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JOSÉ THIAGO MURAT IBRAHIM

Biological and biosimilar medicine logistics challenges, an analysis of the biological medicines supply chain

Rio de Janeiro

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Master's dissertation presented to the COPPEAD Graduate School of Business, Universidade Federal do Rio de Janeiro, as part of the mandatory requirements in order to obtain the title of Master in Business Administration (M.Sc.).

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RESUMO

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O avanço das pesquisas dos medicamentos biológicos tem gerado impactos muito positivos para a sociedade nas últimas décadas, possibilitando o tratamento de doenças em que os medicamentos convencionais (químicos) obtinham pouco ou nenhum resultado. Contudo, esses medicamentos além de possuírem um alto valor agregado, possuem uma estrutura menos estável, necessitando de cuidados especiais de armazenamento, como a manutenção da temperatura em uma região entre 2 e 8° C. Além disso, a produção deste tipo de medicamento é concentrada em algumas regiões do mundo (Europa e Estados Unidos), sendo muitas vezes necessário fazer longos deslocamentos para atender as mais diversas regiões do mundo. Portanto, uma boa estruturação da cadeia de suprimentos se torna vital neste setor, já que o impacto de desperdícios é muito alto, por serem produtos extremamente caros e com alto impacto na vida dos pacientes.

Na última década tem ocorrido a expiração dos prazos das patentes de muitos desses medicamentos, abrindo espaço para os chamados medicamentos biossimilares. Este fato tem gerado consequências importantes nos mercados mais avançados (Europa e EUA), mostrando uma redução de preços e aumento da demanda. Esta ainda não é uma realidade no Brasil, mas o governo brasileiro tem buscado iniciativas para o desenvolvimento deste setor, já que os gastos com medicamentos biológicos representam uma importante parte do orçamento destinado à saúde.

Os resultados mostram que, do ponto de vista logístico, o maior desafio da gestão da cadeia de suprimentos é o controle de temperatura, em especial, garantir esse monitoramento ponta a ponta. Para o desenvolvimento do setor biofarmacêutico no Brasil, com a expectativa que haja uma expansão dos biossimilares, há muitos fatores críticos. A tendência das grandes empresas é manter a maior parte da produção centralizada na Europa e EUA, mas podendo desenvolver alguns polos em outros países para ficar mais próximo de grandes mercados.

O governo brasileiro tem buscado atrair essas empresas e desenvolver esse setor a partir das PDPs (Parceria para o Desenvolvimento Produtivo), porém este programa isoladamente não deverá ser suficiente para esse desenvolvimento. De acordo com os entrevistados (pessoas com experiência nesse setor), qualidade é crucial quando se fala de medicamentos biológico, então pessoas qualificadas, serviços logísticos especializados disponíveis e boa estrutura logística são de grande importância. Além disso fatores como incentivos fiscais e estabilidade político e econômica são fatores decisivos para o investimento de empresas no país. Um último tópico levantado foi em relação a regulação. No Brasil a regulação do setor biofarmacêutico é bastante rigorosa (como realmente deve ser), porém é extremamente lenta. Então, por exemplo, para a aprovação de novos medicamentos, o Brasil leva muito mais tempo que outros países, fator crucial em um setor em que o valor agregado dos produtos é altíssimo e investimentos em P&D são constantes, gerando sempre inovações.

Keywords: supply chain, logistics, cold chain, biopharmaceutical, biological drugs

ABSTRACT

IBRAHIM, José Thiago Murat. Biological and biosimilar medicine logistics challenges, an analysis of the biological medicines supply chain. Rio de Janeiro, 2020. Master Thesis in Business Management – COPPEAD Business School, Federal University of Rio de Janeiro, Rio de Janeiro, 2020.

The advance in biological medicines research has brought many positive impacts for society in the past decades, allowing the treatment of diseases that chemical drugs had small or none success. However, biological medicines, besides the high value, are characterized by having a less stable molecular structure, hence it demands special cares of storage, being the most important of them keep the temperature control in a range between 2 and 8° C. Besides, the production of those medicine is concentrated in specific parts of the world (Europe and USA), hence in many cases long transportations are necessary to take this product to attend the demand in different parts of the world. So, a good supply chain structure is critical in this sector, since the impact of any waste would be too high, for being extremely expensive products and that cause a high impact in patients' lives.

In the last decade, many patents of biological drugs have expired, opening the market for the called biosimilars medicines. This fact generated important consequences for developed markets (Europe and USA), showing a price reduction and a raise on the demand for this kind of medicines. That is not Brazilian reality yet, but Brazilian government have tried to develop this sector, because biological medicines represent an important part of the budget destinated to health care.

The results show that, from the logistics perspective, the biggest challenge of supply chain is the temperature control, especially guarantee the end-to-end control. For the development of biopharmaceutical sector in Brazil, considering that there will be an expansion of demand for biosimilars, there will be many critical factors. For big companies, the trend is to keep the manufacturing centralized in Europe and the USA, but they may develop specific production areas in other countries, aiming to stay close from important markets. Brazilian government have tried to develop this sector trough the initiative called PDPs (Parceria para o Desenvolvimento Produtivo), but this program alone will not be enough to develop the entire sector. According to specialists, quality is crucial when we are talking about biological drugs, so qualified workforce, specialized third party logistics providers and good logistics structure plays an important role to develop the biopharmaceutical sector. Besides, other factors also show important impacts in the decision of a company invest in a specific country, like tax incentives and political-economic stability. In Brazil, the regulation of biopharmaceutical sector is quite strict (as it is supposed to be), but it is extremely slow. For example, in Brazil it takes much longer time to approve a new medicine if compared to other countries, what is a critical point in a sector that works with an extremely expensive product, and high investments in R&D, generating innovation all the time.

Keywords: supply chain, logistics, cold chain, biopharmaceutical, biological drugs

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LIST OF ABREVIATIONS

3PL	Third Party Logistics
ANVISA	Agência Nacional de Vigilância Sanitária
API	Active Pharmaceutical Ingredient
ASTM	American Society for Testing and Materials
CSCMP	Council of Supply Chain Management Professional
DC	Distribution Center
EMA	European Medical Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
IAPO	International Alliance of Patients' Organization
LSP	Logistics Service Providers
OTC	Over the Counter
PDP	Parceria para o Desenvolvimento Produtivo
PSC	Pharmaceutical Supply Chain
R&D	Research and Development
RDC	Resolução de Diretoria Colegiada
SCM	Supply Chain Management
SUS	Sitema Único de Saúde
SUT	Single-Use Technologies
UK	United Kingdom
USA	United States of America
USD	US dollars
WHO	World Health Organizatio

CONTENTS

INTRODUCTION

1.1 CONTEXT, OBJECTIVES AND RELEVANCE OF THE STUDY

Biological drugs are a complex kind of medicines, produced in a living system, like microorganism, plant or animal cell, and are often more difficult to characterize than small molecule drugs (FDA, n.d.). These drugs have grown in importance because they are capable to treat chronic conditions with good results, that are not achieved by regular chemical medicines, like various forms of cancer, rheumatoid arthritis, multiple sclerosis, anemia, control and cure conditions such as AIDS, heart disease, among others (Brajcich, Friesner, & Schibik, 2016; Gurău, 2004).

Biosimilar is a medicine proved to be highly similar to an already approved biological medicine (called "reference medicine") (EMA, 2017a) and can be produced after the expiration of the patent's protection of the original biological drug. The European Union was the first to make moves on the investments on biosimilars and, in 2006, the first of this kind of medicine was approved there, while only in 2013 it begun to be analyzed by Food and Drug Administration (FDA), in the USA (Fuhr & Blackstone, 2013).

Companies believe in the potential of this sector and have invested heavily on it in the past few decades. According to a research of McKinsey consulting firm, from 1995 to 2012, the number of biotech patents applied grew at 25 percent annually in this period (Otto, Alberto, & Schrader, 2014). The website marketwatch.com says that the biosimilar market in Europe reached US$ 2,013 Million in 2017 and it is projected to exceed 9 billion USD by 2023, at a growth of 29% during 2017-2023 (ResearchAndMarkets, 2018). In the United States, the expenditure in this market is expected to quadruple between 2018 and 2020 (Harrington, 2018). These investments are justified by recent results: in 2017, biologic drugs represented 1.9% of all U.S. prescriptions, but 37.4% of net drug spending (Aitken & Kleinrock, 2018).

According to "Agência Nacional de Vigilância Sanitária" (ANVISA - the Brazilian agency that regulates the Brazilian pharmaceutical sector), in 2016 the generics were responsible for 75.7% of synthetic drugs' market in Brazil (ANVISA, 2018), number similar to countries like Netherlands (69.7%) and Canada (70%), and close to countries like the USA (84%) and UK (83.4%). Those numbers are very important because of the current moment of the biopharmaceutical sector. A growing number of patents have been expired since 2013

(Jozala et al., 2016) and may follow a similar trend of generics, even though in a smaller scale, due the price of those medicines (Interfarma, 2012). So, if the demand of this kind of products (that needs an especial care) increases, what will be the challenges for this sector? This study intends to contribute to understand some aspects of that question.

Biological medicines tend to be heat sensitive and must be kept in a temperature between 2 and 8º C (Harrington & Smith, 2015). They are also susceptible to microbial contamination, hence specific cares and structure are necessary, demanding specialized services in the biopharmaceutical supply chain, since the initial manufacturing steps until the application on the final consumer, what is also a new challenge, if compared to most conventional drugs (FDA, 2018; Rodrigues, Martins, Wanke, & Siegler, 2018)

A survey from World Economic Forum in 2017, shows inadequate supply infrastructure as the fifth most problematic factor for doing business in Brazil (World Economic Forum, 2018a). The competitiveness index still shows Brazil in the 73th position out of 137 countries in the infrastructure index, that analyze parameters like quality of overall infrastructure (which Brazil achieved the 108th position), roads, railroads infrastructure, ports infrastructure, air transport infrastructure, among others (World Economic Forum, 2018b). The same survey still shows Brazil with bad customs procedures, what harm business that depend on importation. This infrastructure gap allied to the logistics challenges inherent of biopharmaceutical supply chain makes it be an important issue in the development of biopharmaceutical sector in this country.

Despite the high cost of the biological medicines, the sensitivity of these products to environmental conditions (like heat), their short shelf life, as well as their high prices and impact on patients' lives (Francas, 2018; IAPO, 2013), there are very few studies focused on their supply chain challenges, especially in Latin America. Therefore, the main research question of this study is: *What are the biopharmaceutical supply chain challenges in Brazil?* In order to answer this main question, the specific objectives are: to verify what have been discussed in Brazil and in other countries about biological drugs and biosimilars; to identify important aspects that impact the development of the biopharmaceutical sector (and the biosimilar expansion) in Brazil; to draw the Brazilian biological drugs supply chain; and to identify the main challenges related to the storage and distribution of biological drugs and biosimilars.

Regardless of the main focus in this study be the final steps of the supply chain (storage and distribution), the research will analyze different aspects of the ecosystem, like regulation, that impact the development of the sector in Brazil. In order to have a good reference, the study looks at the European and North American experiences (that are more advanced in the biopharmaceutical sector) as a reference to gather information and bring it to the Brazilian reality.

The relevance of this study lies not only in the theme by itself (biological drugs) and the impact they have on society, but also for having a focus on a little explored field, that is the study of these medicines' supply chain. Those specific needs of storage (that bring with them asks for like specific infrastructure, skills and technology), aligned with the high cost of distribution and the impact on patients' lives, makes the efficiency of the biopharmaceutical supply chain be a very relevant topic for this sector (Lokko et al., 2018). Other products, like fruits, meat, chemical material or even microchips may also demand temperature control storage (Rodrigues et al., 2018), but at this study when we refer to "cold chain", we will be talking about the biological medicines' supply chain.

