was only the 28th largest biopharma exporter in the world, well behind India and China, among other emerging markets.

Table 1: Brazil's Trade Balance in Biopharma Goods, 2010-2014 (USD Million)

Sub-Sector	2010	2011	2012	2013	2014	CAGR
Raw Materials	-$1,458	-$1,946	-$2,184	-$2,493	-$2,336	13%
Laboratory Biotools and Instruments	-$810	-$905	-$808	-$1,184	-$1,014	6%
Consumable Final Goods	-$3,304	-$2,969	-$3,050	-$3,265	-$3,396	1%
Total	**-$5,572**	**-$5,820**	**-$6,042**	**-$6,942**	**-$6,746**	**5%**

Source: Authors' analysis, data collected from UN Comtrade

Despite the large and growing trade deficit in pharmaceuticals, Brazil has begun expanding its world share of exports in specific product categories of biologics, as illustrated in the table below. While still modest, the expansion of shares and growth in value added within specific product categories points to increasing technical complexity of local biologics. Also pointing in this direction is the relative expansion in the participation of advanced markets as export destinations of high value-added pharmaceutical products. See Table 2 for a list of key biologics in which

Brazil increased its exports, and in most cases its share of the global export total, between 2003 and 2013.

Table 2: Brazil's Share of Global Exports in Biologics, 2003 and 2013

World Product Complexity Ranking (n=1220 products)	Product category	Brazil share of world exports (in % and USD)	
		2003	2013
154	Specialty pharmaceuticals	0.7% (USD 41mil)	1.4% (184mil)
531	Enzymes	0.4% (USD 10.4mil)	1.1% (53mil)
39	Micro-organism culture preparations	0.2% (USD 1mil)	0.2% (USD 3mil)
248	Packaged medicines	0.15% (USD225mil)	0.47% (1.63 billion)
435	Unpackaged medicines	0.19% (USD 10mil)	0.15% (USD 16.8mil)
157	Antibiotics	0.13% (USD14.2mil)	0.48% (USD 65.7mil)
42	Nucleic Acids	0.18% (USD28.3mil)	0.25% (USD53.7mil)
17	Laboratory Reagents	0.01% (USD1mil)	0.05% (USD14mil)

Source: Atlas of Economic Complexity, Center for International Development, Harvard University

5. Key Actors in Brazil

Private Sector Actors

As is evident from the previous analysis, Brazil's participation in the biopharmaceutical GVC is relatively limited. The country depends heavily on imports for local drug production, which is largely purchased by the universal healthcare system (SUS) for local consumption. What follows is a brief examination into the key private actors in Brazil's biopharmaceutical industry, focusing on the lead firms – domestic and global – as well as DBFs and CROs active in the country. It is worth noting that our research has not identified any active CMOs in the country.

Lead Firms

The sector is dominated by multinational lead firms and increasingly, domestic pharmaceutical firms largely engaged in generics manufacturing. Despite being generics manufacturers first, many of these firms have recently made the difficult transition into biologics, launching drugs individually and through consortia such as Orygen Biotecnologia (backed by Biolab and Eurofarma) and Bionovis (backed by Aché Laboratórios, EMS, Hypermarcas and União Química). Brazil's current biopharmaceutical strategy (discussed later in this paper) has been to layer a novel set of capabilities onto existing domestic pharmaceutical lead firms. Although the majority of both foreign and large local firms' activities are in manufacturing as well as Phase III of product development, many have begun to foray into earlier stages of clinical trials, often through collaborations with other producers and academia.

A number of global lead firms are active in Brazil, including Roche, Pfizer and Sanofi, large pharmaceutical companies with varying degrees of interest in biologics. For the most part, these firms' activities in Brazil are limited to sales and late stage clinical trials and not drug discovery. However, there are an increasing number of cases of more meaningful engagement. Roche

opened a small molecule production facility in Rio de Janeiro in 1979. Today, it employs 550 people and exports oncology, rheumatology, neurology and hematology drugs to other Latin American markets, and more recently, to some European countries. Pfizer has entered into a strategic partnership with Orygen for the production of various monoclonal antibodies. While these are all biosimilar drugs, a company representative indicated that there is work underway to collaborate on innovator drugs for neglected tropical diseases. Sanofi conducted clinical trials in Brazil for its dengue vaccine, Dengvaxia, which was approved by ANVISA last year. Multinational firms have conducted the majority of clinical trials, sponsoring 84% of trial revenues for a total of USD 266 million in 2013. However, local trials are expected to increase, driven by biologics and biosimilar products.

Dedicated Biotechnology Firms (DBFs)

While large lead firms tend to be the focus of the policy agenda, Brazil does have a small but vibrant biotech startup community. In all, Brazil has over 270 small biotechnology firms, most of which are located in São Paulo (40%), Minas Gerais (25%) and Rio de Janeiro (13%) (Cebrap, 2011). These firms tend to be young, have fewer than 20 workers and have revenues below R$1 million. They all rely heavily on public funding from FINEP, BNDES and state research foundations like FAPESP. According to a 2011 Cebrap survey, about 40% of these firms operate in human health, with the rest distributed among animal health (14%), reagents (13%), agriculture (9%), environment (9%), bioenergy (5%) and other sectors. Overall, private R&D efforts are still modest; however, 40% of biotechnology firms have applied for a patent or had a patent issued, a high number relative to other industrial sectors in Brazil (*Ibid*) Given these firms' dependence on public funds, and the relative paucity of local venture capital, these firms growth prospects are limited. While there are some biotech-oriented venture capital firms in the country like Fir Capital, the country does not have the large pool of venture capital firms that drive growth in other biotech markets such as in the U.S.

