

## Vaccines: From Public Health to Big Business

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**Abstract** *The text presents and discusses the main aspects related to the current dynamics of the vaccine industry in the world and in Brazil, focusing on the demand created by the pandemic of COVID-19. At the global level, it briefly exposes the place currently occupied by Brazil within the scope of the BRICS and sets out and analyzes the options - identities and differences - of industrial policy in Brazil, China and India in the field of vaccines. Next, it analyzes the displacement of the vaccine industry, from a situation of exclusive production of immunizers to a majority control by the large pharmaceutical industry. Further on, it recovers recent fundamental aspects of the vaccine industry in Brazil, with an emphasis on Bio-manguinhos / Fiocruz and the Butantan Institute. Finally, it discusses the successes and limitations of the technology transfer mechanism used by the two institutions, as well as the relevance of their historically assumed commitment to public health policies.*

**Key words** *Vaccines, Industrial policy, Patents, BRICS*

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*Vaccines*  
 “With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction...”<sup>1</sup>

## Introduction

The available literature on global market dynamics and national policies in the field of vaccines gives us Brazilians a feeling of discomfort. In the first decade and a half of this century, relevant academic or non-academic publications praise the so-called “emerging markets” which we were part of. These markets would be new political, technological and productive players in many fields, including vaccines, which in central countries were going close to the strategies and practices of the global pharmaceutical industry and distanced themselves away from public health policies. The Brazilian perception is unpleasant because for the last five years we are no longer being seen by the world as an active component of these emerging markets, being increasingly detached by countries in this group, in particular India and China. The country’s ultra-liberal political reorientation that followed 2016, to which is now added the worsening of the decay of Brazilian industry in general, is the backdrop for our particular vaccine issue, exacerbated by the global earthquake following the COVID-19 pandemic.

### The dynamics of the global vaccine market

Perhaps the most relevant fact that has occurred in the international pharmaceutical landscape in recent decades has been the emergence and current hegemony of drugs developed by biological route, especially in the field of macromolecules, replacing the more than century-old route of chemical synthesis. For large pharmaceutical companies, this posed a problem and opened up an immense opportunity. The problem was the scarce technological and manufacturing competence of pharmaceutical companies on this new route: the opportunity was the discovery of that competence in the vaccine industry. The result was, from the 1980s, the beginning of an intense process of mergers and, mainly, acquisitions of vaccine factories by large pharmaceutical companies<sup>2</sup>. Between 2005 and 2012, the 13 largest purchases and mergers of this type generated around US\$ 220 billion and, in 2012, the pharmaceutical companies GSK, Sanofi, Pfizer, Merck and Novartis became the

largest global producers, being responsible for around 75% global vaccine market<sup>3</sup>. Currently, the ranking may be modified, but the outlook remains the same. The mergers and acquisitions process that we are reporting, among other consequences, caused Big Pharma’s ethical and commercial practices to migrate to the vaccine sector, which was once much more committed to public health. Added to this displacement there is the fact that the emergence of new epidemic threats, some of them affecting countries in the northern hemisphere, increased revenues from vaccine commercialization. Although the vaccine market is much smaller than the drug market (approximately 3% of the latter), vaccines become more and more Big Business and, from what is observed in this pandemic, this trend will grow.

Along with this process of oligopolization, from 1994 onwards another international arrangement entered the scene, this time in the regulatory field. The signing of the TRIPS agreements on the occasion of the creation of the World Trade Organization (WTO) has greatly increased the difficulty of free international circulation of technology-based knowledge, including in the vaccine sector<sup>4</sup>. In this field, countries relevant to our theme have behaved differently. TRIPS allowed a period of ten years for each country to adapt its industry to the new rules. China only joined the WTO in December 2001, India took full advantage of the adaptation period granted in TRIPS (joined in 2005) and Brazil enacted its Patent Law in 1996, just two years after the agreement was approved. Furthermore, Brazilian law includes provisions that go beyond the obligations of TRIPS. This difference in political decision also contributed to modulate the trajectory of the respective national vaccine sectors in the three countries, as will be seen below.