Specifically in the case of Brazil, that is a country with a huge territory and that faces a lot of gaps in its logistics network and structure (Avosani & Malebranche, 2016), understanding the biopharmaceutical supply chain challenges becomes a critical path to enable biological medicines to arrive in the final consumer with the necessary quality and safety, since specific logistics is necessary to keep those standards (Lokko et al., 2018). So, studying the experience of developed countries and the challenges in the market are essential steps in order to better enable a possible expansion of those products (biological drugs and biosimilars) that can generate a positive impact on the quality of life of the Brazilian population. This research also aims to have a broad view of biopharmaceutical sector, bringing the challenges to develop the biological medicines market (considering both, reference and biosimilars) in Brazil.

1.2 RESEARCH DELIMITATIONS

This study investigates some different aspects around the biopharmaceutical supply chain, but there are delimitations in its scope. Despite the focus be the final steps of the supply chain (storage and distribution), the study will also approach aspects like key elements for the development of the sector in Brazil but will not explore deeply all the aspects of

organizations strategy, like scenario analysis, market, competition, among others. By studying those key elements in Brazil, the research also aims to be a source of information to understand challenges that may emerge in developing countries for the expansion of a sector, like the biopharmaceutical, that demands specialized logistics services.

Although Brazilian logistics network is an important bottleneck (that also motivated the research), the idea is not to evaluate the network itself, but challenges inherent of the products that must be overcome. Examples of biopharmaceuticals include a wide range of products, like vaccines, blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins (FDA, 2018), but this study will focus on the called new biological drugs, those with high cost, administrated to treat chronic diseases like cancer, rheumatoid arthritis and AIDS, which patents have started to expire since 2007 and where most investment have been done.

Also, this research will not exhaust all the norms from the main regulation agencies studied, like the European Medical Agency (EMA), Food and Drug Administration (FDA) and ANVISA. The focus will be on Brazilian norms related to regulation of biopharmaceuticals authorization, storage and transport, like RDC 234/ 2005, RDC 55/ 2010 and RDC 304/ 2019. International norms were used to specific consultations and were not deeply studied.

Another delimitation of this research is that it is focused on the perception of executives and specialists of some companies that are part of the biopharmaceutical supply chain (from both public and private sectors) and do not include patients' point of view. Despite bringing professionals from multinational companies to the study, they are based in Brazil, so the field study shows the reality of this country.

Finally, the study will approach the new biological medicines and biosimilar market and their characteristics in general, not covering issues related to any specific medicine.

2. LITERATURE REVIEW

2.1 LITERATURE REVIEW PROCESS

In order to develop a consistent literature review, some steps were followed: (i) observation of a phenomena, (ii) formulation of the research question, (iii) selection of the databases that would be used as source, (iv) selection of the keywords, (v) definition of

research criteria, (vi) reading the abstracts, (vii) selection of related papers, (viii) reading the full text and (ix) paper analysis.

For this research, three different databases were accessed: EBSCO, ProQuest and Emerald. The search terms used were “biopharmaceutical”, “biological drugs”, “supply chain” and “logistics”. At the first search, the filters applied were: only academic papers and journals; with the full-text available; restraining the search to the abstract. The information was listed in a spreadsheet with a total of 11 articles. From those, only 2 were considered after the abstract reading. Having no sufficient information, it was decided to widen the search and look for the same words, but at this time in the full text, keeping the other restrains unchanged. The result was a spreadsheet with 245 papers, from where 7 were selected after the abstract reading. In an attempt to enlarge the amount of information, some searching words were added, but unsuccessfully: “warehousing”, “storage”, “transportation”, distribution” and “risk”. The next step was changing the research filter and look for non-academic texts, what brought another 3 articles for the research. Finally, it was also searched for “cold chain”, “cold logistics” and “vaccines supply chain”.

To complement the data found, a search on Google were made in order to add some important information to the study. In this step, we visited websites from reliable organizations, like ANVISA, The World Health Organization (WHO), EMA, FDA, American Society for Testing and Materials (ASTM), consulting firms, among others.

Table 01 shows the list of academic articles raised in the structured literature review. It is important to be mentioned that other academic articles were used in this research but found in other research mechanisms.

#	Year	Author	Title	Country
1	2015	Nagurney A., Li, D.	A supply chain network game theory model with product differentiation, outsourcing of production and distribution, and quality and price competition	USA
2	2016	Brajcich, A. M., Friesner, D. L., & Schibik, T. J.	Do US pharmaceutical companies strategically shift income to international affiliates?	USA
3	2016	MacCarthy, B. L., Blome, C., Olhager, J., Srai, J. S., & Zhao, X.	Supply chain evolution – theory, concepts and science	China
4	2004	Gurău, C.	Positioning strategies in the value-added chain of the biopharmaceutical sector: the case of UK SMEs	UK
5	2011	Rossetti, C. L., Handfield, R., & Dooley, K. J.	Forces, trends, and decisions in pharmaceutical supply chain management	USA

6	2018	Francas, D.	Supply Chain Planning for Biopharmaceuticals: How to Avoid Inventory Obsolescence	Germany
7	2017	Feifei, Y., Cuiqin, H., & Feifei, Y.	Application of an Integrated Supply Chain Strategy in the Biopharmaceutical Industry	China

Table 01: Academic articles from the structured literature review
Source: Elaborated by the author

2.2 THE PHARMACEUTICAL SUPPLY CHAIN

The starting point to contextualize the biopharmaceutical supply chain and the particularities of its expansion is to understand the pharmaceutical supply chain (PSC), since the last is the base where the first was born.

A supply chain consist in the flow of goods, services and information across organizations connected among themselves, aiming to fulfill a market needs (Pedroso & Nakano, 2009). In the case of the pharmaceutical supply chain, to deliver medicines at the correct places, in time, in the correct quantities and at the lowest possible cost (Yadav, Tata, & Babaley, 2011), in order to be available to patients whenever it is necessary.

The main players at this supply chain are the pharmaceutical companies (responsible for the development and manufacturing of the drugs), the wholesalers (responsible for storage and distribution of the products) and the retailers (who make the sales for the final customers) (Silva, 2018; Chircu, Sultanow, & Saraswat, 2014; Yadav, Tata, & Babaley, 2011; Pedroso & Nakano, 2009). Due to the low technical complexity, the transportation to retail pharmacies can be done by the wholesaler's own fleet of vehicles, a third-party company or by the retailers themselves (Yadav et al., 2011). That figure will be very different in the case of biopharmaceutical products, as it will be seen ahead.

Hospitals and doctors are also present in this supply chain and they will be even more important in the biopharmaceutical chain (Handfield, 2012). Physicians are important influencers to consumers because they have the technical knowledge and prescribe the medicines; hospitals not only prescribe (through their doctors), but are also important buyers of the pharmaceutical producers (Pedroso & Nakano, 2009).

Another important player in this ecosystem is the government. Due to its impact in the patients' life (health and well-being), the pharmaceutical sector has a strict control by the

regulation agencies of each country (like ANVISA in Brazil and FDA in the USA) or region (like EMA in Europe). So, these authorities need to ensure the quality, safety, and efficacy of all medicines in their countries (Sravika et al., 2017), what makes a huge influence on this market operations. Besides, in many countries (like Brazil) the government is an important purchaser of medicines through public hospitals (Pedroso & Nakano, 2009).

Finally, it is important to mention the existence of other suppliers, like chemical producers, packaging companies, etc. Figure 01 shows a simplified model of the pharmaceutical supply chain:

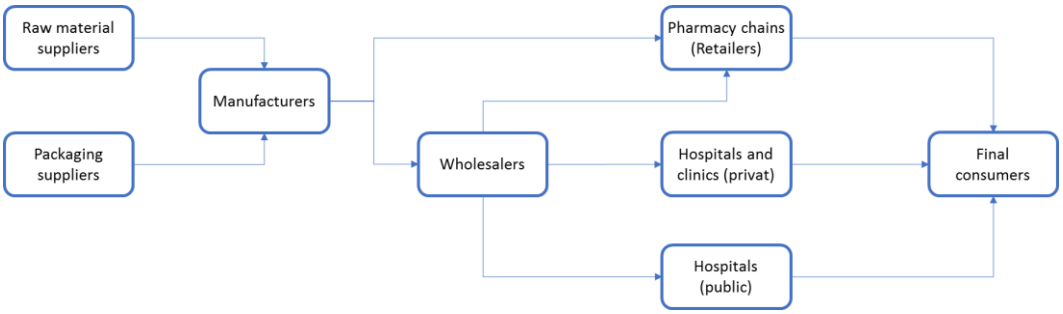

Figure 01 – Pharmaceutical supply chain
Source: Adapted from (Silva, 2018)

Observing the pharmaceutical market was an important step to question the impact of biological drugs on the PSC and the impacts of biosimilars on the demand of this kind of medicines. As it was mentioned before, with the development of generics, the demand showed a considerable growth, so observing the advance of biosimilars is an important step to check if it is showing a similar behavior and to prepare the ecosystem for the ongoing changes.

2.3 BIOPHARMACEUTICAL SECTOR

2.3.1. Biological drugs

Different approaches are used to define biological drugs. Some characteristics highlighted are the following: composed by biosynthesis of living cells, differently from the conventional drugs, that are produced by chemical synthesis (Interfarma, 2012), having complex mixtures (big structures) that are not easily identified or characterized. They also tend to be heat sensitive and must be kept in a temperature between 2 and 8º C and are

susceptible to microbial contamination, hence specific cares and production structure are necessary, since the initial manufacturing steps until the application on the final consumer, what is also a new challenge, if compared to most conventional drugs (FDA, 2018). Besides the heat sensitivity and the need of a special care about contamination, the biological drugs have a shorter shelf life (Francas, 2018), what also turns to be a logistic challenge, especially in the cases that production is concentrated in one (or few) countries to distribute to the world market.

Examples of biopharmaceuticals include a wide range of products, like vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins (FDA, 2018). They are used to treat chronic conditions, with higher prevalence rates, like various forms of cancer, rheumatoid arthritis, multiple sclerosis, anemia, control and even cure conditions such as AIDS and heart disease, among others (Gurău, 2004; Brajcich, Friesner, & Schibik, 2016). The biopharmaceutical sector is not composed only by the new biological drugs. In the biopharmaceutical sector there are also the medicines called biobetters and biosimilars, that have played an important role in the development of this sector.

Fuhr and Blackstone (2013) state that biobetters are biologics that exhibit superiority over the branded biologic in dimensions, such as efficiency or clinical specificity, and their importance is that, for the same component, they permit different approaches to drug delivery administration. The first biological drugs were predominantly used by injections. With the advance of biobetters, more stable (in their chemical structure) than reference medicines, there are different ways to administrate it, such as oral, dermatological and inhaled formulations. Those different encapsulation approaches aim to minimize the biologic instability on the processes of the biological drugs and make it easier to be administrated by patients (Jozala et al., 2016).

A biosimilar drug is a medicine highly similar to another biological existent on the market, the called reference medicine. Companies can market approve biosimilars once the period of market protection of the reference medicine expires. Those medicines must be tested and show no meaningful differences in clinical performance when compared to the reference ones, presenting the same quality, safety and efficacy (EMA, 2017). It is important to be explained that biosimilars are not generic medicines. Due to the natural variability of the biological source and manufacturing process, minor differences can occur between the

biosimilar and its reference medicine. Actually, there may be minor differences even between two different batches of the same manufacturer. For this reason, strict controls are always in place during manufacturing to ensure that minor differences do not affect the way the medicine works or its safety. Thus, these differences are not clinically meaningful in terms of safety or efficacy (EMA, 2017b).

