Production of biotechnological drugs in Brazil:
what we have and what is missing to *catch-up*?

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Summary

This project proposes a study on the possibility of Brazil's advancement in the health biotechnology sector, as this is understood as a new technological paradigm for the creation of new drugs, and a window of opportunity to break the external dependence of the national pharmaceutical industry and to bring benefits to the public health system. The methodology is composed of four lines of analysis: the first one consists in a revision of specialized literature to describe R & D characteristics and the investments made regarding complementary assets necessary for the production and marketing of biotechnological drugs, based on international experience; the second line focuses on the technological capabilities of official pharmaceutical laboratories and national private companies through primary data; the third one consists in the analysis of drug demand evolution, focusing on the evolution of government purchases and drug imports; the fourth and last line attempt to discuss the suitability of the industrial policy to face the challenges presented by the technological capabilities and to make local production of biotechnological drugs feasible. The State of Rio de Janeiro gets special attention in this research due to its intellectual capital, infra-structure, official pharmaceutical laboratories and joint initiatives of the public and private sectors for the development of biotechnology in the region.

Introduction

The Brazilian pharmaceutical industry went through an important restructuring after the economic opening in the beginning of the 1990's. To put it in a simply way, one can state that the production chain of drugs involves two phases: the production of drug substances and the production of pharmaceutical specialties. Gradually, the first one was phased-out in Brazil and replaced by imports. This was due to the pharmaceutical industry being composed mainly of large multinational companies which took advantage of lower production costs in other units abroad, of currency evaluation and of the reduction of commercial barriers to increase their operational margin in the Brazilian market. Besides the productive phases, R&D activities and marketing are extremely relevant for the industry's performance. The structure

of drugs supply in Brazil, as well as in most parts of the world, is of an oligopoly, in which competition between companies does not occur by price war, but by product differentiation. In general, R&D actions concerning pharmacologic substances have precedence in the central countries. However, as far as R&D initiatives concerning drugs are concerned, there has always been a need to find suitability between production and products to be distributed in Brazil. Thus, R&D activities are fundamental for the competitiveness of companies, but not always they are equally distributed among the countries, with a concentration in the developed countries (Bastos, 2005).

The invention process of new pharmacologic substances has been traditionally based on analytical chemistry, a technique utilized to isolate the therapeutic components present in the plants, as well as in the pharmaceutical science, responsible for the formulation and encapsulation of drugs. With the invention of sulphonamide and penicilin, a broad range of possibilities has opened for the development of new drugs, especially antibiotics (Radaelli, 2008). Since they result from chemical processes, these pharmacologic substances are now called pharmachemicals. However, the development of pharmacologic substances through these processes allowed only the production of small and simple molecules. With the scientific progress in molecular biology, it became possible to achieve production of larger and more complex molecules. Proteins, which are very important therapeutically, represent complex chains of molecules that can hardly be produced by traditional chemical synthesis. Before biotechnology, only a few more complex molecules were synthesized, as was the case of insulin, obtained from the grinding of the pancreas of pigs. Technology of recombining DNA and monoclonal antibodies sets the beginning of modern biotechnology. The production of pharmacologic substances starting from genetic engineering and cellular manipulation became a reality and opened new fronts of research and treatment of diseases. Thus, these substances produced by biotechnological techniques became known as biodrugs. In the pharmaceutical sector, the recent progress of nanotechnology brought about possibilities for microencapsulation and a new generation of pills of programmed release (Reis *et al.*, 2009).

Another important point to be observed is that up to the 1970's, *random screening* was the main form of R&D of new drugs. Pharmaceutical companies had large internal groups of researchers, who organized and tested randomly chemical components with a therapeutic potential for a number of diseases. However, little was known on the physiology of diseases and on the functioning of these drugs in the body. With biotechnology, these issues became more understood thanks to the progress of knowledge on the molecular structure of living

beings and to the creation of computer systems applied to the sciences of life. This permitted to leave from a random process towards a rational development process of new drugs, focusing on factors causing diseases and based on nanotechnology (Malerba & Orsenigo, 2002) .