### Brazil, China and India

In order to explore the impact of these two processes, it is appropriate to compare the situation of the vaccine sector in Brazil with two large countries that until recently were considered, like Brazil, emerging economies and that, for this very reason, were brought together in that then novelty called BRICS: India and China. What is the situation in Brazil regarding the availability of vaccines, in due time, in emergencies and out of them? The emergence of vaccines against Sars-CoV-2 in a situation of acute need has put this issue at the center of attention. I think it is worth both an assessment of the performance

of our main public producing laboratories and a debate about Brazil's position regarding our country's technological and productive autonomy in this field.

In India, the vaccine industrial policy, as well as that regarding medicines, was mainly intended for export to central markets. The Indian health system in accordance with "Western" practices until recently reached only about 25% of the population and it was only in recent years that a reform of the health system was initiated with a view to achieving the so-called Universal Coverage, which, however, faces enormous difficulties<sup>5,6</sup>. Much of the health system in India operates around traditional practices known as AYUSH (Ayurveda, Unani, Siddha, Naturopathy, Homeopathy and Yoga), for which there is a specific ministry<sup>7</sup>. The option to conquer the foreign market has generated growing associations with multinational companies, which propitiated an important flow of knowledge of technological bases to India. The partnership between global and Indian companies, at the beginning, was based on a division of competences, with India responsible for producing active ingredients, the final formulation and partial marketing of the finished products while Big Pharma remained responsible for designing products and holding the respective intellectual property rights. The TRIPS impact on the Indian market was highly attenuated because of the country's industrial political orientation, highly protective in relation to the local industry. This option for the foreign market was complemented by an important connection, also external, with the supply of products to the World Health Organization (WHO). Currently, among the 247 presentations of vaccines prequalified by WHO, 73 are produced by Indian laboratories<sup>8</sup>. In 2012, Indian industrial capacity for vaccines comprised four state-owned and 17 private companies, one of which, the *Serum Institute of India*, is the world's largest vaccine producer, which place it still occupies today.

The Chinese pattern, in which the precariousness of the health system was similar to that of the Indian system, including with regard to the coexistence of traditional rationalities within the health system, about a decade ago, started an extensive reform, also aiming to achieve Universal Coverage<sup>9</sup>. Independent evaluations suggest that the reform has achieved many goals, but important challenges still remain<sup>10</sup>. The industrial policy option in the biopharmaceutical field was to stimulate the establishment of private companies

maintaining, however, a certain number of state-owned companies as a strategic component of its policy. Moreover, unlike India, the primary purpose of the policy was to serve the domestic market in conjunction with the reform of the health system without, however, losing sight of the international market<sup>11</sup>. In 2010, there were 46 industrial plants producing vaccines in China, six of which were state-owned, one public-private, four plants owned by multinational companies (GSK [2], Novartis and Sanofi) and 35 Chinese private plants. Chinese vaccine policy in conjunction with health policy has two components, in which a basket of vaccines is provided free of charge to the entire population, provided by state-owned laboratories, and another basket, with more complex vaccines, is provided by private laboratories<sup>12</sup>, being paid directly or through health insurance.

#### **The vaccine industry in Brazil since the redemocratization**

It is worth noting that in Brazil the connection between industrial policy and health policy predates the creation of SUS (Brazilian National Health System), but in the process of discussing it, the connection was an important point of discussion, whose most elaborated product was the construction of the National Self-Sufficiency Program of Immunobiologicals (PASNI), which appeared in 1985<sup>13</sup>. In it, the orientation of priorities in terms of vaccines was closely linked to the National Immunization Program of the Ministry of Health, created in 1973 and also strengthened after the inauguration of SUS. PASNI, conceived as a long-term program, had its action largely aborted by the characteristics of the process of redemocratization in Brazil, excluding and conciliatory; and, at the industrial level, adhering to the indiscriminate commercial opening proposals, aligned with the productive and financial globalization. In a similar way as part of SUS's democratizing and generous impetus were shrunk between 1985 and 1990, PASNI ceased to exist in practice since the Fernando Collor and Fernando Henrique governments. It is worth noting later important initiatives, such as the Innovation Project (Oswaldo Cruz Foundation, 2002) and the INOVACINAS Project (Ministry of Health, 2006), as well as the presence of the industrial health complex as a priority in the three versions of industrial policy developed in this century. I think, however, that despite the quality of the proposals, none of this was able to radi-

cally change the Brazilian status in the sector of immunobiological technology.