Besides the cost reduction of biosimilars compared to the reference products, it is important to remember that biotechnology is expensive, so it can't be expected that biosimilars become as cheap as chemical drugs, at least in a short term. The average cost to develop a biological agent is $1.2 billion dollars and takes from 10 to 15 years in this process, while biosimilars spend from $75 to $250 million dollars and the development takes between 5 and 9 years. It is a great improvement, but the investment can't be compared to regular chemical drugs that demand around $650 million dollars and take 8 years to develop a new medicine, and $3 million dollars and 3 years to develop a generic (Ventola, 2013; IAPO, 2013).

Biologics are considered an important innovation made by the pharmaceutical industry, because they successfully addressed previously unmet therapeutic needs. Since their introduction, they have become each time more important in terms of new products development, clinical use, and health care expenditures (Ventola, 2013). With this expansion and growth in terms of representativeness of the biologics, it gets obvious the importance of the biosimilars. The market price of this kind of drugs is extremely high if compared to conventional drugs and, with the beginning of the expiration of the first patents, it expected that biosimilars follow the same trend of expansion that happened with the generic medicines (Ventola, 2013), even though in a smaller scale due to the price of those medicines (Interfarma, 2012). However, a deeper impact in the sector will happen due to the characteristics of those products, that involves much more money and time to develop (Feifei, Cuiqin, & Feifei, 2013), as well as a more complex structure in terms of technology (Gurău, 2004), production and distribution (Otto, Alberto, & Schrader, 2014; Rodrigues et al., 2018), all that compensated by the positive impact on the patients' life.

An IQVIA report shows that the overall price per treatment day fell up to 39% after the introduction of the respective biosimilar and 18 out of the top-20 branded drugs will be facing the competition of biosimilars until 2023 (IQVIA, 2019). Another IQVIA report shows that, depending on the country and on the specific medicine, the price of a biosimilar, if compared

to the reference product, can be cheaper by more than 60%, what reflects directly on the demand of the product (IQVIA, 2018).

As it was said before, Otto, Alberto, & Schrader (2014), Harrington (2018) and ResearchAndMarkets (2018) show that this price reduction is confirming the expectations of a demand growth on developed countries market. The data presented show also that the investment growth on this kind of technology tends to keep this trend for some time, affecting the investment on the ecosystem as a whole, like packaging, transporting and warehousing.

2.3.2. Vaccines

As it was mentioned before, vaccines are a kind of biopharmaceutical. However, vaccines are not something new in the world and its supply chain exists since the 1970s (Nomi, 2017). Hence there are a bigger number of studies on this supply chain in the literature and it has grown in the past years (Chandra & Kumar, 2019b). Due the fact that vaccines are also a kind of biopharmaceutical, it shares some logistics challenges with the called new biological drugs as, for example, the need of being kept in a controlled temperature between 2 and 8º C (Fontainha & Leiras, 2017).

A big growth on the vaccines' demand can be a concern for this cold chain in developing countries because of the capability of the existing supply chain structure to absorb a new demand (Chen et al., 2014). The expansion of biosimilars (one of the concerns of this research) can generate a similar problem, demanding a growth from the structure of the biological drugs supply chain, showing the importance of a previous planning for the possibility of this expansion. So, observing the existing similarities can be a good source of information to study the biological drugs supply chain.

However, vaccines have other kind of challenges in the supply chain, like seasonality, uncertainty on demand, and high lead time (Sadjadi, Ziaei, & Pishvaee, 2019). High research and production costs or high prices, for example, were not found in the literature. Some important vaccines, like for hepatitis B, don't cost more than 3 dollars per dose (WHO, 2005), what can help to explain the lack of worries about costs and represents a huge difference in terms of the supply chain management, when compared to the new biological drugs. Vaccines are a way to prevent some diseases (Fontainha & Leiras, 2017) while biological drugs represent new possibilities (with good results) for diseases that couldn't be properly treated so far. Another important difference is related to product waste. According to WHO (2004), the

acceptable level of waste for vaccines varies a lot depending on the local situation (of each country), among other factors, but it can vary from 5% to 50%. Even in the most conservative situation (5% of waste), it would be too much for products as expensive as the new biological medicines. Bringing to the Brazilian reality, even though Brazil has great experience with vaccines, it is not possible to assume that this country has the necessary supply chain structure to face a possible increase in demand for biosimilar medicines. In this sense, although they share some challenges, vaccines and new biological drugs can be considered two different businesses.

As the objective of this research is to understand the challenges of biopharmaceutical supply chain and the challenges that a possible expansion of the new biological drugs (and biosimilars) can bring to this supply chain, vaccines supply chain literature were used just as one of the sources of the research (especially for the logistics challenges), not going in depth into it.

2.3.3. Regulation in the biopharmaceutical sector

Regulation is also an issue to be addressed. Currently, each country has its own rule (FDA in the United States, EMA in Europe, Anvisa in Brazil etc.), despite the existence of guidelines from the World Health Organization (WHO, n.d.). On this literature review, regulation will be seen with two different focuses: international and Brazilian norms. The objective of doing so is to compare different standards and to show what are the main discussion and worries in each of them, to check how Brazilian regulators are working if compared to international standards.

Several sources highlighted the strong regulation of the sector and that it is getting stricter, not only academic ones (Rossetti et al., 2011; Feifei et al., 2013), but also non-academic sources (Shanley, 2018; Harrington, 2018).

Regarding the *international regulation*, the main concerns related to the biopharmaceutical supply were storing conditions, transportation and biosimilarity.

European Union was pioneer in approval of biosimilar drugs. According to the organization IAPO (2013), EMA's first guidelines for biosimilar medicines were in 2005. In 2007, there were already biosimilars available in this region, while the United States entered in that run later, producing this kind of medicine just in 2013 (Fuhr & Blackstone, 2013), after the creation of the first abbreviated approval pathway for biosimilars in 2010 (FDA, 2016).

Since then, discussions, norms and lots of investment have been made in order to regulate and develop this market.

Biosimilarity still is an important discussion because each country (or group, like European Union) has its own regulation, hence the standards varies all over the world. The World Health Organization (WHO) published its first guideline for biosimilars approval in 2010 (IAPO, 2013), what was an important first step, but it does not guarantee its full accomplishing by local agencies.

It is interesting to notice how non-academic sources get worried about temperature control and the regulations around it (and its expansion). Some of them show worries about temperature control through all the biopharmaceutical supply chain. Long periods out of the correct range can harm the effectiveness of the drugs, what becomes an important issue for regulatory agencies, due to the impact on patients' lives (Transparency Market Research, 2017; Harrington, 2018). For companies, not only the impact on the quality of the medicines, but also the huge financial impact of losing a batch becomes a major worry, due to the value of these drugs. Shanley (2018) focus on specific shipping regulation that considers not only temperature control concerns, but also other issues during the transportation, like shocks, leaks and contamination. This author highlights that there is no international shipment condition defined, a gap that had been fulfilled by specific organizations that developed some standards.

In Brazil, ANVISA is the government agency responsible by the regulation of the sector. There are several norms that contain pieces of different aspects of the biopharmaceutical industry. The first norm covered by this study dates from 2005 (RDC 234/2005), that regulates the quality of biological products in Brazil in a broad way.

Brazilian regulation does not use the definition of "biosimilar". At RDC 55/2010, ANVISA brings some types of biological products, being the focus of this study the two following (in a free translation from Portuguese): new biological products (*Produtos biológicos novos*); and biological products (not new). The first one would be those that have been called just as "biological drugs" at this paper so far, and the second one, the "biosimilars".

However, in Brazilian norms, the registration of biosimilars can follow two different paths, originating other two classifications: *Biological products registered by comparability*

(via de desenvolvimento por comparabilidade) – it is necessary to pass through all the tests of comparability, just like the biosimilars. (Interfarma, 2012); and *Biological products registered in a single way (via de desenvolvimento individual*) - it is a simpler and faster way to approve certain medicine, making no comparation to the reference drug; it requires information about development, production, quality control and clinic and non-clinic data to demonstrate quality, efficacy and safety of the product (ANVISA, 2010b). Figure 02 represents this classification:

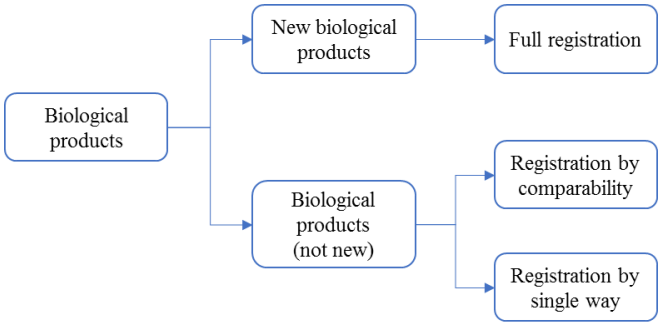

Figure 02: Brazilian classification of biological products scheme
Source: Adapted from Interfarma (2012)

Brazilian legislation about biological drugs and biosimilars is complex and tend to approach the subject in a broad way (Peres, Padilha, & Quental, 2013). Despite having some particularities, Brazilian norms try to follow international standards, like the good manufacturing practices (GMP), from the 37th technical report from the World Health Organization (WHO) (ANVISA, 2010a).

ANVISA also brought a guide for transportation of biological products that brings some guidelines for producers and suppliers, but does not bring the power of a norm and is not very specific in some aspects (ANVISA, 2017).

In the material studied in this literature review, it could be realized that Brazilian norms have a strong focus on registration of new medicines in the regulation agency, even bringing different classifications if compared to the world's benchmark (EMA, WHO and FDA). However, it is a complex, decentralized regulation and still needs a more specific and technical approach when related to storage and transportation conditions.

2.4 The biopharmaceutical supply chain

Also known as “cold chain” due to especial needs of these medicines to be stored (being one of them, the temperature control), the biopharmaceutical sector has shown impressive growth around the world in the past years and it is expected to keep receiving even more investments (IQVIA, 2019).

2.4.1. Impact of biological drugs and biosimilars on the pharmaceutical sector and the main challenges in the biopharmaceutical supply chain

As it was commented before, biological drugs won’t impact just patients’ lives, for being capable to generate better results on the treatment of some diseases when compared to regular drugs. The expansion of those products will impact the ecosystem as a whole, from regulation agencies, researchers and the producers’ suppliers, to distributors and retailers.

The raw material necessary to produce biological drugs is very different from the synthetic ones; therefore, many suppliers are also different companies. The website Pharmaceutical Outsourcing supports the idea of a more complex raw material supply, because producers needs specialized compounds, with smaller volumes, resulting in a greater number of suppliers, from different locations around the world (Singh, 2016).

Due to the needs of environment control (temperature and humidity), the cold chain requires a specialized distribution network (Rossetti et al., 2011). Hence, just the distributors able to attend those requirements will be kept in this new supply chain, opening space for new specialized companies. It is worthy to remember that some biological products are not something new, like vaccines, however the demand for this specialized warehousing and transportation service will grow and new legislations have been created for the new products, so even companies with some kind of environment control in their operations, must adapt to receive this new demand.

For Rossetti et al. (2011), a huge innovation in the supply process to be explored is the direct shipment combined with patients management. As some medicines can be applied by patients’ themselves, a service to support them in information regarding administration of the product, how to proper store it at home and other issues are also roles to be played and it can be done by different players in the supply chain, depending on each company strategy. That kind of service is also a demand brought with the advance of biological drugs.

Biological products must be stored in a cold, temperature-controlled environment; otherwise, it can harm the efficacy of the drugs, resulting in a loss of the batch or a risk to patients. The high value of biological medicines makes the distribution control even more critical, rising the impact of the risks (Harrington, 2018). Those products can be so sensitive to environment control, that long travels, through different climate zones, become a risk to be controlled by logistic operators, just like the number of hands-off, due to shocks that loads can suffer on the way from production centers to the final consumer (Harrington, 2018; Shanley, 2018).