The knowledge base for the invention of new drugs were substantially altered: from chemistry to biology and, even if there are still important meeting points between both sciences, one can consider that there has been a change in the technological paradigm. Such change means that the companies must acquire new competences to operate and innovate based on this new knowledge, and that these competences are not found in the area of the previous domain (Dosi, 1982).

From a theoretical perspective, one of the points discussed is that whenever changes in the technological paradigms take place, a window of opportunity is opened so that new companies may enter the market and compete in equal conditions with the companies already established, since all of them have the same knowledge base concerning the new technology. These windows represent a possibility for the companies to leap to a new paradigm without having to master the previous one (Perez, 1992). As far as technological revolutions are concerned, such as the one observed with the technologies of communication and information and biotechnology, the window of opportunity is also opened so that the nations may overcome their foreign dependence and enter as leaders in the new technological paradigm, as this is a possible path for economic development. However, this opening is temporary: as companies and nations migrate to the new technology, they acquire competitive advantages due to their pioneering condition and establish barriers for the entry of late competitors (Perez, 2010).

Even if this possibility is observed in the history of several industrial sectors, in the case of biotechnology some points must be considered. Even with the creation of new biotechnology companies, they have not resulted in a wave of creative destruction in the pharmaceutical industry. Since they were born small, usually as university and research institutes *spin-offs* and sponsored by *venture capital*, they lacked the complementary assets (Teece, 1986) to compete with pharmaceutical industry giants. Thus, the insertion of new biotechnological drugs in the market took place mainly through strategic alliances with the traditional pharmaceutical companies (Radaelli, 2008). Therefore, the capacity to explore new biotechnology opportunities, seems to be more deeply connected with the large and already

established pharmaceutical industry corporations than with the small emerging companies and biotechnology laboratories (Malerba & Orsenigo, 202; Fialho, 2005).

As a new technologic paradigm, biotechnology brings opportunities to the consolidation of the universal project of public health in Brazil, especially concerning the access to drugs, according to the Federal Constitution of 1988. If we think that the new drug components substances are resulting more and more from biotechnology, that the patents of traditional drugs are about to expire and that there are already several competing manufacturers of generic drugs, it is strategic to thing about the local production of technological drugs in Brazil.

If now the trend is that the treatment of diseases and their drugs will depend more and more on biotechnology, the local production could bring about at least two social benefits: first, the increase in efficiency of government budgets, since the final prices of drugs could be reduced: and, second, the broadening of the capacity to supply with the pharmaceutical assistance programs and clinical treatment of the *Sistema Único de Saúde (SUS)* – the Government Health System. Studies indicate that Brazil has progressed in this direction. The production of generic drugs in the country, for example, has reduced the average expenses in the purchase of drugs for the pharmaceutical assistance programs of hereditary coagulopathys and hypertension and diabetes, which has permitted to broaden the service capacity of SUS (Aurea *et al.*, 2011).

However, such benefits cannot be reached if certain challenges are not properly faced. In spite of the increasing number of manufacturers of generic drugs in Brazil, including national capital companies, the products involved (pharmachemicals) are mainly imported even by the national companies. A consequence of this is that the final price of drugs, including generic drugs, is always subject to currency exchange variations. The dismantling of the sector has also restricted the national capacity to launch new pharmacologic components based on chemical synthesis (previous paradigm). It is obvious that the fundamental role played by government pharmaceutical laboratories must be considered concerning the national health policies, that even having to face a number of difficulties, has added to the learning, copying and manufacturing of similar drugs in the chemical and biotechnological sectors (Oliveira, Martins & Quental, 2008; Oliveira, Labra & Bermudez, 2006).