Despite these hurdles, several emerging Brazilian biotech companies have reached significant milestones. One of the country's most successful startups to date with internal R&D capabilities is Axis Biotec, currently a holding company for four firms founded in the mid-1980s by a medical student at the Universidade Federal de Rio de Janeiro (UFRJ). The company currently has 10 ongoing clinical trials with the University of São Paulo (USP), Escola Paulista de Medicina, Unicamp and even some Federal Hospitals. Their refractory angina therapy is currently in a multisite phase III clinical trial and will likely be the first cell therapy approved by ANVISA. Recepta is another key DBF in the Brazilian market. It was the first company in the last decade to run a phase II clinical trial in Brazil. Furthermore, it was the first company to develop a cell line in Brazil, in partnership with the Instituto Butantan. In addition, in 2015, Recepta signed an $86m deal that will allow a U.S. company the right to produce Recepta's monoclonal antibody for cancer treatment. Finally, what was once one of the largest insulin producers in the world (Biobras) spawned Biomm, the first publicly traded biopharma company

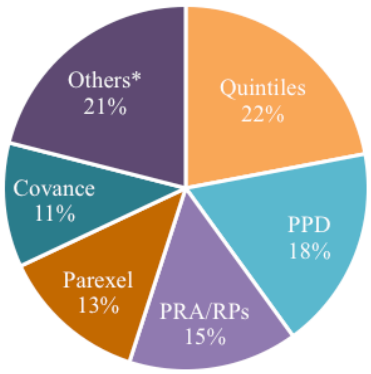
in Brazil. The company aims to begin commercial recombinant human insulin production in the coming years.

Contract Research Organizations (CROs)

There are a number of foreign and local CROs in Brazil, led by global suppliers like Quintiles, PPD, and PRA/RPS. The scope of action of CROs is influenced by the regulatory infrastructure around clinical trials. The clinical trials market generated USD 317 million in revenues in 2013, and is expected to reach USD 449 million by 2019, with a concentration in therapeutic segments around diabetes, rheumatoid arthritis, and cancer, and a majority of trials being conducted in Phase III (Frost & Sullivan, 2013). The presence of global CROs presents opportunities for small firms to operate as service providers in the area of data management. Currently only 30% of CRO contracts are with local firms, but multinational firms have shown a willingness to outsource more in the future. The top services provided by CROs in Brazil include: product development strategy; early clinical development; Phase I-II clinical trials; Phase II and III clinical trials, observational research, and product marketing and sales.

According to industry executives, quality is the primary consideration when pharmaceutical and biopharmaceutical companies select CROs. Currently, the top five CROs hold 79% of the total CRO market in Brazil, led by Quintiles with a 22% market share, and followed by PPD at 18% (see Figure 7). But these two market leaders are considered to be exceedingly expensive, even by international companies, which constitutes an opportunity for home-grown CROs. Furthermore, the international structure of these CROs has been cited as being problematic as it relates to communication between parties (Frost & Sullivan, 2015). Again, local CROs could leverage their knowledge of the Brazilian market to better serve local companies as well as local affiliates of multinational firms.

Figure 7: Brazil CRO Market, 2013



Source: Frost & Sullivan

**Others includes Intrials, Newco Trials, GC2 and PHC among others*

Capital Providers

It is worth mentioning that new private sector actors are emerging in Brazil to work with and around the challenges of developing the country's biotech industry. Biozeus, founded in 2012 by a Brazilian venture capital fund, works with university researchers to identify early-stage drug candidates at Brazilian universities and invests in translating the research into commercial applications. Biozeus envisions itself as part of the drug development process, bridging the commercialization gap that exists in Brazil. As one of the partners of Biozeus stated "having a company with a portfolio of university projects rather than just one means that if a project dies, the company can continue. This is an intermediate model that seems to fit Brazil." To date, Biozeus has licensed seven university-based technologies. Many interview respondents claim that there is good science in Brazil. The issue is finding science with commercial potential, and supporting scientists and entrepreneurs in the early stages. Biozeus employs a portfolio approach to investing in biotech startups. But what makes it truly unique is its ability to identify promising technologies in an unstructured and underdeveloped environment through relationships with universities, labs and individual researchers.

Key Public Sector Actors

Funding and Regulatory Agencies

It almost goes without saying that without key public sector actors, both in terms of finance and in terms of regulation, there would be no biopharma industry in Brazil. BNDES has been the industry's primary financing agency and the developer of the country's overall biopharma industry strategy (discussed later in this paper). The primary BNDES program to support the biopharma industry is Profarma (established in 2004). While Profarma initially focused on supporting the development of the pharmaceutical industry, it oriented itself more towards biopharma in 2013 with the launch of Profarma – Biotechnology, a $800 million program aimed at supporting biotechnology production, R&D and exports. A much smaller program, Criatec (established in 2011) provides seed funding (not to exceed $745K) to biotech startups with revenues of at least $3m. FINEP has also been a funder of the biopharma industry primarily through Inova Saúde also launched in 2013, part of the Inova Empresa effort to supply grants to innovative projects proposed by industry. Inova Saúde's funding to date of $370m (60% of which has gone to biotech) has mirrored the BNDES strategy and focused primarily on the development of biosmilars, supporting emerging biotech companies to a lesser extent.

ANVISA, founded in 1999, has created the regulatory environment for the emergence of the biopharma industry and has overseen quality control, enforcement and the provision of guidelines for the development of new markets within Brazil, specifically biosimilars, which were put in place in 2010. The general consensus among our interview respondents is that ANVISA is a solid, if slow, institution that has gained credibility inside and outside of Brazil

despite the fact that it often modifies international standard practices to create Brazil-specific processes.

Lastly, the Ministry of Health is the primary customer of biopharma products, the clinical trials overseer (through CONEP) and a critical player in the process of technology transfer, through the management of productive development partnerships (PDPs). PDPs incentivize technology transfer from private companies to public counterparts over the course of five years. In exchange, companies obtain exclusivity in public procurements of the related drug. Given that Brazil's public healthcare system is the largest of its kind in the world, this is a very attractive proposition. Between 2009, when PDPs were first offered for pharmaceutical products, and 2013, there were 87 partnerships established. Various interview respondents suggested that PDPs have been successful, especially for the production of vaccines. Involving large local firms and foreign players, these partnerships are expected to help reduce the trade deficit and increase R&D investments, which currently represent about 2% of overall pharmaceutical sales.

The Ministry of Health has been pushing for decentralization in the country's pharmaceutical industry, towards the development of a national Health Industrial Complex (CIS), with the Fiocruz Foundation as the organization in charge of implementation. The goal of this complex is to increase support for regional research and production initiatives, as well as make strides towards the decentralization of overall pharmaceutical production, which has traditionally been concentrated in the southeast of the country. With this initiative, each region is expected to specialize in different sectors: biodiversity in the north, pharmaceuticals in the central-west region, and diagnostics and biologics in the south.