According to the Association of Official Pharmaceutical Laboratories of Brazil (ALFOB), there are four producers of human vaccines in Brazil, namely, Ataulpho de Paiva Foundation, Immunobiological Technology Institute (Bio-Manguinhos/Fiocruz), Butantan Institute and Ezequiel Dias Foundation (FUNED). These four laboratories produce 16 vaccines, almost entirely supplied to the National Immunization Program. From this product basket, Bio-Manguinhos contributes with eight, Butantan with six and FUNED and Ataulpho de Paiva with one vaccine each. Bio-Manguinhos also produces two types of erythropoietin, which is a biopharmaceutical<sup>14</sup>. The national BCG was result of technology developed locally (1927) and the yellow fever vaccine had the technology assigned by the Rockefeller Foundation (1937). The Diphtheria-Tetanus (DT), Diphtheria-Tetanus-Pertussis (DTP) and Hepatitis B vaccines were developed and produced at Butantan Institute. All other products were developed, improved and produced locally through technology transfer processes from foreign laboratories as a part of the purchase contracts for the products for exclusive use in the public health system. The sellers of the technologies were two French, two Cuban, six British, and two North American laboratories, as well as one from Switzerland<sup>15</sup>.

Brazil's current difficulties in obtaining SARS-CoV-2 vaccines have once again stimulated the discussion on the need, if not sovereignty, at least for national self-sufficiency in the field of vaccines. The debate has several aspects, with emphasis on the country's dependence on active ingredients (APIs). Recognizing the importance of the debate on self-sufficiency, as well as the emphasis on dependence on APIs, I believe it is essential to add to it the topic on relations between the Brazilian vaccine industry and public health policy. I believe that the configuration of our vaccine industrial park was built on these relationships and that they ended up generating their successes and, also, their remaining difficulties and challenges.

When comparing the options of China and India with the Brazilian in the vaccine field in terms of their relationship with health policy, we have three distinct strategies that, summarily and roughly, could be described as follows: the Indian, in which industrial policy was developed entirely off health policy, the Brazilian one, where industrial policy was governed by public health

policy and the Chinese one, which chose an intermediate path, valuing the connection with the health system while aiming at the foreign market, in particular with regard to API's.

#### **The transfer of technology as a self-sufficiency strategy and the connection with the public system as a health policy strategy**

The world has witnessed major advances in the field of technologies for vaccine production. Alongside traditional production technologies using attenuated and inactivated viruses, platform-based vaccines have been developed in recent decades, understood as vaccines that use a carrier as a nucleic acid, a viral vector or a liposome that, in some way, interact with an antigenic target of the pathogen in question<sup>16</sup>. In terms of the technologies involved, both Butantan and Bio-Manguinhos dominate the more traditional ones and the most important challenge in this respect is an entry into this new universe of platform-based vaccines. In this context of COVID-19, Butantan chose to develop a product whose traditional technology (inactivated virus) it mastered for a long time. Bio-Manguinhos chose another path, which was to bet on a platform-based product (viral vector), whose technology it will have to dominate from now on. In other words, the choice of Butantan favored the minimization of technological and productive risk, while Bio-Manguinhos favored the possibility of entering a more modern technological route, although with greater risks for the complete technological mastering.

