

The role of public producers of medicines and strategic actions in the Covid-19 pandemic

O papel dos produtores públicos de medicamentos e ações estratégicas na pandemia da Covid-19

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DOI: 10.1590/0103-11042022132011

ABSTRACT In the Covid-19 pandemic, public pharmaceutical laboratories gained greater visibility because of their initiatives to fight the disease and maintain the various pharmaceutical assistance programs. The article aimed to analyze their daily activities during the pandemic, to understand their strategic character for the Unified Health System (SUS), highlighting the Butantan, Bio-Manguinhos, and Farmanguinhos Institutes, given their leading role in relation to vaccines and medicines, respectively. Through a multiple case study, with a qualitative-descriptive approach, it presented data that indicate the change in profile that has been demonstrated in recent decades. The most relevant actions in combating the pandemic were identified, with the cut-off date of July 2021. As a result, it brought current information about its activities and products, stage of the Partnerships for Productive Development, staff, weaknesses (internal and external), and current challenges. It is concluded that these State Institutions are important to guarantee universal access to the SUS and the development and production of essential medicines and health products, ranging from the most basic to those with greater complexity and added value. Thus, the need for an agenda of changes is identified, aiming at long-term sustainability and expanding the contribution to strengthen the Economic-Industrial Health Complex.

KEYWORDS Public production. Vaccines. Medicines. Covid-19. Health Economic-Industrial Complex.

RESUMO Na pandemia da Covid-19, os laboratórios farmacêuticos públicos adquiriram maior visibilidade em consequência de suas iniciativas para enfrentamento da doença e manutenção dos diversos programas da assistência farmacêutica. O artigo objetivou analisar as atividades cotidianas desses laboratórios durante a pandemia, a fim de compreender seu caráter estratégico para o Sistema Único de Saúde (SUS), destacando os Institutos Butantan, Bio-Manguinhos e Farmanguinhos, haja vista o protagonismo em relação a vacinas e medicamentos. Mediante estudo de caso múltiplo, com abordagem qualitativa-descritiva, apresentou dados que indicam a mudança de perfil que vêm demonstrando nas últimas décadas. Identificaram-se as ações de maior relevância no enfrentamento da pandemia, tendo, como data de corte, julho de 2021. Como resultados, trouxe informações atuais sobre suas atividades e produtos, estágio das Parcerias para Desenvolvimento Produtivo, quadro funcional, fragilidades (internas e externas) e desafios atuais. Conclui-se pela importância dessas instituições do Estado para a garantia do acesso universal do SUS e desenvolvimento e produção de medicamentos e produtos de saúde essenciais, envolvendo desde os mais básicos até os de maior complexidade e valor agregado. Destarte, identifica-se a necessidade de uma agenda de mudanças, visando sustentabilidade em longo prazo e ampliação da contribuição para fortalecimento do Complexo Econômico-Industrial da Saúde.

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PALAVRAS-CHAVE Produção pública. Vacinas. Medicamentos. Covid-19. Complexo Econômico-Industrial da Saúde.



Introduction

Access to medicines and health products is an important indicator of a population life quality¹. Despite its relevance to global health, the research, development and production are concentrated in the hands of a few leading companies guided on commercial interests, generally originated in developed countries². That fact can lead to exclusion from access to health care of significant portion of humanity, called neglected populations.

In Brazil, since the universal right to health was ensured by means of the 1988 Federal Constitution, access to services and medicines has been expanded, favoring improvements in health conditions and in the country's economy³ and promoting changes in the population epidemiological profile⁴. Major transformations have occurred since then, such as changes in the conception of the Unified Health System (SUS) principles, in the organization and in the relation of the federal government with states, municipalities and civil society, as well as in the pharmaceutical assistance programs⁵.

The changing society has influenced the implementation of public policies, aimed, among other things, at guaranteeing access to medicines and health products. In that context, the State, albeit the incipient way, has fostered the development of the productive and technological foundations of health and local innovation system. The support has been given through financing, protectionist measures and implementation of industrial and health policies, including: the National Medicine Policy (1998), the Industrial, Technological and Foreign Trade Policy (PITCE) (2003), the Productive Development Policy (2008), the Plan Brasil Maior (2011) and the National Strategy for Science, Technology and Innovation (ENCTI) (2012).