However, one may consider that the absence of policies in the biotechnology industry sector in Brazil would have as a consequence a replication of the historical evolution observed

in the pharmaceutical industry based on chemical synthesis. Before 1930, Brazil and the United States presented similar conditions concerning the production of drugs from the extraction of plants with therapeutic properties. However, from 1930 to 1950, the United States were able to migrate to the new paradigm of chemical synthesis and to build a strong pharmaceutical industry, while Brazil became dependent on foreign technology (Fialho, 2005). This process may be repeated regarding biotechnology. If the large multinational companies already established in the market are capturing biotechnology innovations, whether due to the formation of strategic alliances, or due to the acquisition of biotechnological companies, these are the organizations which tend to control the market. The result would be the continuation of the present reality: R&D activities abroad and the import of new biodrugs manufactured in lower cost regions. As a consequence, there would be an expansion of foreign dependence for the public supply of drugs to the population, considering a possible increase in the participation of biotechnological drugs in the future.

Therefore, the development and strengthening both of R&D activities and the manufacture of biodrugs in the Brazilian productive chain requires a national policy to structure the sector. Studies point out that major difficulties concern the sector regulation, the lack of infra-structure, especially to support pre-clinical and clinical tests, the absence of funding for small biotechnology-based companies, since the traditional banking system (including BNDES) requires solid guarantees, and the only capital of these companies is intangible (knowledge), and also the dismantling of the national health innovation system. Our attention is drawn to the fact that Brazil presents a science and technology health infra-structure relatively advanced with specialized expertise, but the rates of innovation, both pharmaceutical and biotechnological are very low when compared with the world average (Gadelha, Quental & Fialho, 2003; Reis *et al.* 2009; Paranhos, 2010; Hasenclever *et al.*, 2011).

Therefore, in observing the recent evolution of the pharmaceutical industry and the public health system in Brazil, some questions that the present research project intends to answer are raised: is the country ready to take advantage of the opportunity of this change of technological paradigm to reduce its foreign dependence in supplying drugs for the population? The official pharmaceutical laboratories and the national private companies are in condition to migrate to the new technological paradigm? What investments are necessary for health biotechnology and what type of companies have been successful in the sector? What is the gap between the technological capabilities existing in Brazil and that necessary for the

production of biotechnological drugs? Is the present scientific and industrial policy sufficient and adequate to promote the reduction of this gap and make the local production of biotechnological drugs feasible?

Justification

Data obtained from the Ministry of Health (2009) demonstrate that even if the quantities of biotechnological drugs purchased are small as compared to the total of drugs purchased, about 2%, the value of these purchases is extremely significant: more than 40% of the total expenses. The increasing weight of biotechnological items in the public health sector leads to investigate on the possibilities of price reduction. One of the paths could be the broadening of supply and competition to promote the reduction of prices and the increase of efficiency of public expenditures in the health sector.

The pharmaceutical industry evolution in the recent period presents certain challenges to this task. In analyzing the coefficient of penetration of imports in the pharmacologic and pharmaceutical products, it is observed that there is an expressive growth in foreign dependence (See Chart 1). In 1996, the coefficient was of 18%, rising to 31% in 2010. This means that the value of imports on the apparent expenditures in Brazil (production less exports) has been increasing gradually. When analyzing only the pharmaceutical products (composed mainly of drugs for human use and pharmaceutical products), the coefficient increased from 12%, in 1996, to 26% in 2010. This situation suggests an increase in imports both in the pharmachemical substances and in the final drugs sector.