Research Institutions

Brazil has a number of world-class public and private research institutions at both the federal and state levels. Several public research institutes form the cornerstone of the government's biopharmaceutical capabilities and engage in both the production of medicines as well as basic and applied R&D. The Oswaldo Cruz Foundation (Fiocruz) includes Bio-Manguinhos/Fiocruz, the Immunobiological Technology Institute focused on the development and production of vaccines, reagents and biopharmaceuticals, and Far-Manguinhos, the Institute of Drug Technology, the largest pharmaceutical lab engaged in pharmaceutical drug production as well as R&D. Instituto Butantan, overseen by the State of São Paulo, is also an important resource for basic and applied research and training as well as the production of immunobiological products in Brazil.

These institutions have helped to build Brazil's reputation for quality vaccine production, as well as its reputation as a center for innovative scientific research. For example, Bio-Manguinhos/Fiocruz recently partnered with GE Healthcare and iBio to create a plant-based multipurpose biopharmaceutical and vaccine manufacturing facility that will move plant-based

protein production to the next level. Another important research center is the Brazilian Biosciences Laboratory (LN Bio), a part of the Brazilian Center for Research in Energy and Materials (CNPEM). LN Bio offers open facilities, thematic programs, as well as training and education through graduate and postdoctoral programs, sharing infrastructure and skills with the academic and industrial sectors in human health and other biotechnology applications.

Universities

Brazilian universities have increased their research into bio-related subjects significantly in the last decade, particularly in the areas of bio-agriculture and bio-fuels. In 2008, Brazil had close to 7,000 researchers in biotech-related fields, over 90% of which worked in universities (Niosi et al., 2013). Health-related research dominated bio-related research in Brazil representing almost 70% of all biotech publications between 1996 and 2011. Brazil's academic publications, in terms of numbers, were less on a per-capital basis than in Argentina, but higher than in Mexico. The top five centers for research include University of São Paulo (USP), Federal University of Rio de Janeiro (UFRJ), the State University of Campinas, Fiocruz and Federal University of Minas Gerais (see Figure 7). Number of publications of course does not necessarily say anything about quality. But in general, the science in Brazilian universities is considered strong though the ability to translate that science into patents or commercial applications is not. Not surprisingly, the centers for biotech innovation and emerging cluster activity are in São Paulo, Rio de Janeiro and Minas Gerais.

Table 3. Health Biotech Publications in Argentina, Brazil, and Mexico – Top 15 Organizations (1996 – 2010)

University or Public Laboratory	Country	Number of Biotech Publications
University of São Paulo (USP)	Brazil	1276
CONICET	Argentina	611
UNAM	Mexico	594
Federal University of Rio de Janeiro	Brazil	518
National University of Buenos Aires	Argentina	462
State University of Campinas	Brazil	455
FIOCRUZ	Brazil	405
Federal University of Minas Gerais	Brazil	346
Instituto Politécnico Nacional	Mexico	340
Federal University of São Paulo	Brazil	333
Paulista State University	Brazil	295
Federal University of Rio Grande do Sul	Brazil	267
Federal University of Paraná	Brazil	181
National University of La Plata	Argentina	180
UAM	Mexico	179

Source: Niosi et al, 2013

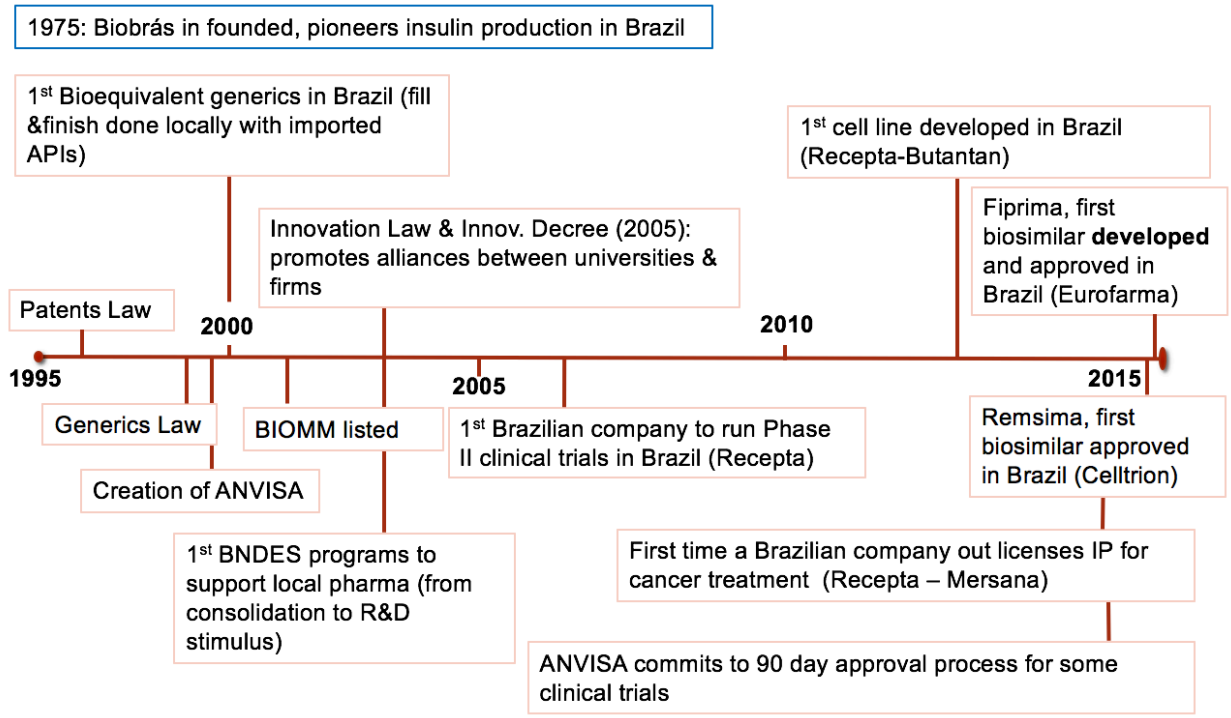
6. Institutional Context

Industrial Policy

This section examines Brazil's biopharmaceutical-related industrial policies, as well as policy-related shortcomings that the country will need to address in order to compete in this dynamic, global industry. By way of background, Brazil's pharmaceutical industry began to grow in earnest with the passage of the 1999 Generics Law. By 2011 over 50% of the Brazilian pharmaceutical market (and over 70% of the generics market) was supplied by Brazilian companies like EMS, Aché, Euroframa and Grupo Hypermarcas (Pieroni, 2011; Fraunhofer, 2012). Brazil's success in the generics market is founded on the important accomplishments made in quality control over the years by the Brazilian pharma companies, which lay the groundwork for expanding into a larger biopharmaceutical market.