Temperature control is so important for biopharmaceuticals that new technologies has been adapted to support logistics activities. When we are talking about packaging, there are two basic categories related to temperature control: active and passive systems. Active systems use an energy source combined with thermostatic control to maintain temperature, while the passive ones, use conventional packages associated with materials such as water/ice or dry ice to keep products at the desired temperature (Harrington & Smith, 2015).

Blockchain is a shared, immutable ledger that facilitates the process of recording transactions and tracking assets in a business network (Gupta, 2019). So, aiming to control the temperature trough the supply chain, internet of things (IoT) and block chain are also technologies with a good suitability to the cold chain, being able to keep the record of the medicines' temperature during its life, providing a higher level of supply chain visibility and security that complements the container's temperature security (Hampstead, 2018).

Leaks and bacterial contamination, water hammer and stress (in shipping transportation) are also issues to be cared and more critical if compared to regular pharmaceutical supply chain (Shanley, 2018). Francas (2018) also highlights the constraints of a shorter shelf life of biological medicines.

2.4.2. Third party logistics (3PL) and the cold chain

A practice that has grown in the past decades in several sectors is hiring specialized logistics service providers (LSPs) to take care of some activities of the supply chain, like warehousing and transportation (Maloni & Carter, 2006; Marchet, Melacini, Sassi, & Tappia, 2017). There are three main reasons for a company hire third party logistics providers: (1) cost reduction, due to the expertise and economies of scale of 3PL providers; (2) service

improvements, resulting from 3PL provider focus and specialization; and (3) intention of the company to focus on its core competencies (Maloni & Carter, 2006).

This trend has not only been followed by the pharmaceutical sector as a whole, but it seems to be especially coherent to be practiced for the biopharmaceutical sector (Grand View Research, 2019). Biological drugs producers, as it was mentioned before, are very specialized companies (demanding focus and investments from them), but that also needs a specific body of competences in the logistics operations. Hence, all the three reasons to use third-party logistics services seem to fit very well in the biopharmaceutical sector.

2.4.3. Innovation on consumer experience

As it was said before, the first generation of biological drugs were predominant used by injections, so they should be administrated by trained professionals; however, researchers have put effort to develop biological medicines capable to be used by other simpler ways, like oral. Despite being easier to be administrated, biobetters still must be stored in proper conditions and some of them may need guidance for application, so there are companies beginning to improve the final consumer experience by providing services, due to the special characteristics and conditions that biological drugs must be kept (Rossetti et al., 2011).

In this sense, in order to deliver more to the client and become more competitive, the pharmaceutical companies have tried to create more value by adding service to products, a process known as servitization (Baines, Lightfoot, Benedettini, & Kay, 2009). It means that they are not just worried to make products available for clients to buy, but also seeking to make the purchase experience easier, more pleasant, faster, less risky and supportive, so that clients can perceive value in the company's product or brand. Products and services are not a binary choice for companies provide to their clients. Actually, they are two sides of a spectrum, where in one extreme is "service" and in the other is "product". A company can be closer to provide just something tangible (pure product) or pure service. However, most of them tend to have a mix of products and service (and be positioned delivering more of one or the other) (Slack, 2013) and it is each time more common to have this complementarity.

So, as it was said before, if a pharmaceutical company develops a strategy of delivery more than just a product, like patients support to store, administrate, stock control or other services, it can be saw as a servitization process.

2.4.4. *Parcerias para o Desenvolvimento Produtivo* (PDPs)

Brazilian government considered biological medicines so strategic that created the Productive Development Partnerships - PDPs ("*Parcerias para o Desenvolvimento Produtivo*"), defining its rules in 2012 and reviewing them in 2014 (Rocha, 2019). In 2016, 26 biological drugs represented 51% of the government budget destinated to purchase medicines to distribute to the population (Maciel, 2016). At that time, the biopharmaceutical sector was not well developed in Brazil (except for vaccines), making the Brazilian government have huge expenses to import these medicines.

The idea of PDPs is to create a joint venture, bringing together three stakeholders: a governmental institution to receive the technology; an institution (private or governmental) to produce the APIs (Active Pharmaceutical Ingredients) in the Brazilian territory; and the institution that holds the technology to transfer to the first one (Varrichio, 2017). The advantage provided to the technology developer is that the Brazilian government guarantees the purchasing of the medicine for a determined period of time and price stated in a contract.

The objective of this program is to enlarge the access to strategic medicines and to reduce the vulnerability of the Brazilian public health system (SUS); reduce technological and production dependency; improve government investments; incentive national technological development; develop the production of strategic medicines in the country; among others (SAUDE, 2019). The Brazilian government aimed to save about R$5.3 billion (approximately 1.5 billion dollars) per year with this program (Maciel, 2016). It is important to say that biological drugs are not the only product at this program, but they have an important role on it.

2.5 Literature review findings

Aiming to have a better general view of the main findings of the literature review, it was decided to group it in dimensions. There is no agreement about what are the critical dimensions when we are talking about supply chain management (SCM) (Deshpande, 2012), so different researches will chose the proper ones, depending on the focus of their analysis, as it could be seen in different studies (Chandak, Chandak, & Dalpati, 2019; Chandra & Kumar, 2019a; Dalal & Athavale, 2012; Deshpande, 2012; Kess, 2012; Miranda, 2002; Sahay, Gupta, & Mohan, 2006). So, based on the focus of this research (to study the biological medicines supply chain) and on the just mentioned authors, the information gathered about the SCM

were organized in five dimensions: cost, customer relationship, logistics, supply network and quality.

However, since this research doesn't limit itself only on information about the biopharmaceutical supply chain, but also analyzes aspects related to the ecosystem as a whole, it was necessary to look for a theoretical framework to support the analysis of the business environment that companies are inserted. PESTEL analysis is a tool used to support the identification and to organize the macro forces existing in the external environment of an organization. It is an acronym for six factors: political, economic, social, technological, environmental and legal (Oxford College of Marketing, n.d.). Those factors fit well to provide the dimensions that were lacking (even though with small adjustments) to organize the findings of this literature review about the impact of the biological medicines on the business as a whole: political, economic, social, technological, environmental and legislation/ regulatory. Table 02 shows a brief description of the parameters used.

	Dimensions	Description
Business	Political	What is related to political stability, taxation policies, trades, etc.
	Economic	Impacts from the economy (world or specific country) and consumer purchasing power
	Social	Cultural trends, attitudes, lifestyle, customers' needs
	Technological	Technological innovation, new materials, new methods
	Environmental	Corporate sustainability responsibility
	Legal/ Regulatory	Related to laws and regulation
SCM	Cost	Related to the product cost
	Customer Relationship	Related to consumer and their behavior
	Logistics	Related to technical challenges of logistics
	Supply Network	Everything that impacts biopharmaceutical network
	Quality	What directly impact in the quality of the product

Table 02: Dimensions description
Source: Elaborated by the author

Therefore, table 03 presents a summary of the findings of the literature review, considering the parameters presented in table 1, and separating the information gathered from academic and non-academic sources.

Dimension	Specific issue	Academic Literature	Non-academic Sources
Technology	Long time for development	Feifei, Cuiqin, Feifei (2013)	IAPO (2013) - International Alliance of Patients' Organizations Otto, Alberto & Schrader (2014)
	New and more specific raw materials and equipment		Singh (2016) Otto, Alberto & Schrader (2014)
Supply Network	Qualification of 3PL	Rodrigues, Martins, Wanke, & Siegler (2018)	Shanley (2018) Harrington (2018) Transparency Market Research (2017)
	New Supply Chain	Feifei, Cuiqin, Feifei (2013) MacCarthy, Blome, Olhager, Srai, Zhao (2016)	
	Centralization (home countries)	Brajcich, Friesner & Schibik (2016)	
	Decentralization		
Logistics	Temperature	Rossetti, Handfield, & Dooley (2011)	Shanley (2018) Harrington (2018) Handfield (2012) IAPO (2013) - International Alliance of Patients' Organizations Transparency Market Research (2017)
	Humidity	Rossetti, Handfield, & Dooley (2011)	
	Short Shelf-life	Rossetti, Handfield, & Dooley (2011) Francas, David (2018)	
	No specific legislation for shipping		Shanley (2018)
	Leaks and contamination		Shanley (2018) Singh (2016)
	Shocks		Shanley (2018)
Legal/ Regulation	Strict regulation	Rossetti, Handfield, & Dooley (2011); Feifei, Cuiqin, Feifei (2013)	EMA (2017) - Biosimilars in the EU Information guide for healthcare professionals Harrington (2018) Otto, Alberto & Schrader (2014)
	There is a guidance of WHO, but regulations definitions are responsibility of each country government		IAPO (2013) - International Alliance of Patients' Organizations WHO
	Storage and transportation norms		Anvisa (2017)
Economic	Patents expiring and price reduction		Ventola (2013) Handfield (2012) IQVIA (2018) - The Impact of Biosimilar Competition in Europe Aitken & Kleinrock (2018) ResearchAndMarkets (2018)

	Growing market and investments		Ventola (2013) Harrington (2018) Handfield (2012) IQVIA (2018) - The Impact of Biosimilar Competition in Europe Aitken & Kleinrock (2018) IAPO (2013) - International Alliance of Patients' Organizations Otto, Alberto & Schrader (2014) ResearchAndMarkets (2018)
Customer Relationship	Direct sales	Rossetti, Handfield, & Dooley (2011)	
	Servitization	Rossetti, Handfield, & Dooley (2011)	
	New channels to deliver to the final consumer		Handfield (2012)
	Physicians playing a more important role		Handfield (2012)
Cost	High cost of R&D	Feifei, Cuiqin, Feifei (2013)	IAPO (2013) - International Alliance of Patients' Organizations Otto, Alberto & Schrader (2014)

Table 03: Summary of the literature review
Source: Elaborated by the author

3. METHOD

3.1 DEFINITION OF THE RESEARCH QUESTION

The first step for defining the research question was to identify the importance of biological drugs, their investment and register growth in the past decade, as well as the special conditions they need to be produced and stored. Besides, it was fundamental to check during the literature review the growth of the biosimilar industry, especially in Europe and United States, with a substantial number of patents expiring. Allying that two information was the key point to develop the main research question: *What are biopharmaceutical supply chain logistics challenges?* More specifically, *what are the main challenges of storage and distribution faced by this industry in order to properly delivery those medicines to the final consumer?*

These questions are very important in a country like Brazil, that has a huge territory and a deficient logistics structure (Avosani & Malebranche, 2016). Understanding storage and distribution challenges becomes imperative to enable biological medicines to arrive in the final consumer with the necessary quality and safety, since specialized logistics are necessary

to keep those standards. So, it becomes a part of the path to develop the biopharmaceutical sector in this country.

3.2 RESEARCH TYPE

Research approaches are the guidelines for data collection, analysis and interpretation. The choice of an approach should be based on the research problem or issue being addressed. The method can be classified as qualitative, quantitative or mixed (Creswell, 2014).

Quantitative approach aims to test objective theories, examining the relationship among the selected variables using statistics as an essential tool. On the other hand, qualitative research involves emerging questions and procedures, using inductive data analysis to build from particular to general themes to generate an interpretation of the data collected. Finally, mixed methods use both qualitative and quantitative approaches in order to provide a more complete understanding of the research problem, generating and testing theoretical frameworks (Creswell, 2014).

A qualitative research has some characteristics, like interpretation rather than quantification, subjectivity, flexibility during the work and focus on the process observed, among others (Kohlbacher, 2006). Using this mindset, it was analyzed the goal of the study and the qualitative approach showed to be the natural path for this research, using an inductive process, where knowledge is built from the data found, generalizing to a broader theme or model (Creswell, 2014).

Considering the just mentioned elements, the qualitative approach showed to be the natural path for this research, using an inductive process, where knowledge is built from the data found, generalizing to a broad themes or model (Creswell, 2014). Besides, during the literature review, it was shown a gap in the knowledge when looking for information about the biopharmaceuticals supply chain and their logistic challenges, due to the small amount of studies found around this issue. Intending to contribute to fulfill this gap, the logical way was making an exploratory overview about the theme.