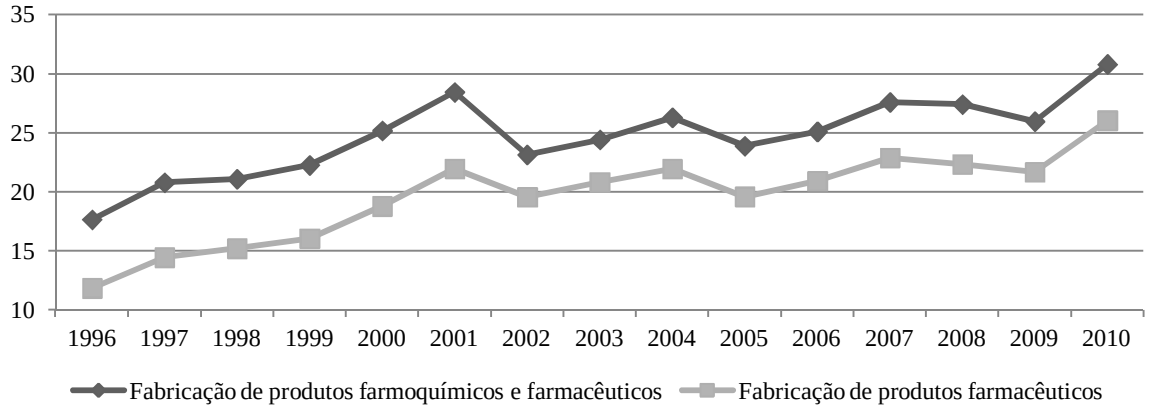

Chart 1 – Coefficient of penetration of imports of pharmachemical and pharmaceutical products, Brazil: 1996-2010 (%).

Source: Funcex (2011).

The data presented above reinforce the importance of the local productive development. It is certainly for a reason that the so-called "industrial health complex" involving, besides the pharmaceutical and biotechnological health sectors, medical and hospital equipment, entered the list of priority sectors of the federal government industrial policy since 2003. Officially launched in 2004, the Industrial, Technological and Foreign Trade Policy (PITCE) sets a new beginning of a more active industrial policy in Brazil after the economic opening of the 1990's. In 2008, the Productive Development Policy (PDP), was launched, as an improvement of the previous policy, which presented a revision of goals and the inclusion of new objectives. Presently, the Plan 'Brasil Maior' (PBM), launched in 2011 and devised to last until 2014, establishes some measures for the sector, aiming to nationalize production and to develop local technological competences. Among these, one can mention the creation of a margin of preference in government purchases of up to 25% for national products and services in bidding processes and the strengthening of the public production of drugs for the Government Health System – SUS (Ministry of Development, Industry and Foreign Trade, 2011). Since the launching of the PITCE up to this moment, eight years have passed. Even if structural changes need a longer period to become real, it is believed that this period is already sufficient for the first approach concerning the results and the suitability of the industrial policy instruments to achieve the goals intended.

The subject is especially relevant for Rio de Janeiro since the industrial production presented an absolute fall in this same period. The chart below shows the evolution of persons engaged and the gross value of industrial production in the pharmaceutical products sector, according to CNAE, which includes those for human use in the State. In 2007, the number of persons engaged in the sector represented a little over 60% of the percentage observed in 1996. The same is valid for VPBI, which shows that the level of production in 2007 was a little below the percentage of 60% of the volume registered in 2006.

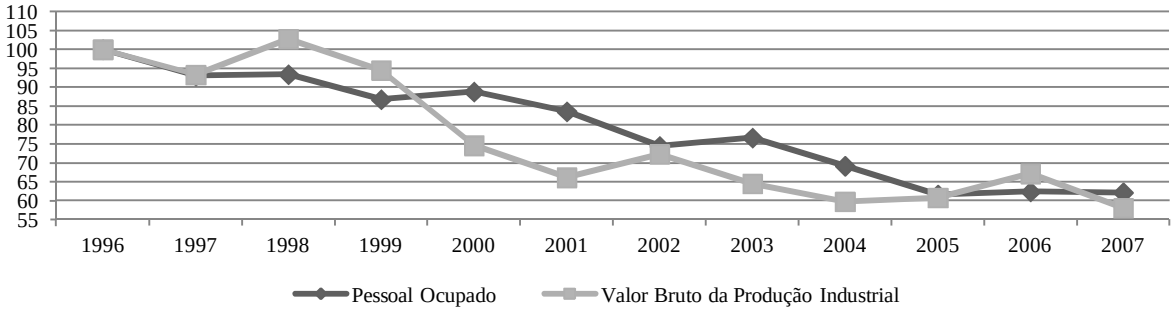

Chart 2 – Persons engaged and gross value of industrial production in the manufacture of pharmaceutical products in Rio de Janeiro (index number, base 1996=100): 1996-2007.