Historically, the Brazilian pharma industry was characterized by high prices, low product quality and lack of good manufacturing practices, with firm strategies directed at hiding problems rather than attempting to upgrade. There was little ability by the state to monitor production and enforce quality standards. Led by ANVISA, these problems were overcome, allowing for the emergence of a strong foundation upon which to build a biopharma industry (Del Campo, 2016). Figure 8 outlines the evolution of Brazil's biopharma industry from the founding of Biobrás in 1975 to the development and approval of Brazil's first biosimilar drug. It is important to emphasize that the infrastructure for building a biopharma industry in Brazil was established only fifteen plus years ago and thus this is a relatively young industry in Brazil.

Figure 8: Evolution of Brazil's Biopharma Industry

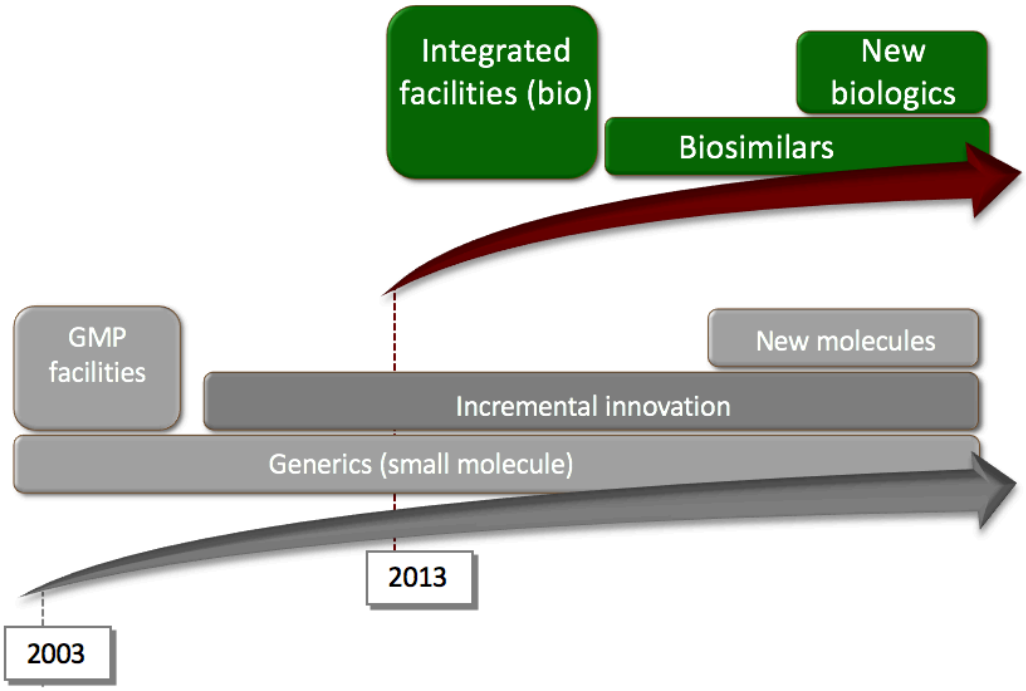


Source: Authors, based on interviews with industry representatives

Biologics have become a growing percentage of the Brazilian Ministry of Health's budget, and imports of biologics have grown at an increasingly rapid rate (37% a year between 2005 and 2010 (Pieroni, 2011). Today, they comprise 43 percent of all public health expenditures but only 5 percent of medicines purchased by Ministry of Health. These drugs are vital as the country seeks to improve patient outcomes while reducing costs. To accelerate the process of localization, BNDES announced plans (before the current economic crisis) to invest up to USD 4 billion in biopharmaceutical production between 2014 and 2016.

Brazil's strategy for developing biotech capabilities is anchored by efforts to develop biosimilars for some of the most important biologics-based drugs used in the country. These include the drugs Remicade, Herceptin and Humira, which represented markets of R$400 million, R$313 million and R$285 million respectively in 2013 (Pieroni, 2013). In 2010, led by ANVISA, Brazil provided guidelines and a 'comparative pathway' for the production of biosimilars in the country. The robust, specific, and relatively clear regulatory requirements to register biologics and biosimilars resemble FDA and EMA requirements.

Figure 9: BNDES Biopharmaceutical Upgrading Strategy



Source: BNDES Presentation

BNDES's strategy for upgrading from generics to biologics is presented in Figure 9. The strategy envisioned by BNDES aims to build biotech capabilities in the country through the introduction of biosimilars developed through tech transfer agreements between multinational companies and Brazilian partners (i.e, Orygen and Bionovis). Through this process, it is hoped that Brazilian companies will eventually be in a position to develop innovator drugs. As a BNDES representative claims "We believe that biosimilars are only the first step. If Brazil wants to think about new biologics, we need to have these big companies and their capacity. You need to have them investing in R&D." This position is disputed by some who disagree that the path toward biologics is through large, established pharma companies and biosimilars. As one biotech company executive said, "Brazil does not need national champions." Multiple strategies, discussed later in this paper, may need to be pursued.