3.3 DATA COLLECTION AND ANALYSIS

As it was said before, the literature review was not limited to academic information due to the small number of works about the studied issue, so non-academic sources were used

in order to gather more information and develop a better overview about the biotechnological sector. After reading the literature review articles, the field research was done in two stages: in the first stage, two industry experts were interviewed in order to increase the understanding on the theme, considering the Brazilian reality, and to permit an adequate direction to the second stage of the field research. Based on the literature review and on the guidance of these two specialists, the author developed an interview script that was applied in the second stage (Appendix 02).

For the second stage of the field research, the interviewees' choice was made seeking to cover different perspectives of the sector, so the idea was to bring different players of the supply chain to the research, like producers and distributors, from both the public and private sectors. It was also intended to interview people with a higher level of seniority (leaders, managers and senior professionals), who could bring a broader view of the ecosystem. Besides, it was also interviewed professors to bring an academic view. The seniority of interviewees, their experience in the biopharmaceutical sector and the fact of they come from different stages of the supply chain were the main driver for the choice of the list of participants. However, it was not possible to contact more people with the supply chain background.

Different ways were used to contact the interviewees. First, it was made a list of candidates provided by other researchers, then some contacts gave positive answers and others gave negative answer for not being exactly their field but suggested other people. Searches on LinkedIn were also a way to contact professionals from the market. Besides, during the interviews, contacts were suggested by the interviewees. Finally, 10 interviews were made, and Table 04 summarize the profile of those people. It is important to mention that all the answers provided by the interviewees represent their own opinion, based on their experience, so they don’t represent the companies’ position about the studied topics.

Table 04 - Interviewee's profile
Source: Elaborated by the author

Interviewee	Sector	Business	Size	Position
1	Private	R&D and Production	Big	Team leader
2	Public	R&D and Production	Medium	Strategy analyst
3	Public	University	Small	Professor
4	Public	R&D and Production	Medium	Director
5	Private	Distribution	Big	CEO
6	Private	R&D	Small	Project manager

7	Private	Production	Big	Commercial director
8	Public	University	Small	Professor
9	Privat	Logistics Provider	Big	B.U. CEO
10	Private	Vaccine distribution and application	Startup	Head of operations

Interviews were previously scheduled based on the availability of the interviewees, being three of them conducted in person, one using a video software and one made by telephone. In order to give a better dynamism to the conversation and let participants comfortable to expose their point of view, the interviews were recorded (always with the consent of the respondent) to latter be analyzed and transcribed by the researcher. Each interview lasted between one hour and one and a half hour. All collected data have been compiled into a file to latter be analyzed in order to find convergences and divergences between the answers and, finally, to bring coherent answers to the research questions.

The interviews consisted on open-ended questions, approaching broad perspectives of the biopharmaceutical supply chain, covering not only the main topic of the research, but also some strategic issues, like understanding the main drivers that companies analyze to determinate where to implement an operation, and other aspects like bringing a discussion about the regulation of the sector, what is a critical issue for all the players in the ecosystem.

Besides the open-ended questions, there were two other specific ones: the first, was focused on mapping the biological medicines supply chain and on drawing it. The second one asked to each interviewee to list the three main challenges in the biopharmaceutical supply chain (Table 07) and give a grade to each of them (from 1 to 5) in four different parameters: impact on the business; cost; producer capacity to execute; and supplier capacity to execute, (table 05). Those parameters were chosen based on the GUT matrix and on the perception of the previous conversation with specialists, to address one of the core questions of the research and be able to plot and analyze it.

		Difficulty to accomplish		
Grade	**Impact on the business**	**Producer capacity to execute**	**Supplier capacity to execute**	**Cost**
1	Low impact	Easy to execute	There are several suppliers able to do it	Low cost
3	Medium impact	Can do it, with some difficulty	There are few suppliers able to do it	Medium cost

5	High impact	Can't do it	There are almost no suppliers able to do it	High cost
N/A	Non-applicable	Non-applicable	Non-applicable	Non-applicable

Table 05: Parameters rating
Source: Elaborated by the author

From the two parameters related to capacity to execute (producer capacity to execute and supplier capacity to execute) it was chosen the best grade to be considered the "difficulty to accomplish". That choice was done because the important is knowing if somehow the company will be able to face the challenge, being less important who will solve it (the company or a third party).

Then each challenge was classified into a dimension (the same used to classify the finding in the literature review) aiming to group it and find what aspects the participants are giving more focus. Finally, it was segmented according to the business where each interviewee worked, that because it was expected that participants of each stage of the supply chain tended to have different perspectives.

3.4 METHOD LIMITATIONS

Among the limitations of the study, it can be listed the following:

- Qualitative method is subjective by itself. The data analysis is impacted by both interviewees' perspective and the author's interpretation, what can impact the results of the study and bring some bias.
- Geographic limitation: despite getting some interviews in multinational companies and with professionals from Rio de Janeiro and São Paulo, it is still a very limited amount of information to have a good picture of the Brazilian market.
- Number of interviews: despite bringing people from different business of both public and private sectors, biotechnology is a very specific market, so it was hard to bring a bigger number of professionals willing to support the research. It was also hard to bring more professionals with a supply chain background.

Specialist professionals: as the interview script covered different areas, usually interviewees were able to answer just the questions related for their previous experience.

4. RESULTS AND ANALYSIS

In this research it could be seeing that due the choice of interviewing people who work in different stages of the supply chain and with different expertise, the result of the research brought different perspectives, which converged in some cases, but there were different approaches in other.

It was gathered information about the main challenges of the biopharmaceutical supply chain, strategic aspects for those involved on it, their perspective about regulation and about the future of the sector. It was also drawn the biopharmaceutical supply chain in order to better understand the logistics challenges studied.

4.1 BIOPHARMACEUTICAL SUPPLY CHAIN

4.1.1. Brazilian biopharmaceutical supply chain map

In the literature review, it was not found a model structuring in a visual way the biopharmaceutical supply chain, so during the interviews it was asked the interviewees about it in order to make a map of this supply chain. The final result is presented in figure 03:

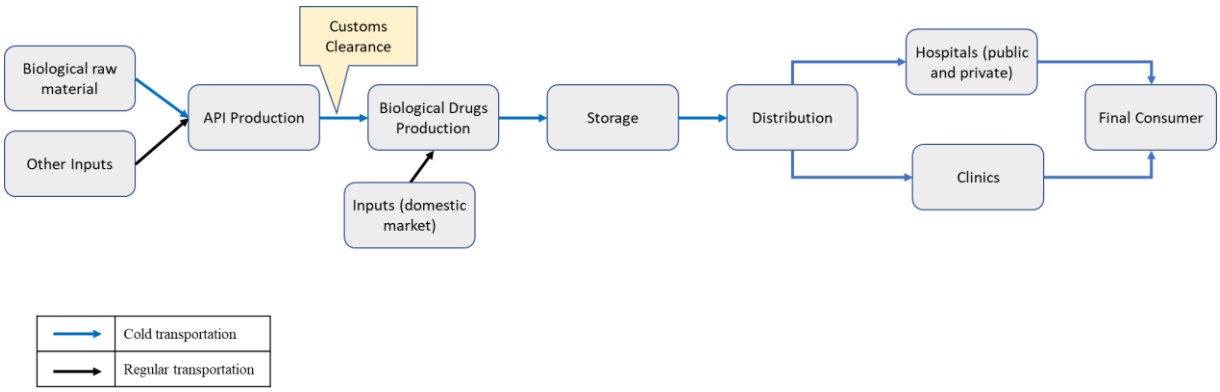

Figure 03: Biopharmaceutical Supply Chain in Brazil
Source: Elaborated by the author

Biological raw material: the medicines itself are not the only biological product in this supply chain. In order to manufacture those drugs, other biological material, like culture media and proteins, are used in the process (Jozala et al., 2016). So, the cold chain starts on the production of those materials. Producers are also specialized and supply biological material where living cells will grow.

Other inputs: to produce biopharmaceuticals, inputs that don't need temperature control are also required, like specific machinery (for example, chromatograph and

bioreactors), water, glass, among others. Some of them also demand high quality and specialized producers (like machinery and deionized water), while others are just regular suppliers.

As it was mentioned before, the production of a biopharmaceutical can be made in two stages: first, the active pharmaceutical ingredient (API) is made and, then, the production is finished. API's production is not made in Brazil, so it is an imported input for local manufacturers. Because of that, three implications can be highlighted: 1) dependence on external producers; 2) higher costs (because it is the most complex stage); 3) greater complexity in the supply chain, because of the longer transportation and especially because of the customs clearance.

Customs clearance was highlighted in this supply chain draw because of its impacts on the process. In Brazil, this stage can take days, reinforcing the bad result of customs procedures in the World Economic Forum survey (World Economic Forum, 2018b), what adds risk to such a sensitive process. It not only rises the time that logistics operator must keep the material in a cold temperature during transportation, but the biological products also must pass through another handoff and inspection, what makes harder to keep temperature control and adds stages where the process can fail. Frequently, specialized companies are hired to provide customs services in order to make a better management on this stage.

Production (final stages) can be made by the public or private sectors, often with the incentive of PDPs. Usually, they are located in the southeast of Brazil (Rio de Janeiro and São Paulo). It requires less-complex activities if compared to API production, but still demands qualified workforce and high quality control, including, of course, temperature control. After produced, the biological drugs are stored in a controlled environment and follows to distributors.

There aren't many distributors for biopharmaceutical medicines in Brazil, so it is a very concentrated market. Their operations are spreader when compared to producers, but it is still present in a few states. Those are specialized companies that concentrate purchases and deliver biological drugs to hospitals, clinics and, in very specific cases (like insulins), to drugstores. They concentrate not only the demand from different places, but also different biopharmaceuticals (called specialties) that demand the same kind of temperature control, like biological drugs, insulins and vaccines.

Most demand for biological drugs comes from the Brazilian government that is obligated to provide treatment in hospitals (including providing the necessary medicines). Then, as a general rule, those drugs go to public hospitals and clinics, where they are administrated to patients (the final consumers).

This visual model is important not only to understand the biopharmaceutical supply chain and its actors, but also brings the perception that it is not just a small variation of the classic PSC. The changes are so relevant that it can be considered that it was created a new supply chain, also called the cold chain. To analyze this statement, we looked for definitions of supply chain (in a broad sense). Among others, it was found at the Council of Supply Chain Management Professional (CSCMP) website the definition gave by Vitasek (2013, p. 186): "*The material and informational interchanges in the logistical process stretching from acquisition of raw materials to delivery of finished products to the end user. All vendors, service providers and customers are links in the supply chain*".

MacCarthy, Blome, Olhager, Srai, & Zhao (2016) also argue that new supply chains may emerge for different reasons, like technological breakthrough or creation of new products, what fits with the rising of biological drugs.

The raw material necessary to produce biological drugs is very different from the synthetic ones; therefore, many suppliers are also different companies. The website Pharmaceutical Outsourcing supports the idea of a more complex raw material supply, because producers needs specialized compounds, with smaller volumes, resulting in a greater number of suppliers, from different locations around the world (Singh, 2016), what support the idea of different suppliers.

Using the definition of supply chain of Vitasek (2013) and the information from MacCarthy, Blome, Olhager, Srai, & Zhao (2016); Rossetti et al. (2011) and Singh (2016), we could realize that, if compared to the PSC, the biopharmaceutical supply chain use different raw materials, having different suppliers and demanding some different services, with different characteristics, so, in the interpretation of the author, those really are different supply chains.