In any case, as mentioned earlier, the two institutions, in most of their successes, have based their technological and productive activity in the technology transfer strategy and the main factor involved in this story is the close connection of the two with the public health system. In addition to the international prestige of both, the great demand of the National Immunization Program has made it attractive for technology holders to sell their products with technological compensation clauses, which has provided a good part of their training in this field. However, this important mechanism presents several and already known difficulties, in addition to an exhaustion that will be synergistic with the technological modernization in the vaccine field. Traditional problems are, among others, the possibility of transferring obsolete technologies whenever the contract does not provide for updates, the non-transfer of all

technology, leaving the buyer in permanent subordination to the seller and the limitation of markets and prices for locally produced products. The reason for the likely future narrowing of this path is that new platform-based technologies will in many cases not be for sale as compensation for the purchase of finished products. Not only for commercial reasons, but also for the technical difficulties involved in a possible transfer<sup>17</sup>. Furthermore, for vaccines, the technological and manufacturing path observed in the case of generic drugs will not be allowed, as it was already in the case of biological drugs. Therefore, these traditional and future obstacles put at the forefront of the historically preferred strategy of Bio-Manguinhos and Butantan will need to be relativized, or better said, complemented by other paths.

If the traditional paths of vaccine development strategies are narrowed, it follows that an approximation of the situation of self-sufficiency comes into the agenda and, for that, the entry into the field of modern vaccines linked to platforms should be followed with greater intensity. With that, a new order of challenges arises. Vaccinologists usually use the terms upstream and downstream to organize development and production over time, the first referring to the earliest stages of the process and the latter to the later ones. And, given the need to imagine products created and developed in an autochthonous way, it is necessary to delimit the extent to which Butantan and Bio-Manguinhos' responsibility goes in the most upstream stages of this process, that is, to define at which point a plant becomes responsible for conducting the process. A Brazilian success story helps to clarify this point.

Between 2002 and 2004, a series of decrees were signed to oblige blood banks to install molecular tests to identify contamination by HIV and Hepatitis C viruses in the bags. For the development of this test, a partnership was formed between the Institute of Molecular Biology of Paraná (IBMP – Fiocruz/PR), UFRJ and Bio-Manguinhos to develop the product in the country. After a few years of lab work, in 2009 a plant was opened at IBMP to produce the molecular biology components of the kit. The product was scaled and industrially produced at Bio-Manguinhos, being registered at the National Agency of Sanitary Surveillance (ANVISA) in 2010 and today it is widely used in the blood center network<sup>18</sup>. The project was conceived in the country, as well the lab work and the production of components under conditions of good practices. Despite being present since the beginning, Bio-Manguinhos led the

process only in the industrial production and scaling stage. What emerges from this success story is that the most upstream steps were not in charge of Bio-Manguinhos', but in lab research groups that worked with good practices from the beginning. In addition, it should be noted that there were imported components, but the center of the project, its design, was 100% autochthonous. This is just an example of an autochthonous development practice that could be followed by our two institutes, with the essential observation that there will always be early stages of development that will not depend on Butantan or Bio-Manguinhos, but on research groups that are located elsewhere in universities and research institutes.

The last paragraphs emphasized the need to adjust the strategies for technological and productive training. However, there is another dimension, mentioned above as a public health strategy, essential for both institutes and the health system. As noted earlier in this article, the relationships between the vaccine industries and public health systems when comparing Brazil, India and China have been quite different. With China in an intermediate position, India and Brazil opted for 100% distinct and opposite strategies. Here, the existence of the two producing institutes has always been closely linked to public health policies. Perhaps it was correct to say that in recent decades the reason for their existence has been the public health policy. In India, on the contrary, the weakness of this healthcare policy has led vaccine manufacturers to other markets, which are certainly more profitable, but in great debt to the health of Indian citizens. Some analyzes have commented on the Brazilian option, suggesting that it would have resulted in an organizational and management deficit and that this difference explains the greater success of the Indian experience in the development and production of vaccines. There will always be room for organizational and management improvements and they must be implemented. However, these microeconomic approaches in institutions should not impact this strategic relationship between the two institutes and public health policy. On the other hand, it is important to highlight other differences in political conduct between the two countries, for example in the treatment of the respective intellectual property policies mentioned above. Brazil's unconditional and early adherence to the TRIPS rules removed degrees of freedom in the management of an intellectual property policy that was more adequate to the activities of Butantan and Bio-Manguinhos.

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