Institutional and Other Challenges

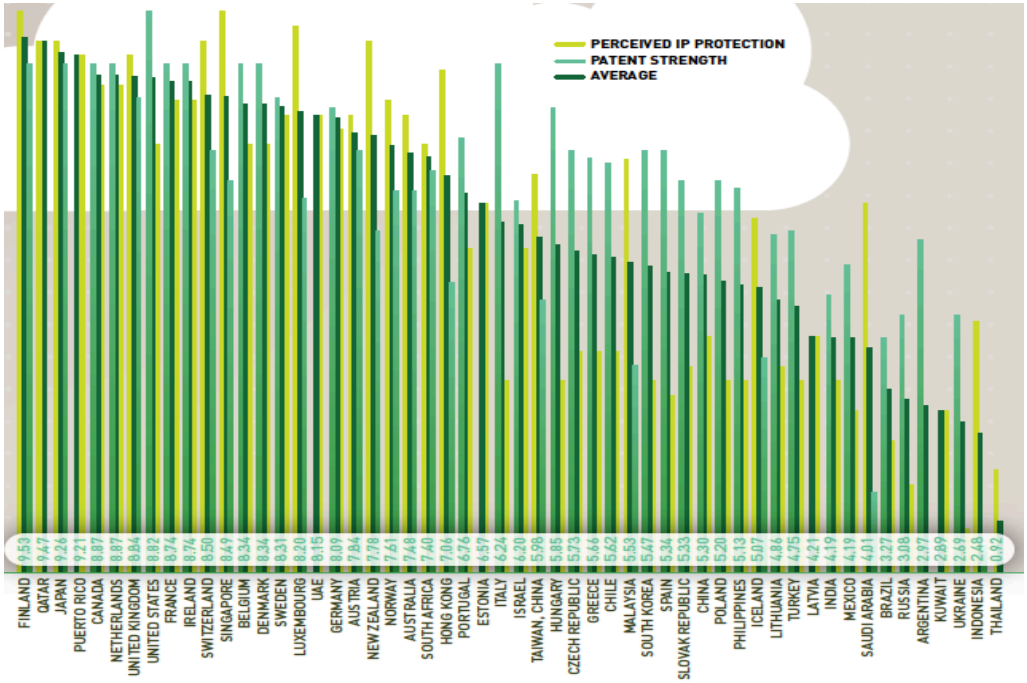
Any industrial strategy's success is contingent upon the quality of a country's broader business environment and is subject to limitations imposed by a country's institutional context. Some of the challenges faced by Brazil's young biopharmaceutical industry are listed below. Some of the principal difficulties that firms in the biopharma industry face include a slow approval process, uncertainty surrounding intellectual property rights and lack of support for early stage clinical trials. More broadly speaking, the business environment is particularly complicated for

entrepreneurial companies as the insular nature of the country's trade policies impedes these firms' access to foreign knowledge-intensive inputs.

Intellectual Property Rights

The National Institute for Intellectual Property (INPI) did not issue pharmaceutical patents until 1997. It has since been flooded by patent applications. One industry representative claims that if it were to just deal with its backlog of applications, INPI would not get through its existing caseload until 2042. The capacity gap at INPI is problematic for firms developing innovative drugs. For biopharma companies that want to bring an innovative drug to the world market, they will likely first and foremost file in the U.S. or Europe to achieve both the legitimacy and the protection. Companies in Brazil, in biotech and in other industries, do not believe that the Brazilian IP system will protect their ideas, assuming they receive a patent in the first place, which on average takes 10-12 years (see Figure 10). As one industry representative remarks, "patent rules have discouraged local development…companies don't bring cell lines to Brazil. For example, Lonza refused to sign such an IP agreement because it didn't have enough protection." But it also presents biosimilar producers with challenges as well. INPI cannot tell them when a patent is set to expire, meaning that biosimilar producers have trouble finding out when they can begin producing a drug. This slows down the process of biosimilar production, and leaves producers open to lawsuits from the large pharmaceutical companies that hold the original patents.

Figure 10: Rankings by Country of Perceived IP Protection, 2015



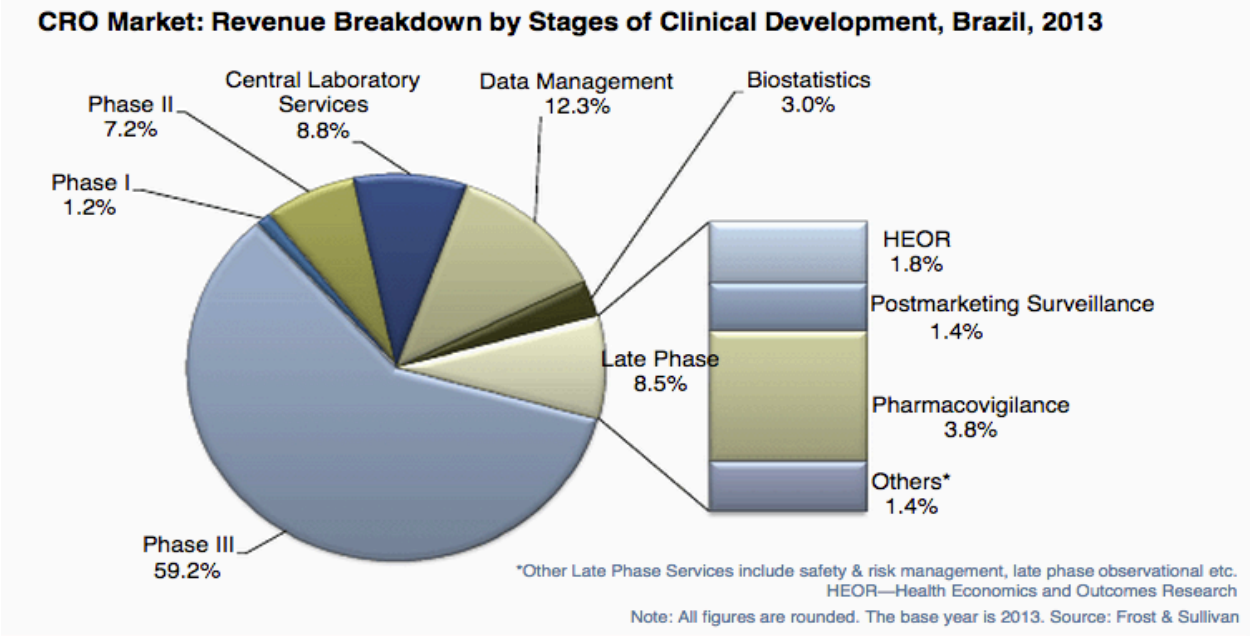
Source: Scientific American, 2015

Clinical Trials

Brazil constitutes the largest market in Latin America for clinical trials. But although the government has made recent advances towards reducing approval times, the process is still unacceptably slow. There has been a significant reduction in the number of trials since 2011. The relatively low number of trials in Phases I and II has been problematic in the government's efforts to expand local R&D efforts. The time to approval for a clinical study protocol has averaged 24 weeks in Brazil, compared to 10 weeks in other countries. In February of 2015, ANVISA passed a ruling that streamlined the authorization of some clinical trials, reducing approval times to 90 days and granting automatic approval for low-risk cases, should ANVISA not issue a decision within the 90-day window. But some industry representatives claim that this only accelerated the approval process for drugs that have already been approved elsewhere, meaning that multinational firms are the beneficiaries, not local firms. CONEP, the National Commission for Research Ethics, a division of the Ministry of Health, is also seen as part of the problem in terms of the time it takes for trial approvals.