Despite being different supply chains, for companies that produce both kinds of medicine (biological and synthetics) it was found at the interviews that it is possible to share a few resources, even though there were different opinions about how deep is this possibility. The perspective got about this topic is the possibility of gains in economies of scope. The

main resources that can be shared are warehouse, even having two separate warehouses, one for cold temperatures and the other for regular ones, they can be at the same site, generating saving; transportation, just in cases where synthetics medicines have to be at the same range of temperature of biologics (it is not usual, but possible); office work, using the same idea of shared service organizations. One last possibility is to share the logistics supplier (if this company is able to provide both services), having one bigger contract and negotiating better conditions. From the perspective of production, it is very unlikely that those two kinds of medicines can share resources.

4.1.2. Challenges

Looking at the technical challenges, as it was expected, the most quoted was the temperature control, as it happened during the literature review process (Handfield, 2012; Harrington, 2018; IAPO, 2013; Rossetti et al., 2011). However, different from previous studies, other cares about the storage and transportation of biological drugs were not mentioned as important issues, like shocks, that was highlighted by Shanley (2018). Leaks and contamination, present in the articles of Shanley (2018) and Singh (2016), is taken more like an operation challenge and a general requirement, that is well controlled by the players, just like the short shelf-life, mentioned by Francas (2018) and Rossetti et al. (2011), is a characteristic of the product that demands a better stock control and in some cases higher investment on transportation (air transport rather than shipment, for example), being more a management issue and less a technical one. Another important care for logistics is about humidity, as pointed out by Rossetti et al. (2011). However, during the research, the issue mentioned about humidity was about moisture and not allow the package to get wet, otherwise it may damage it or erase printed information like shelf-life, so usually there is no specific control of the air humidity.

When questioned about what could impact the quality of biological drugs during the storage, some interviewees said that it will also depends on the specific product we are talking about. Storage conditions (and even production) will be determined by what can affect the product stability, and each kind of biological product may be sensitive to different exposure, like those mentioned before (especially temperature) and others, like sunlight or even package material and raw material quality (like ionized water).

Considering management challenges, there are also very interesting issues about storage and distribution, usually related to the temperature control. This control cannot fail in

any moment of the supply chain, so keep this tracking through all the way until the final consumer is an important challenge and, as pointed by Harrington (2018), the more handoffs there are in this process, the more complex it will be. The use of IoT and blockchain is and advance in that challenge, making this control more transparent and more reliable (Hampstead, 2018).

Another attention point in this supply chain is the customs stage. In Brazil, it can take a long time (days), so even containers with active temperature control have to be checked not to run out of power.

As it was told in the method, another part of the research was trying to identify what each interviewee considered the main challenges in the biopharmaceutical sector, so it was asked them to list the three main challenges and choose a grade (from 1 to 5) in 4 parameters: impact on the business; cost; producers capacity to execute; and supplier capacity to execute. From the last two parameters, it was chosen the lowest grade to be the difficulty to accomplish, that because the important is know if somehow (doesn't matter who will solve the challenge) the company will be able to face it.

After being classified into a dimension (the same used to classify the finding in the literature review), the challenges could be grouped, so it could be found to what aspects are the participants giving greater focus. Finally, it was segmented according to the business where each interviewee worked, generating charts to represent the perspective of each stage of the supply chain. The variable chosen to be the axis of the graph were "impact on the business" and "cost", while "difficulty to accomplish" is represented by the size of the circle (the bigger, the more difficult it is). In the plot area of the chart, it is written the grade given to the "difficulty to accomplish" variable. That was done to make it easier to know the size of the circle and to know how many challenges were there when two or three of them are plotted on the same spot. To make it easier to know from which dimension the challenge represents, the number is written with the same color of the respective subtitle.

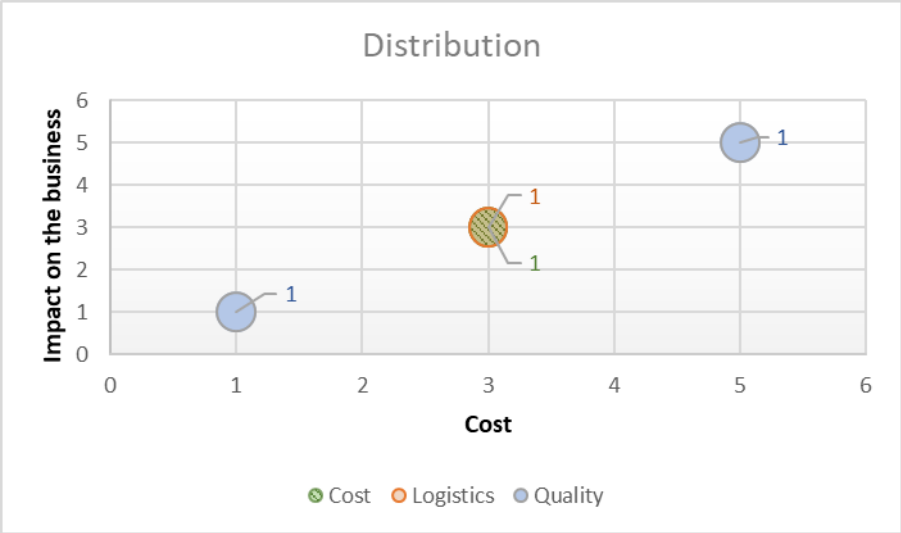

Figure 04: Main challenges raised by distributors
Source: Elaborated by the author

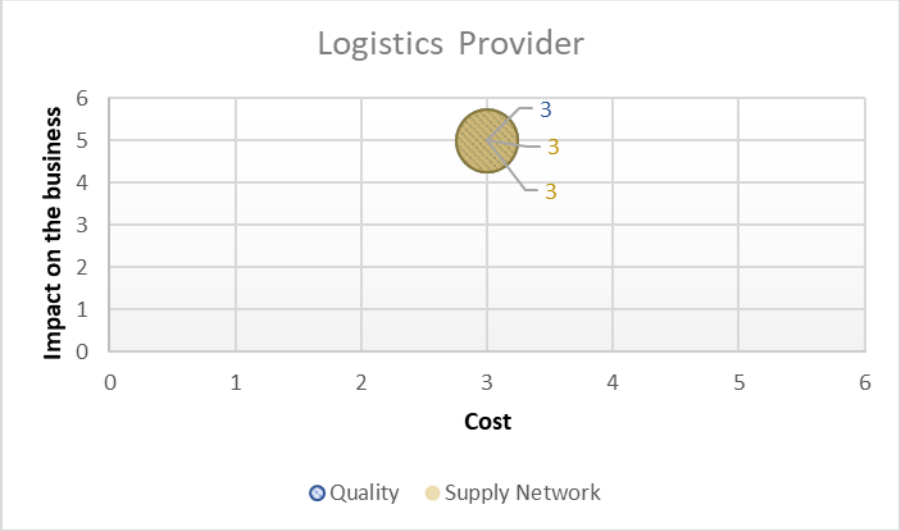

Figure 05: Main challenges raised logistics providers
Source: Elaborated by the author

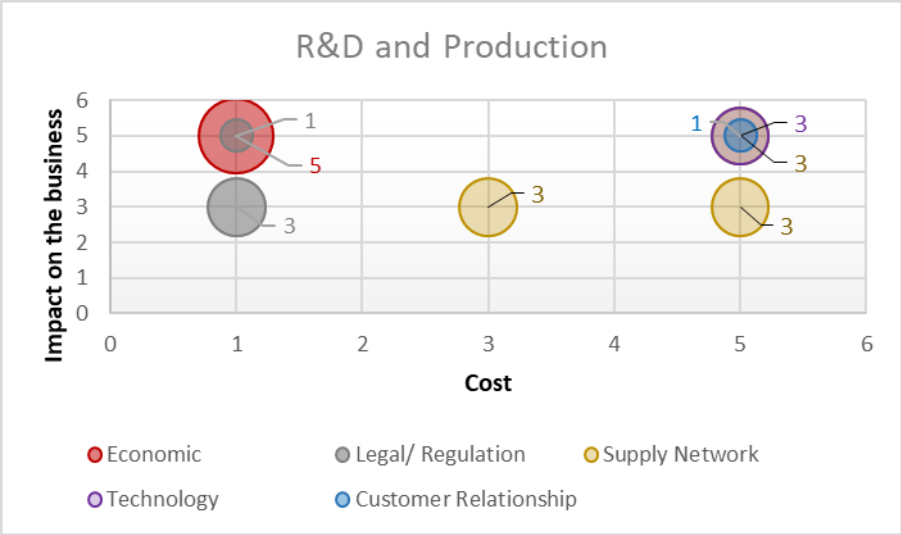

Figure 06: Main challenges raised by R&D and production
Source: Elaborated by the author

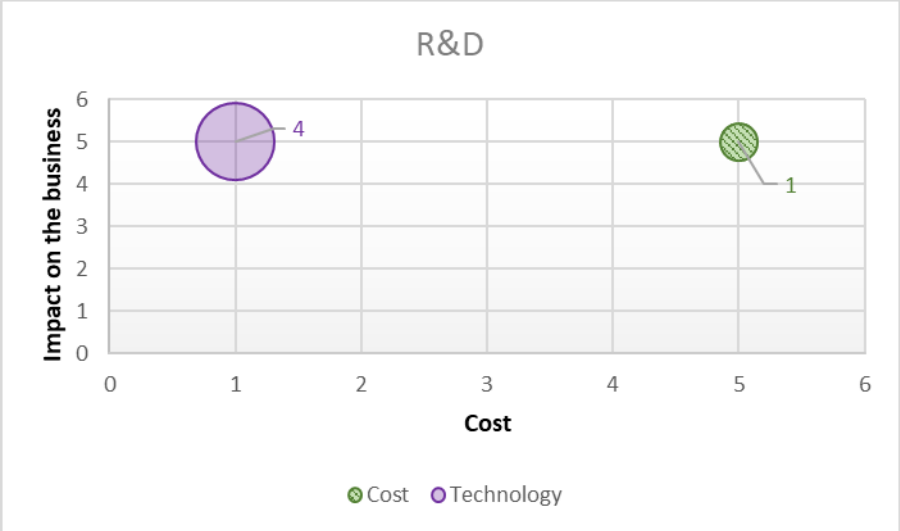

Figure 07: Main challenges raised by R&D
Source: Elaborated by the author

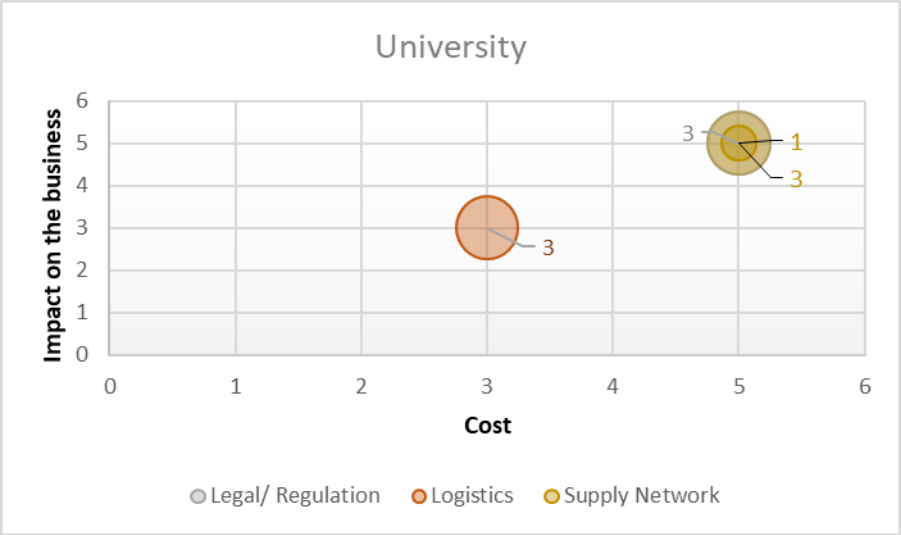

Figure 08: Main challenges raised by University
Source: Elaborated by the author

Analyzing the data gathered, we can see that distributors were one of the few participants that showed a bigger concern about cost. This fact can show that they are the stage of the supply chain that is the most worried about the profit margins. In the biopharmaceutical sector, it may have more direct competition in this stage than in manufacturing or R&D, for example. Cost was also important for R&D, due the huge investments of money and time necessary to develop new products.