The Health Economic-Industrial Complex (Ceis), whose concept was developed in the

early 2000s to capture the inseparable relation between health and development, has the pharmaceutical industry as the greatest relative weight among its other segments – equipment, medical supplies, services². Its characteristic is the presence of a wide network of public laboratories dedicated to almost exclusively meeting SUS needs as for medicines, serums, vaccines, diagnostic kits and health products.

Known as Official Pharmaceutical Laboratories (LFO), their products and services qualify them as strategic providers of pharmaceutical assistance programs and as important actors in the development of national science and technology. The study aimed to analyze the trajectory, challenges and potential of these laboratories, as well as to identify their actions to face the Covid-19 pandemic, in particular those of Butantan Institute, the Institute of Technology in Immuno-biologicals (Bio-Manguinhos) and the Pharmaceutical Technology Institute (Farmanguinhos), contributing to the thinking on the role of these Public Institutions in guaranteeing universal access to the SUS and Ceis strengthening.

Material e methods

The article is divided into two sections, a general and a more specific one. The first refers to the network of public laboratories, bringing information about its history, profile, current reality of the Partnerships for Productive Development (PDP), its challenges and weaknesses. The second part concerns the actions carried out by Butantan, Bio-Manguinhos and Farmanguinhos Institutes regarding to prevention, detection and protection of national health as to vaccines and medicines against Covid-19. We opted for a multiple case study of the three official laboratories, which was carried out through qualitative research that combined the bibliographical and the documentary

review by means of a descriptive approach. The choice of the three prominent institutes is due to the leadership they exercise in their areas of expertise, namely immunobiologicals, vaccines and medicines, and the relevance of their actions in fighting the pandemic.

The bibliographic search was carried out in the Virtual Health Library (VHL) and Scientific Electronic Library Online (SciELO) databases, using keywords such as ‘official laboratory’ and ‘Ceis’ and ‘development’ or ‘access’, choosing publications from 2000 to date. A total of 145 publications were found, of which 21 were selected for their content relation to the researched institutes. Based on the content of selected publications and with the aim of deepening the investigation and obtaining timely and recent information, a document and secondary data research was carried out, having July 2021 as cutoff date.

The first was based on official reports and documents from the researched institutes; and the second was retrieved from the Ministry of Health (MS) electronic website, from Oswaldo Cruz Foundation (Fiocruz), the Association of Official Pharmaceutical Laboratories of Brazil (Alfob), the Brazilian Association of Fine Chemical, Biotechnology and Specialties Industries (Abifina) and from websites of the 20 official laboratories currently under operation. For the construction of *graph 1*, the Brazilian Health Regulatory Agency (Anvisa) database was consulted to confirm the valid number of medicines licensed. *Table 2* concerning PDP adopted the most recent spreadsheets made available by the Ministry of Health’ Secretariat of Science, Technology and Strategic Inputs (SCTIE), updated until September 2020.

Results e discussion

The Official Pharmaceutical Laboratories

A BRIEF RETROSPECTIVE

Over time, they began to integrate the pharmaceutical assistance policy, gradually moving from just considering the demand for primary care to including medicines of different natures, such as, for example, antiretrovirals. The list of these medicines also extended to drugs with greater added value and high technological content, giving rise to the strategic component of pharmaceutical care⁷.

The Butantan Institute (1899, São Paulo) and Fiocruz (1900, Rio de Janeiro) were created in the course of the bubonic plague epidemic aiming at the national production of serum and vaccine against the disease, given the difficulty of acquisition from the Pasteur Institute, France, where the serum was produced^{8,9}. At the beginning of the 20th century, were created the Marine Pharmaceutical Laboratory (LFM, 1906); the Ezequiel Dias Foundation (Funed, 1907); and the Instituto Vital Brazil SA (IVB, 1918). The LFO network expansion throughout the country coincided with the adoption of development-oriented policies due to the need to strengthen the national chemical-pharmaceutical industry. Within the period 1964-1974, eight LFO were created¹⁰.