As one company executive notes, it is difficult and costly to do early stage clinical trials in Brazil. In Canada for example, the government matches the amount a company invests in clinical trials. If the company invests $500,000, the government invests $500,000 as well. Australia has become what one venture capitalist calls "the Eldorado for phase I trials" by speeding up the process. Industry insiders argue that Brazil has great research centers and great principal investigators (PI), but the approvals process is too slow. By the time a global trial might be approved in Brazil, the trial is almost over. This represents a lost opportunity for Brazil on many fronts. First and foremost, patients in need of new treatments are left out of testing frontier drugs, researchers and hospitals lose an opportunity to link with global companies and institutions engaged in the trial, and PIs and hospitals lose financial resources that can support their work. The breakdown of Brazil's CRO market into clinical stages shows the relative paucity of early stage activity in the country (see Figure 11).

Figure 11: CRO Market in Brazil, 2013



Other Institutional and Cultural Issues

Beyond the previously elaborated challenges around clinical trials and intellectual property, there are other institutional and cultural challenges to developing the biopharma industry in Brazil. For example, with respect to **translational research**, universities, where basic scientific research in bio-related fields is considered quite strong, do not have the know-how to facilitate the development of potential drug targets from the lab toward commercialization. The Technology Licensing Offices at universities do not have the expertise (which is quite specialized) to facilitate this transition, and more broadly, the ecosystem to support it is lacking. As one biotech executive said, "there are very few people in Brazil who know how to build a biotech company." As discussed earlier, Biozeus is attempting to help bridge this gap and develop drug targets just to the point that will interest potential partners or acquirers. This lack of know-how in the biotech ecosystem limits the role of universities as engines of translational research and innovation. Despite the fact that approximately 90% of all biotech companies in Brazil have some formal agreement with universities or research centers (Cebrap, 2011), firms find it difficult to translate research project results into specific products or services.

More broadly, there is a sense that Brazil's outlook for biopharma is driven by service to the domestic market and that policy and leadership **lack a global outlook** for Brazilian companies. Our research has identified this to be an issue across industries. However, given the outsized role of the state in the biopharma industry, the insular approach to industrial development is especially problematic. The strategy of enabling local pharmaceutical firms to engage in generics production has been carried over into biologics, with some of the same firms being driven to produce biosimilars for the domestic market. The drive to lower the cost of drugs has limited the

country's role in the development and production of innovator drugs. Otherwise stated, these strategies limit the extent to which Brazil can build a globally competitive biopharma industry, which ultimately will help bring better medicine, talent and economic growth to the country. As one international biotech investor stated, "If you live in a big country like the US and you're a startup company, its fine. You're in the biggest pharma market in the world. In Brazil, it's not like this. If you're a Brazilian company, you need to go abroad."

Finally, several challenges face **entrepreneurial biotech companies**. As one CEO of a biotech startup stated, "There are few, but good opportunities for small biotech firms, but those firms need money to grow; they have infrastructure needs, human capital needs." In general, industrial policies in Brazil have not been geared toward supporting startups in this area, though there are signs that this is changing. The central issues of accessing **talent** and **financial capital** remain. In generally, the environment in Brazil is considered "hostile" toward new ventures, not only because of these challenges but also in terms of **regulation and taxation**.

7. Looking Forward: Brazil's Biopharma Strategies and Potential Opportunities for SENAI ISIs

As this paper has highlighted, the biopharma industry is a highly complex, highly regulated industry that presents significant opportunities for Brazil but also significant challenges. While Brazil has a number of assets upon which to build – a solid if slow regulatory environment that emphasizes quality, strong science in its universities, a small, but vibrant base of biotech startups, and importantly, a large and growing market – it has had trouble capitalizing on these to drive industry growth. Policies that have prioritized national champions and biosimilar production over innovation-driven growth have stunted the development of the country's biotech capabilities. As one CEO of an emerging biotech company said, "The BNDES strategy of focusing on large firms allows them to solve problems, so that it may become easier for smaller firms to follow them. At the same time, I think the U.S. model is better [for innovation], because it allows small firms to emerge and thrive." Overall, the Brazilian climate for entrepreneurial companies, particularly in a capital-intensive industry like biotech, is challenging. In addition, the country has been difficult to navigate for international companies interested in investing, whether in clinical trials or in R&D.

In the end, there is no one single pathway or strategy for Brazil to follow to develop its biopharma industry, but several that should reflect experiences in other countries while remaining mindful of the Brazilian context. Some of these strategies are currently being deployed in Brazil. Others have not received sufficient attention form policymakers, and should be prioritized moving forward. We list three such potential strategies below, emphasizing that they can and should be pursued simultaneously to ensure that the country achieves its aims of

lowering the cost of drugs for the general population and encouraging firms to develop innovator drugs to address unmet medical needs in Brazil and around the world.

1. *Prioritize biosimilar production capabilities through tech transfer from multinational firms to newly established 'national champions' with a longer-term goal of developing innovator drugs.*
This strategy, currently in place, addresses the pressure to reduce the cost of biologics and helps to build biologics production capabilities in the country. Biosimilars will be an important part of the Brazilian biopharma market over time and thus need to be developed in an efficient manner that builds capabilities in the country. However, given the pace of change in the biopharma industry, there is likely to be newer, more effective drugs on the market by the time these biosimilars are produced in Brazil, keeping the country at a distance from frontier drug development. Whether the strategy of moving from biosimilar production to innovator drug production can be realized remains to be seen. Orygen and Bionovis, the national champions focused on biosimilars, have already begun to explore the possibility of developing innovator drugs in concert with their backers, Brazilian generics companies, as well as the foreign biopharmaceutical companies with which they are already engaging for the tech transfer of off-patent drugs. As senior Brazilian pharma executives acknowledge, this is new territory for the companies and requires both new knowledge, gained largely through international partnerships, and a new culture of innovation within Brazilian pharma companies.