As it was mentioned in one of the interviews, quality is imperative in biopharmaceutical sector. So, challenges related to it were mentioned by different players, usually with high rate of impact on the business. It is also important to mention that even in challenges classified in the "supply network" dimension, in some of them there were also a relation to quality, for example the availability of specialized suppliers (that is a challenge related to the supply network, that shows a worry about the quality of the service provided). Logistics providers also realize this importance, seeing quality with high impact on their business, recognizing it is a qualifying factor, what means that it is imperative to be on this market.

Supply network was also a general concern, confirming the statement that the ecosystem of biopharmaceuticals is still under development in Brazil. Raw materials and machinery still need to be imported and specialized 3PLs (for warehousing and

transportation) is critical for this market. Those factors also result on the high cost of this ecosystem (what can also be seen in the graphs).

Most manufacturers have their own R&D and must hire logistics services providers, so they have a broad perspective of the sector and, of course, are those whose products are used by the final consumer, so customer relationship is also a critical point for them. Producers must be alert to everything - regulation, advance of new technologies, demand, suppliers -, and the challenges listed by them show us that they have important challenges in different dimensions analyzed. It is still different when we are talking about government companies and private companies. Those managed by Brazilian government must follow specific regulations (that will be more explored in a specific topic), so their processes are less flexible, for example, purchasing materials, hiring services and people, advertising, everything is slower and have stricter norms.

The topics brought by those in the university were very interesting. Despite all of them have a technical background (as a researcher), most had experience as manager, so the perspectives were not only focused on technology and cost (as happened with those on R&D), but they also could see critical challenges on logistics and on the supply network. Besides, they also feel how the gaps on the biopharmaceutical ecosystem can affect all participants, for example the lack of national raw material supplier and how the lack of a more specific regulation can make the process of approval of a biopharmaceutical (new, biobetter or biosimilar) take much longer time in Brazil if compared to Europe, for example, and how it can affect the development of this sector in this country.

So, the results presented in this topic aimed to show that different stages of the supply chain have a convergent perspective about what dimensions impact the sector as a whole but depending on the business of each participant of the supply chain, the importance of each challenge may be different. Besides, it also shows that quality, specialized services and the development/ integration of the supply network are crucial at biopharmaceutical sector.

4.1.3. 3PL importance

A very recurrent word about the cold chain during the interviews was “quality”. Due the sensitivity of the product, the impact on patients’ health and its price, the chain can’t fail

in any point or the losses will be huge. Hence, logistics suppliers become key players in this supply chain, as pointed out by Feifei et al. (2013).

All the interviewees said that their companies (producers and distributors) hire logistics service providers. The most common is outsource transportation service, but a few players in this sector also hire a company to manage their DC, while others prefer to do this activity in order to keep a better control on these centers, for being strategic. The main reason to outsource transportation was the expertise of the third party suppliers (this is a very specialized service), cost reduction (the volume of each producer or distributor is not so high, so 3PLs can scale up and make it cheaper), besides, the supplier takes the responsibility for the quality assurance of this stage of the supply chain, spreading risks. This perception is aligned with the literature, in which we could see cost reduction , service improvements and focus on core competencies as the main reason to outsource a logistics service (Maloni & Carter, 2006).

When questioned about risk of 3PLs, quality was an important issue to worry. For being expensive services, prioritize cost over quality can be a trap for the hiring company due to the losses that a failure in these services can generate. Losing the full control over the process also is a worry for some interviewees. For example, on one hand it is good that 3PLs consolidate the demand from different companies and have gains of scales; on the other hand, the hiring company loses part of the control about timing and itinerary. Of course, one of the risks is creating dependence of this partner, but it is not necessarily a big trouble. An interesting strategy observed on the market is having two logistics partners. The number of suppliers is a parameter to assess the supply risk of a company (Kraljic, 1983), so having just one partner raises risk, for depending on a single supplier. However, keeping a small number of partners (two or three, for instance) allows not only to choose good service providers, but also to keep a close partnership, building a trust relationship with them, hence even improving the service provided, correcting imperfections on the processes and overcoming unexpected situations. This strategy is aligned with Feifei et al. (2013) findings, which state that close relationship with contractors is a fundamental aspect in biopharmaceutical sector. However, this strategy of having few suppliers can be not possible for all participants of the supply chain because, for example, some distributors need capillarity to cover as much part of Brazilian territory (that is very big) as possible, so looking for regional suppliers may be necessary, what doesn’t invalidate the importance of a close and trustworthy relationship with them.

4.2 PERSPECTIVES OF THE SECTOR

4.2.1. Brazilian regulation perception

Overall perspective about regulation in Brazil was very similar. ANVISA's norms are aligned with EMA's legislation and WHO's guidelines that are considered world's benchmark. The norms are very strict (in a good sense), but every process that depends on the regulation agency is very slow, and it is very bad for the development of the sector in the country. In some cases, the approval for a new medicine can last years, what creates a very unattractive environment for a company to invest in production in this country. One of the interviewees mentioned that not only the political instability of the last years, but also currency variation and even changes in the government incentives also bring uncertainty for companies that are planning to invest in Brazil.

When we are talking about the regulation in the supply chain as a whole, ANVISA is also seen as an effective agency in most part of the SC, but having some difficult in the inspection of the last distributors in some cases, especially the smallest, what can harm all the work made until that point. However, one of the interviewees pointed out that the norm RDC 304/ 2019, published by ANVISA in September 2019, stablishing good practices for distribution, storage and transportation of medicines, can be very helpful for the regulation agency make this supervision. This norm focuses on quality management requests that companies must follow.

The attempt of Brazilian government to develop the biopharmaceutical sector through the PDPs in general has been seen as an important incentive to develop technology in this country. According to an interviewee from the public sector, the planning of the program is to internalize the development knowledge step by step, first doing the final production stages, to have time to train people and build proper plants, and later be able to produce the API (the most complex stage). However, the PDPs' program by itself is not enough to develop this sector. An interviewee highlighted that there are other parts of Brazilian ecosystem that need to be developed, like machinery and biological raw material suppliers.

Due this uncertain environment, with an ecosystem not fully developed, Brazil still struggles to stop being a good "copier" of pharmaceutical processes (like it happens with the

generics) to become a developer of top technology, always depending on this kind of government influence, like PDPs, to become an attractive place for multinational companies, despite of its market potential.

4.2.2. Other strategic issues

During this exploratory study, other strategic issues (different from those previously approached) for this supply chain players could be gathered during the interviews. The most relevant of them were chosen to be discussed at this topic.

Aiming to understand the dynamic of the sector and the most important issues for the players, it was questioned during the interviews what are the key issues on the decision to go to a certain market and what is considered to implement an operation in a specific country or region (in the case of expansion in Brazilian territory).

The current structure of most producers is centralizing it in a few places, specially Europe and USA, for being close from research centers and raw material suppliers (some of them are also biological products and need the same storage conditions of the medicines) and for those places be where the plants are already installed, so they already have a well-developed supply chain (with good multimodal logistics structure and specialized suppliers) to distribute the products and expanding the existing network allows them to achieve economies of scale and improve their efficiency.

Those areas are also where the biggest markets are, so being close from the final consumer reduce risks and costs, what are also impacted by their political-economic stability. Specialized workforce was also mentioned, because this sector requires a totally different training from synthetic medicines, being a valuable resource that is not so easy to find.

This perspective is consistent with Brajcich et al. (2016), who studied US pharmaceutical sector, but they highlighted the complexity of transferring this kind of technology to other countries and that government incentives is also a factor for manufacturers implement their operations in the US. In our research it could be seeing tax incentives were key decision point for distributors to decide in which state implement a distribution center. Brazilian taxation is complex, and some state taxes can be high enough to, when considered the high value of biological medicines, be worthy to implement an operation on a place different from the sweet spot of the logistics perspective.

4.2.3. Future of the sector

The analysis of the future of biological drugs was focused on three main perspectives: expansion, production and new ways to distribute those medicines. As it was expected, when we were talking about the future of the sector, different points of view emerged, so here we will try to consolidate them and bring a perspective aligned with all the information gathered on the study.

As it was said before, biopharmaceutical sector has grown in developed countries, due the expansion of biosimilars and investments to develop new biological medicines (Harrington, 2018; Otto, Alberto, & Schrader, 2014; ResearchAndMarkets, 2018). However, in the perception of most interviewees, in Brazil we still can't see this expansion of biosimilar products as a reality. It is expected to happen in the next few years. PDPs' program is trying to accelerate it, encouraging national production, aiming to reduce government costs with those medicines, allowing a bigger part of Brazilian population to have access to those treatments. For example, Biomanguinhos (a government laboratory) is investing in new plants to achieve PDPs' program goal of a national production, absorbing this new technology.

One interviewee brought the information that some countries like Brazil, China, India, Mexico and Japan, are investing to develop the biopharmaceutical sector internally, what was aligned with BioPlan Associates (2018) research, that gathered the main countries where 222 companies had facilities. It was also brought the perspective that in the coming future, we may see just a small decentralization up to a point that make sense, considering being close from markets, like Asia and South America, that are big enough to allow economies of scale and logistics cost reduction (due smaller distance and risks for transportation). So, we can infer that regional poles may be emerging, especially pulled by the expansion of biosimilars.

Rossetti et al. (2011) saw as a trend in the pharmaceutical supply chain its fragmentation in three major product types: OTC and generics; brand name drugs and therapeutics; and cold-chain. It is a similar point of view of one of our interviewees, to what he called specialization. He believes that companies tend to focus their operations in biologicals or synthetic medicines. That kind of strategy probably would generate spinoffs, creating different brands under the same holding.

An interesting point raised in this study is about the need of economies of scale in the biopharmaceutical sector. It is true that biological drugs demand complex structure in terms of technology (Gurău, 2004), production and distribution (Otto, Alberto, & Schrader, 2014; Rodrigues et al., 2018) and scale and continuous production are important factors to reduce costs. However, the emerging of single-use technologies (SUT) can bring the flexibility and cost reduction that allows small manufacturers to be competitive. Lopes (2015) adds reduced capital investment, increased speed (fast construction) and safety to the list of features brought by this new technology that improve the producer competitiveness. So, this technology also may contribute to the capability of emerging countries develop their own production, since scale may not be so crucial for competition in the future.

As it was said before, biobetters can bring more stability for the structure of the reference biological drugs, making possible to administrate it in different ways, such as oral, dermatological and inhaled. That not only brings more comfort to patients but may generate a big impact on the supply chain. Most interviewees agree that the way that biological medicines will be distributed tends to change with the advance of those researches. In cases that patients are able to administrate the medicines by themselves, the trend is that they take those medicines at home, instead of going to hospitals and medical centers every time they need to administrate it. That brings two consequences: 1) new distribution channels, like direct shipping, may expand; and 2) patients must be trained on how to store those medicines, otherwise it may harm drugs' efficacy, both also were part of the research of Rossetti et al. (2011). That brings another challenge: how to control the quality of biological medicines after they are held by patients? Some companies already have specific phone number for this kind of advisory, but actual control is more difficult. This kind of training and orientation for patients is a trend that takes biopharmaceutical producers and distributors to move a little bit more to the servitization process.

The possibility of direct shipment may bring new possibilities in the market. One interviewee talked about the raising of companies specialized in this kind of delivery service, and it is very similar to the business of the company where another person interviewed works: a startup that administrates vaccines wherever the patient is. As it was said before, despite not being the focus of the study, vaccines are also a kind of biopharmaceutical, hence demanding the same kind of temperature control, what makes it a good source for comparison when we are talking about logistics.