Sourse: Pesquisa Industrial Anual, IBGE (1996-2007).

If in terms of manufacture of pharmaceutical products, the scenario is unfavorable for Rio de Janeiro, on the other hand, in terms of R&D, the State presents a great potential. The official laboratories present in the region have contributed significantly to the health national policy. The Oswaldo Cruz Foundation (FioCruz), linked to the Ministry of Health, has two official laboratories. The Technology Institute of Immunologic Products (Biomanguinhos), responsible for the technological development and production of vaccines, reactives and biodrugs, and the Technology Institute of Biodrugs (Farmanguinhos), responsible for the technological development and the production of pharmachemical and natural therapeutic products. In the city of Rio de Janeiro there is also the Laboratory of Pharmaceutical Chemistry of the Air Force (LAQFA), the Laboratory of Chemistry and Pharmaceutics of the Army (LQFE) and the Pharmaceutical Laboratory of the Navy (LFM), which add to the production and distribution of drugs to low income population. Besides, Rio de Janeiro has a valuable human capital, with the presence of important federal and state universities. The Vital Brasil Institute (IVB), in Niterói, serves the entire country with research and production of serums and drugs for epidemiologic diseases.

The construction of the *Parque Tecnológico da Vida*, at the Vital Brasil Institute with units spread throughout the State, opens new perspectives of support to the biotechnology-based companies, for offering infra-structure, R&D support and integration between academic research, production units and centers for the training of personnel. Decree 43.315, approved on November 25, 2011, created the Executive Group of the Industrial Complex of the Sciences of Life of the State of Rio de Janeiro (Gevic), with the objective of creating and implementing state policies for the development of industry, and encompasses a number of institutional agents: Investe Rio, Codin, IVB, Faperj, Bio-Rio Foundation, among others. This demonstrates that the State is able to play a fundamental role to change the technological paradigm and the development of the health biotechnological sector in Brazil, in spite of the transfer of private production of drugs to other regions of the country.

In general, the transition of a technological paradigm to another, even if this means a window of opportunity for the new participants, certain barriers must be overcome. Besides scientific knowledge, a competence in the production and commercial techniques is necessary. The identification of these competences in the pharmaceutical industry and official pharmaceutical laboratories will permit to assess the possibility to change the paradigm and the local production of biotechnological drugs. However, this possibility is limited by the

capacity of establishing a minimum level of production, which ultimately depends on the real demand concerning such drugs in Brazil. Therefore, one must evaluate the potential for the growth of demand and at what point the chemical synthesis based drugs have lost space to new biotechnological drugs. In Brazil, the purchase of drugs by the government health program (SUS) represents an important source of demand for biotechnological drugs. Therefore, the possibility of local production of biotechnological drugs and the reduction of foreign dependence for the supply of drugs in Brazil depends both on technologic knowledge and productive capacity and the increase of demand.

Objectives

General Objective

To evaluate the technological capabilities of the official pharmaceutical laboratories and private companies and Brazil, emphasizing the State of Rio de Janeiro, for the local production of biotechnological drugs.

Specific Objectives

a) To specify the characteristics of R&D activities in biotechnology and to compare the national technological capabilities with those necessary for the development of biotechnological drugs.

b) To specify the investments made in complementary assets necessary for the production and commercialization of biotechnological drugs and to compare the national infra-structure with what is required for this activity.

c) To evaluate the trends concerning the purchases made by the SUS and the imports of biotechnological drugs to analyze whether the volume of transactions made is capable to guarantee a minimum local production scale to justify the R&D public and private investments, the production and commercialization of these products.

d) To discuss the suitability of the industrial policy in respect of the problematic issues found for the development of biotechnology in Brazil and in the State of Rio de Janeiro (to be identified in the research) and the results obtained since 2004.