2. Increase the focus on and support for entrepreneurial biotech companies.
These firms leverage the country's unique scientific capabilities to develop innovator drugs that can both address unmet medical needs and increase value capture on the part of Brazilian firms in the biopharmaceutical GVC. Firms like Recepta, Axis Biotec and Biomm are examples of Brazilian DBFs that have succeeded through organic growth or through acquisition and partnerships. In many cases, what has made them successful is adopting a global outlook from the outset. This global outlook has meant pursing intellectual property strategies that prioritize gaining protection in established markets like the U.S., Canada and Europe. Furthermore, international partnerships have allowed these firms to access talent, funding and market opportunities abroad. The challenge is that these firms are exceptions rather than the rule. Most Brazilian DBFs depend heavily on public funds and when successful, are obvious investment targets for large multinational biopharmaceutical lead firms. Increasing the number of viable biotech startups starts upstream, in the translation of university research into commercially viable opportunities. Innovative business models, like the one adopted by Biozeus, may facilitate the mining process involved in finding and extracting ideas otherwise lodged in university labs, and bringing them before investors. Improving university TLOs could facilitate the tech transfer process as well. Given the scientific capabilities in the country, the unique biodiversity the disease challenges specific to the region, and the significant size of the market, Brazil has an opportunity to become an important player at the frontier of biotech development. Much more is needed to provide a dynamic and supportive ecosystem that can help these companies grow and

survive the long development process. Like in most parts of the world, international partnerships are a critical part of the pathway to success for these entrepreneurial firms. The growing dynamism and size of the Brazilian biotech community is reflected in the increasing participation from Brazil in the annual BIO conference in the U.S. As is the case with the rest of Brazilian industry, a global outlook is necessary if Brazilian firms are to thrive.

3. Make Brazil a more attractive location for multinational R&D biotech investment.
Brazil could carve out a more valuable niche in the global biopharmaceutical value chain by playing a more important role in lead firms' innovation networks. At present, most multinational lead firms active in Brazil operate little more than marketing and sales offices. Upgrading to higher value added activities will involve attracting more early-stage R&D spending, larger investments on the part of global suppliers like CROs and CMOs and improvements to the current clinical trials framework. Firms may be reluctant to localize early stage R&D for innovator drugs, especially in light of the government's current biosimilar strategy, as well as the weak intellectual property rights regime. Multinational firms are often catalysts for technological upgrading in developing countries and emerging markets, and their presence should be better leveraged to ensure that Brazilian scientists and engineers are exposed to new ideas and technologies that might encourage them to build their own businesses one day.

Efforts should be made to find common ground between these three strategies, as they can fulfill the government's twin aims of reducing the cost of drugs and driving innovation. All of these strategies, and especially the third, need to be supported by an improvement in the overall biotech innovation ecosystem and business environment, including the streamlining of clinical trials approvals, the strengthening of the intellectual property rights regime, the development of capabilities and talent as well as the attraction of talent from abroad, and the integration of Brazil into the global biotech industry through more favorable trade policies, increased partnerships, and the flow of ideas, talent, goods and services. Regardless of the specific strategy, for the Brazilian biotech industry to grow to its full potential, there will need to be an increase in overall investment in the industry by the private sector, not just the public sector, which will require clear pathways for risk-taking by entrepreneurs, investors and larger firms.

The Role of Third Parties and the ISIs
Unlike other technology areas that can be applied across multiple industries (microelectronics, lasers, polymers), the biopharma industry requires a unique set of skills that are not necessarily transferable to other industries due to the circumstances of working with products that are consumed by humans. Thus, for third parties to play a role in the support of the biotech industry, they must be highly capable and meet high standards set by international regulatory bodies.

As has been highlighted in this paper, the challenges facing the Brazilian biopharma industry are numerous: institutional challenges (IP, clinical trial approvals), lack of financial investment,

particularly from the private sector (lack of risk capital), human capital shortages, lack of support for and know-how on growing entrepreneurial biotech companies, and the need for a global mindset and focus.

Some third-party entities like Biominas help address some of these challenges, particularly with startups, while others like trade associations such as Interfarma take on some of the institutional challenges associated with IP and clinical trials. But currently, there are no technology-oriented third parties (such as CESAR or Eldorado in electronics) that work with biopharma companies on applied R&D.

However, there are some existing models that may provide examples for third-party participation. Often this involves more downstream manufacturing-related work rather than the more specialized upstream R&D. This could involve early-stage biomanufacturing services for companies that want to avoid investing in costly equipment and could benefit from shared facilities. Supporting biopharma companies with manufacturing support can help reduce their costs and reduce the time often lost using a private contract manufacturing organization.

A few models may offer some guidance to SENAI as it thinks about its potential role in supporting the biopharma industry in Brazil:

1. In Germany, the Fraunhofer Institute for Interfacial Engineering and Biotechnology based in Stuttgart and affiliated with the University of Stuttgart, addresses a wide area of industries including Medicine, Pharmacy, Chemistry, Environment and Energy across multiple competencies including Molecular Biotechnology and Cell and Tissue engineering. In its specific work in Cell and Tissue Engineering in GMP production (Good Manufacturing Practices) it works in preclinical research and clinical application for the development of GMP-compliant manufacturing processes for tissue engineering.

2. In Massachusetts, the Biomanufacturing Lab at the Center for Innovation & Entrepreneurship at the University of Massachusetts at Dartmouth provides training, mentorship, consulting services and access to equipment to local and start-up biotech companies. (see Figure 12). The Lab was created with the financial support of the Massachusetts Life Sciences Center, a state entity created to support the growth of the life sciences in the Commonwealth of Massachusetts.

In both of these cases, the centers are affiliated with or directly part of a university where they can access and retain highly skilled employees. They combine training for students with support services and applied R&D work with companies. Their success depends upon maintaining high quality human capital and responding to market demand from the regional biopharma industry.

The new ISI for Biosynthetics in Rio de Janeiro might also provide a model for a biopharma ISI in terms of partnering with industry and responding to industry demand. The Biosynthetics ISI is focused on developing sustainable solutions through chemistry and industrial biotechnology using both renewable and non renewable resources to deliver new products and processes to industry.