4.3 Contributions to the literature

As it was said before, there is a very limited number of academical studies around the biological medicines supply chain. Table 06 complements the information brought in table 02 (presented in the literature review) with the findings of this research, so all the information gathered can be easily compared.

Dimension	Authors	Academic Literature	Non-academic Sources	Research
Cost	Academic: Feifei, Cuiqin, Feifei (2013) Non-academic: IAPO (2013); Otto, Alberto & Schrader (2014)	• High cost of R&D	• High cost of R&D	• High costs of R&D, storage and transportation
Customer Relationship	Academic: Rossetti, Handfield, & Dooley (2011) Non-academic: Handfield (2012)	• Direct sales • Servitization	• New channels to deliver to the final consumer • Physicians playing a more important role	• New channels to deliver to the final consumer • Servitization
Logistics	Academic: Rossetti, Handfield, & Dooley (2011); David (2018) Non-academic: Shanley (2018); Harrington (2018); Handfield (2012); IAPO (2013); Transparency Market Research (2017); Singh (2016)	• Temperature • Humidity • Short Shelf-life	• Temperature • No specific legislation for shipping • Leaks and contamination • Shocks	• Temperature • Humidity/ moisture • Short Shelf-life
Supply Network	Academic: Feifei, Cuiqin, Feifei (2013); MacCarthy, Blome, Olhager, Srai, Zhao (2016); Brajcich, Friesner & Schibik (2016); Rodrigues, Martins, Wanke, & Siegler (2018) Non-academic: Shanley (2018); Harrington (2018); Transparency Market Research (2017)	• New Supply Chain • Centralization in home countries • Qualification of 3PL	• Qualification of 3PL	• Different Supply Chain from the PSC • End-to-end control (specially temperature) • 3PL management • Ecosystem not so developed (Brazil) • PDPs program is an important incentive from Brazilian government, but alone it is not enough to develop the sector in Brazil • In general, centralized production. Possibility to a small decentralization to a few countries, aiming to be closer to some markets • Possibility of specialization of producers. A brand for biologicals and another for

				synthetic medicines
Quality				• Qualified workforce • Quality as a main driver • More investments in quality control, like devices to control the temperature
Political				• Political stability
Economic	Non-academic: Ventola (2013); Handfield (2012) IQVIA (2018); Aitken & Kleinrock (2018); ResearchAndMarkets (2018); Harrington (2018); IAPO (2013); Otto, Alberto & Schrader (2014)		• Patents expiring and price reduction • Growing market and investments	• Taxation • Economic stability • Higher competitiveness, price reduction and higher demand is a reality in Europe and USA. However, it is still an expectation in Brazil
Technology	Academic: Feifei, Cuiqin, Feifei (2013); Lopes (2015) Non-academic: IAPO (2013); Otto, Alberto & Schrader (2014); Singh (2016)	• Long time to develop • Single-use technologies (SUT) can change the level of advantages of scale in biological medicines sector	• Long time to develop • New and more specific raw materials and equipment	• Single-use technologies (SUT) can change the level of advantages of scale in biological medicines sector • Biobetters being developed to be more stable, hence making possible new ways of administration
Legal/ Regulation	Non-academic: EMA (2017) - Biosimilars in the EU Information guide for healthcare professionals; Harrington (2018); Otto, Alberto & Schrader (2014); IAPO (2013) - International Alliance of Patients' Organizations; WHO; Anvisa (2017)		• Strict regulation • There is a guidance of WHO, but regulations definitions are responsibility of each country government • Brazilian guide for storage and transportation good practices	• Long time for approvals (Brazil) • Strict regulation • EMA and WHO are the most advanced • Brazilian norms are good, but the regulatory agency is too slow on its processes • Regulation in the sector (in Brazil) is good, but could be better on the distribution stage of the SC. RDC 304/2019 may help to improve this gap

Table 06: Academic literature x Non-academic sources x Author's contribution
Source: Elaborated by the author

As the table 06 summarizes, in this research we could put together the information found in academia and in the market, as well as bring new contribution for the knowledge about the biopharmaceutical supply chain. The different sources bring temperature control as the main challenge for logistics in this supply chain, we still highlight the importance of the

end-to-end control in this process and that, in Brazil, specialists say that the last stage of distribution is the most critical one, where flaws may happen.

For developing countries, this research still brings some perspectives about what is important to develop the biopharmaceutical sector. The trend is that most part of R&D and production of the new biological drugs stay in Europe and USA, but it is possible to have a small decentralization to a few countries to be closer from big markets due to logistics cost. So, good regulation (strict and agile), political and economic stability, as well as tax incentives have shown to be factors that impact on the investment decision in this sector. Availability of qualified workforce and specialized 3PLs providers are factors necessary to install a biopharmaceutical industry. The entire ecosystem must be ready.

Despite not being present in many articles, academics, non-academic and the interviewees agree that the way that biological drugs will arrive to final consumers is changing, so companies must adapt. Researchers are developing new (easier) ways to administrate those medicines, so patients don't have to go to hospitals to take it. So, new channels to deliver biopharmaceuticals may raise and a servitization process to, for example, orient patients about how to proper store those medicines will also be necessary. Production also may have a few changes that can generate opportunities. The use of single-use technologies can give the necessary flexibility, so economies of scale may not be a necessary condition anymore, and medium-size production plants can become economically viable.

As it was mentioned before, biosimilars are already showing an expansion in developed countries, but it is still an expectation in Brazil. So, observing all the factors brought in this study is important to understand critical points that need to be improved, in order to create a favorable environment to the development of biopharmaceutical sector and the return on the investments made by Brazilian government with the PDPs be positive, according to the expected.

5. CONCLUSION

Most part of the researches about biological medicines focus on technical issues and just a few approach businesses issues. This research aimed to fulfill part of this gap, studying the biopharmaceutical supply chain and the critical factors for Brazil to develop this sector, especially due the fact of the expiration of the patents of important biological medicines and,

consequently, a growth in the number of biosimilars, what can generate an expansion of the demand for those medicines.

The new biological medicines are a complex kind of drugs to be produced and can generate good results for treatments of diseases that chemical drugs couldn't show good efficacy, what makes those biopharmaceuticals very expensive products. In Brazilian reality, the main buyer is the government, what means that the advance of biosimilars can reduce the annual expenses and make those medicines accessible for more people. However, it is necessary to make those medicines arrive to patients and for that, a specialized supply chain is necessary due the storage condition that biopharmaceuticals must be kept. Understanding biopharmaceutical supply chain and the most important challenges that must be overcome in order to develop biopharmaceutical sector were the main motivators of this research. To look for the answers, an exploratory study was made, interviewing ten senior professionals with experience in the biopharmaceutical sector.

The results indicate that the main logistics challenge for the biopharmaceuticals is the temperature control. Humidity is also a worry, but smaller. Other factors will depend on each medicine. However, the big challenge raised in the research is the end-to-end temperature control through all the supply chain, that because any failure in any point of the supply chain put in risk all the work done until that point, resulting in losses of a very expensive product, or worse, because if the failure is not detected, it will harm the efficiency of the patient's treatment.

Another important finding of this research for many companies in this supply chain is the relation to the patients. Most of the biological medicines need to be administrated in clinics and hospitals, but researches have been done to produce more stable molecular structures, which can be administrated in easier ways (like oral), hence patients can use it at their own home. Due to these facts, new channels to deliver the biological drugs to patients will be created and this final consumer will have to be trained in how to proper store those medicines at home, so the efficacy is not harmed. Hence, companies will have to be able to attend those new demand, especially if, due to the expansion of biosimilars, more people have access to this kind of medicine.

Brazilian government has done efforts to develop the biopharmaceutical sector in this country. PDPs program aimed to develop the sector giving a guarantee of purchasing

determined medicine, while the private company should transfer the technology for a Brazilian company (invested by the government). However, this program alone is not enough to develop the whole sector; there must be adequate logistics structure, as well as skilled workforce and reliable suppliers. In other words, the ecosystem as a whole must be developed, and quality is mandatory in this sector. Taxation and political and economic stability are also important aspects that Brazilian government should improve for the development of the sector, because they are factors analyzed in the decision of a company's choice about where to implement an operation.

This research also aimed to bring the different perspectives of each participants of the supply chain and raise what are the critical challenges for each of them and classified them into a list of proposed dimensions (Political, Economic, Social, Technological, Environmental, Legal/ Regulatory, Cost, Customer Relationship, Logistics, Supply Network, Quality). As a general rule, we can say that quality is imperative through all the supply chain, due the sensibility of the product and the high value. Supply chain network was also a general concern, because it is important to have a good control end-to-end in the supply chain, because any failure can harm the work done by all the participants in the chain. However, it was found also some characteristics of companies from specific stages of the supply chain. For example, manufacturers have a broad perspective, because they must be worried about the raw material, 3PLs and they are also the brand of the medicine, so they also must be worried about the final consumer (patients) and the relationship with them. Third party logistics suppliers already understood that quality is mandatory in the biopharmaceutical sector, so they must keep it as a priority to be able to be the suppliers of big companies. Distributors are also in a complicated position, because keep cost low is important to be profitable, but, as it was mentioned before, quality is mandatory through all this supply chain and the must face the logistics challenges. Charts were plotted to allow the interpretation of the challenges of different stages of the biopharmaceutical supply chain.

The biopharmaceutical sector is very important because of the impact it can causes in the life of millions of people around the world. So, this was a preliminary study, that aimed to raise important factors to develop this sector and that were not found in the literature. Future studies can investigate deeply each one of the aspects raised at this research or even explore stages of the supply chain that were not the focus here, for example what is the Brazilian capacity to produce the biological raw material necessary to produce the medicines? Another suggestion is to use the challenges raised and ask interviewees to rate all of them in the

proposed parameters. In this study it was not possible to return to the interviewees to rate all of the challenges listed, so they analyzed just the ones each of them proposed. Besides, it has been a sector with dynamic environment in the past few years and now it is possible to develop biopharmaceuticals for a specific individual. So, what are the applications of those medicines? How big is this market? Is that viable now? Those questions can be addressed for this next generation of biologics.

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7. APPENDIX

Appendix 01

Table 07: Challenges rating
Source: Elaborated by the author

#	Changes/ Challenge	Impact on the business	Producer capacity to execute	Supplier capacity to execute	Cost
1					
2					
3					
4					
5					

Appendix 02
Interview script:

1. In what company do you work?
2. What is your job title? How long have you worked in this position? What is your background in the pharmaceutical industry?
3. What services does your company provide? (e.g. manufacturing, distribution, retail, patients support, etc.)
4. Is your company's (or customer) manufacturing centralized in one country or is it decentralized?
    a. Where are the plants? Why chose this place?
    b. How have worked the other companies in the sector?
        i. Centralized or decentralized?
        ii. Where?
5. What kind of special cares are necessary for the biological drugs and biosimilars in your portfolio?
6. What are the greatest challenges in storage and distribution of biological drugs and biosimilars?
7. Do biopharmaceuticals share any kind of resources with chemical drugs in your company?
8. How the expansion of biopharmaceuticals is affecting the pharmaceutical supply chain?
9. Do you have 3PLs for storage and distribution services? Why? What are the benefits and the risks?
10. What impacts do you see coming with the expiring of patents of biological medicines and a possible expansion of biosimilars?
11. What is your evaluation about regulation of storage and distribution of biopharmaceuticals in Brazil and in the world? Are they clear and precise?
12. What is your perspective about the future of biological medicines and biosimilars in Brazil and in the rest of the world? Specially about the following topics:
    a. Production
    b. Expansion
    c. Distribution channels and relationship with final customers
13. (draw the biological drugs supply chain with the interviewee)
14. What are the 3 main challenges or changes that you see for the expansion of biological drugs? Can you fulfill the table (Table 07)? The parameters are in table 05.