Method

To specify the R&D characteristics and the investments made in complementary assets for the production of biotechnological drugs, this work proposes a comparative study between India and Brazil, starting from the revision of specialized literature. The choice of India is

justified since that country was an example of *catching-up* in the production of chemical-based drugs and is presently migrating to biotechnology, as pointed out in several studies (Ray, 2008;Chatuverdi, 2009; Arthreye, Kale & Ramani, 2009; Guennif and Ramani, 2012). The point of depart is the possibility that the similar economic conditions existing between Brazil and India make that country more suitable to be utilized as a parameter to compare the research now proposed than the developed countries now present in the sector, like the United States and Germany, for example. Therefore, the case of India will be representative of the technological capabilities and of the investments made in complementary assets necessary for the development of the biotechnology industry in emerging countries. In other words, the case of India will be utilized as an ideal type case. It is important to emphasize that the historical and institutional differences between Brazil and India will be respected as additional explanatory factors for the definition of what is necessary, in terms of R&D and complementary assets to migrate to the technological biotechnology paradigm.

In order to analyze the technological capabilities of private companies and official pharmaceutical laboratories in Brazil, a questionnaire will be applied to a representative sample. The universe of private companies will be defined according to a research made by Paranhos (2010), while the universe of public official laboratories will be obtained from the Association of Official Pharmaceutical Laboratories of Brazil (Alfob).

The objective is to identify what type of technological capabilities exists in the country, the routine or innovating type, according to a methodology proposed by Figueiredo (2004). Then, based on the data gathered, a diagnosis of technological capabilities in health biotechnology, and a comparison of these national capabilities with those necessary for the structuring of industry, defined from the Indian experience. The questionnaire will cover questions related to the dimensions of R&D, the production and commercialization of biodrugs. In this approach, the technological capabilities involve not only the technical-scientific knowledge, not necessarily available in the companies, but also the organizational capabilities for research, development, production and commercialization of drugs. Besides, most part of the technological capabilities accumulated is found in the universities (Paranhos, 2010). One of the characteristics of developing countries is that the innovation systems present weak links between universities, research centers and companies. It is expected that, through such data, it will be possible to demonstrate how far the technological and productive border is from the national industry.

In relation to the potential growth of demand for biotechnological drugs in Brazil, three analyses are proposed. The first one will cover the purchases of drugs made by the Ministry of Health. The data obtained from the Administration System of General Services (Siasg), that stores all the material purchased by the federal government, according with the methodology presented by Aurea *et al.* (2011). The second analysis will be made based on the importation data regarding biotechnological drugs. The source utilized will be the historical series of imports of products in accordance with the *Nomenclatura Comum do Mercosul* (NCM), of the Foreign Trade Secretariat (Secex) of the Ministry of Development, Industry and Trade (MDIC). These data will be compared with the internal production, which will be obtained from the Annual Industrial Product Research (PIA-P) of the Brazilian Institute of Geography and Statistics (IBGE), whose goods are classified in accordance with the List of Industrial Products and Services (Prodlist). However, the comparison between both statistics will be possible thanks to the correspondence charts between NCM and the Prodlist prepared by the National Classification Commission (Concla). The third analysis will be made based on the Satellite Health Account (CSS), prepared by the IBGE, which systematizes information on the economic activities related to the goods and services of health, allowing a separate analysis of the public health data and those of goods and services of the private sector.

Finally, the study proposes a revision of the tools and governmental measures devised for the development of the health biotechnology industry in Brazil contained in the three last federal government industrial policies, namely: PITCE, of 2004, PDP, of 2008, and the Plan 'Brasil Maior', of 2011. A preliminary evaluation was carried out by Hasenclever *et al;* (2010), but focused on the production and offer of generic antiretroviral drugs. Within the State sphere, the efforts of the government are analyzed to promote the sector, like the creation of the Geciv and other local actions. Based on this revision and on the analysis of data gathered from this work (field research and official statistical data), it is proposed to discuss the results obtained by such policies and their suitability to overcome the deficiencies possibly identified in the technological capabilities in Brazil.