Figure 12: UMass Dartmouth Biomanufacturing Lab

Mission Statement

1. Provide education and workforce development for biotechnology and biopharmaceutical industries.
2. Support local and start-up companies for process and product development.

Objectives

1. Offer wet lab courses such as bioengineering lab and others.
2. Support faculty research in the areas of molecular biology, biochemistry and bioengineering.
3. Provide lab and bench space, equipment, instrument and mentorship to students for their thesis research and capstone projects.
4. Provide equipment, instrument and engineering expertise for start-up companies to develop their products.

Capabilities

1. Molecular cloning and expressing genes in bacterial systems.
2. Fermentation and bioreactor design.
3. Isolation and purification of recombinant proteins.
4. Isolation and purification of plasmid DNAs.
5. Chemical analysis, biological assay and testing.

Instrument and Equipment

1. Atomic absorption spectrometer (Perkin Elmer AAnalyst 300)
2. Autoclaves (Vernitron Majestic, Napco Model 8000-DSE, Tuttnauer)
3. Balance and scale (Mettler Toledo PB 303-S, A&D FR-300)F
4. Biological safety hood (Baker SteriGard)t
5. Centrifuges (Eppendorf 5415 R, Fisher Scientific Centrific)
6. CO_2 incubator (Sanyo MCO-17AIC)e
7. Coliform incubator bath (Precision Scientific)
8. Energy dispersed X-ray spectroscopy (Oxford Instruments INCA Energy)
9. Fourier transferred infrared spectrophotometer (Perkin Elmer Spectrum 100)
10. Freezer (Revco PLUS ultra-low temperature freezer)
11. Etc.

With the right team, investment in equipment and most importantly, demand from industry, SENAI could be in a strong position to provide shared equipment and services to the biopharma industry, particularly small and medium-size firms that do not have access to the resources available to larger firms. It is also potentially in a good position to provide training of technicians and other positions that work on post-discovery activities along the value chain. Finally, as with some of the ISIs, a SENAI ISI in biotech could be a node in the larger 'ecosystem' helping to facilitate relationships and broker services, again in particular for the small and medium-size businesses. However, unlike some of the other ISIs, biopharma is highly specialized with a small though growing community of researchers, industry leaders and regulatory and government

participants. SENAI will need to clearly carve out its niche and contribution to the industry based on acquiring strong capabilities and credibility within the industry.

8. Conclusion

The biopharmaceutical industry is structured in a way that reflects both the uncertainty and the high cost associated with large molecule drug development. Each step of the value chain, from discovery to production, involves significant risk and requires significant collaboration on the part of various private and public actors.

The industry's fragmentation has gone hand in hand with its globalization. Although early stage development and R&D remain largely concentrated in regional clusters in industrialized countries, the industry's fragmented structure has allowed for the global dispersion of certain scalable activities like clinical trials management and manufacturing services, which are now often the purview of global suppliers like CROs and CMOs. Developing countries and emerging markets often participate in the biopharmaceutical GVC late in the clinical development process, in production or purely on the commercial side. More recently, a number of emerging markets have begun to engage in biosimilar production as well. The high cost of biologics has long been a burden on public health systems like the SUS in Brazil, spurring the development of a regulatory pathway for the production and commercialization of biosimilar drugs, as well as the implementation of industrial policies that create national champions for their production within the country's borders.

Brazil's role in the biopharmaceutical GVC has evolved considerably in the last 16 years, a relatively short time period in which to enter and develop a new, complex industry. The country remains dependent on imports and focuses almost exclusively on the domestic market. Brazil counts on three types of lead firms: multinational companies, biosimilar manufacturers and DBFs. Multinational firms do little more than sales and marketing in Brazil, Roche being one of the few that is engaged in local manufacturing, albeit with imported APIs. The biosimilar manufacturers, which include Orygen and Bionovis among others, are beginning to produce biosimilar drugs locally, often in partnership with multinational firms with drugs facing patent expiration. Finally, Brazil has a small but vibrant community of DBFs engaged in the complex process of large molecule drug development. While large, global CROs like Quintiles are present in the country, they focus on late stage clinical trials. There are a number of public institutions like the Instituto Butantan, which are internationally recognized and engage in the production of medicines as well as in basic and applied R&D. Finally, Brazil has a large and vibrant scientific community spread across various universities like USP and UFRJ.

Interview respondents claim that Brazil does not have an environment conducive to innovation in the biopharmaceutical industry. There is a great deal of uncertainty surrounding the intellectual

property rights regime, with innovative firms often filing patents abroad, and biosimilar manufacturers expressing difficulty in simply finding out if and when a patent is set to expire. Furthermore, the drug approval process remains slow – up to 24 weeks in Brazil while just 10 weeks in some other countries – and costly. While universities are well regarded in terms of their scientific output, they are seen as lacking the translational capabilities necessary to bring new ideas to market. Finally, as is common in Brazilian industry in general, the biopharma sector lacks a global outlook that is sorely needed.

Given the country's current role and the well-documented challenges associated with accelerating innovation in this important industry, what are Brazil's options moving forward? The strategy outlined by BNDES involves linking national champions with multinational firms to produce biosimilars, and to then engage in the development of innovator drugs. But the country could also do more to bolster its base of entrepreneurial biotech companies, and encourage them to venture outward in search of international partners. There is also an opportunity to find novel ways to tap into the country's rich scientific community, either by strengthening TLOs, or by leveraging innovative business models that are able to seek out promising technologies and draw them out (i.e. Biozeus). It is important to recognize that the country can and should pursue multiple strategies at once, as they each yield different, but equally important results. The biosimilar strategy reduces the cost of drugs, making them more widely available. Tapping into universities and startups is the most direct route to developing indigenous innovator drugs. Regardless of the specific strategy, the goal must be to encourage and support greater risk taking by entrepreneurs, firms and investors that can tap into and take advantage of the strong scientific capabilities in the country as well as the large and growing market for biopharmaceuticals.

Finally, there is a potential role for third parties, like the SENAI ISIs. We have argued that there are successful models upon which to draw. With the right team, investment in equipment and capabilities and most importantly, demand from industry, SENAI could be in a strong position to provide shared equipment, services and training to the biopharma industry, particularly small and medium-size firms that do not have access to the resources available to larger firms. An initiative will require sustained support over decades, not years, to develop the requisite capabilities and credibility within the national and international biotech communities.