Goals

Chart 1, below, specifies the phases of research, the goals of each phase and the results expected, in chronological order:

Phase	Goal	Result Expected
Research and analysis of specialized literature	To identify the characteristics of R&D in health biotechnology and the investments made in complementary assets made by the companies of sector	*Position paper* on the question of innovation in the biotechnology industry in the world, with emphasis on India.
Study of national technological capabilities in health biotechnology	To prepare a diagnosis of technological capabilities (routine or innovating) and to compare with the representative case (India)	*Paper* on the technological capabilities of national companies and pharmaceutical laboratories.
Study on the demand of biotechnological drugs in Brazil	To identify the potential growth of demand of biotechnological drugs based on the analysis of purchases made by the Ministry of Health and imports	*Paper* on the evolution of demand of biotechnological drugs in Brazil in the recent years.
Discussion on the industrial policy for health biotechnology in Brazil	To review the industrial policies and to discuss their limitations to take advantage of the opportunity offered by health biotechnology and nanotechnology.	*Fina lReport* containing the previous analyses and a discussion on the challenges to take advantage of the opportunity offered by biotechnology and nanotechnology in the Brazilian case

Chart 1 – Phases, goals and results expected from the research.

Expected Results

Based on the research, it is proposed that at least three articles be prepared, submitting them for publication on indexed periodicals and with Capes rating. As to the *position paper*, described in Chart I, one will seek to clarify the fundamental factors to structure the biotechnology industry applied to health in the world, focused on the apparent success of India. This first work will serve as a reference to compare the national biotechnology capabilities, which is the object of the second *paper* proposed.

With the application of the questionnaire it is expected to obtain a general and representative scenario of the technological capabilities of private companies and official pharmaceutical laboratories to replicate or even innovate in terms of biological drugs. This second work expects to contribute to a diagnosis both in respect of R&D and the production of biological drugs in Brazil.

The third article reflects a study on the trends of the demand for biotechnological drugs. The main focus will be about the purchases made by the Ministry of Health for the SUS system, but also data obtained from other sources will be explored. It is expected to demonstrate the potential growth of demand for these products, which would reinforce and also permit to analyze economic feasibility of the national production, since a minimum scale of production is required to justify the investments made in R&D and complementary assets in this complex industry.

The final report will incorporate, besides the previous works prepared, an approach on the industrial policies since 2004 focused on the biotechnology and nanotechnology sectors, treated here as a background scenario of the general analysis, but of extreme importance to answer the basic research question: will Brazil be able to *catch up* in health biotechnology? The research does not propose an evaluation method about the industrial policies and their results, it will only carry out a discussion based on the results obtained as opposed to the instruments and measures adopted by the federal government to stimulate the productive development of health biotechnology in Brazil.

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Chronogram

Chart 2, below, presents the chronogram of activities necessary to achieve goals previously established, throughout the 36 months. In order to simplify the presentation of chronogram, the activites were organized by semesters.

Activity	1st sem.	2nd sem.	3rd sem.	4th sem.	5th sem.	6thsem.
Research of specialized literature	X					
Analysis of specialized literature	X	X				
Writing of *position paper*		X	X			
Preparation of questionnaire			X			
Application of questionnaire			X	X		
Tabulation and analysis of primary data				X	X	
Writing of *paper* on the national technological capabilities					X	
Research and tabulation of secondary data	X	X				
Analysis of secondary data		X	X			
Writing of *paper* on the evolution of demand for biotechnological drugs in Brazil			X	X		
Revision of biotechnology and nanotechnology industrial policies since 2004	X	X	X	X		
Analysis and discussion of industrial policies					X	X
Preparation of *Final Report* with conclusions						X

Chart 2 – Chronogram of execution of research activities.