Until the beginning of the 20th century, LFO activities were characterized by the production of topical medicines, vaccines and anti-venomous serums⁶. During the 1970s, the creation of the Medicine Center (Ceme)

led those laboratories to fulfill a large part of the demand for medicines coming from the country's public health system. In 1976, were created: the Farmanguinhos laboratory, later raised to the status of an institute, carrying out the mission of developing production technologies, adapting transferred technologies and developing chemotherapeutic and prophylactic products so to meet the needs of health programs and the requirements of the National Security⁸; and the Bio-Manguinhos, an institute dedicated to the promotion, development and production of immuno-biologicals addressed to public health⁹. Both institutes pertain to Fiocruz.

The approval of the Organic Health Law (Law No. 8080/90) creating SUS caused the need to expand the local supply following the embedded paradigm of integrality. In 1998, the National Medicine Policy (PNM) – Ordinance No. 3916 – induced laboratories to supply new types of medicines⁵.

The pharmaceutical care decentralization policy was more closed observed (Ordinance No. 2084/05) in 2005, ceasing the Ministry of Health to acquire, in a centralized way, many drugs used in primary care services, drugs for mass distribution policies. That allowed for municipalities and states to buy directly from any pharmaceutical company, generating a significant reduction in demand, which caused market loss and low utilization of installed capacity and technological expertise¹¹.

Therefore, the mission of official producers was expanded. Covering market breaches, they began to increasingly absorb medicines and products of interest to strategic public health programs, even of reduced demand¹¹, such as Sexually Transmitted Diseases (STD)/Aids and the National Immunization Program (PNI). Those medicines, due to monopolistic and oligopolistic practices of the pharmaceutical market, generally carry a high cost, restricting their acquisition by to SUS^{7,12}.

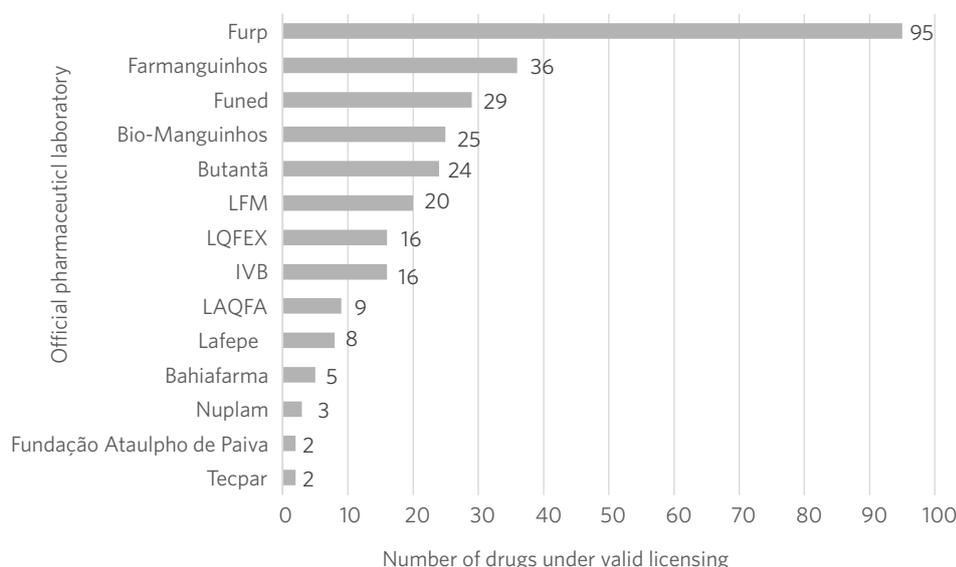
PROFILE AND MISSION

There are currently 20 LFOs forming the Brazilian Network of Public Production of Medicines (RBPPM), created in 2005 (Ordinance GM/MS No. 2.438) with the objective of integrating and improving the performance of a conjoint of public laboratories. The LFOs main mission is to produce drugs listed in the National List of Essential Medicines (NLEM-Rename) to meet SUS demand. Some stand out for their installed capacity, such as Farmanguinhos, Bio-Manguinhos and Butantan, being the latter two specialized in vaccines and immuno-biologicals.

Their sales are destined almost exclusively to the MS and to state and municipal health secretariats, with exception to Bio-Manguinhos, a Fiocruz division, which participates in international bids called by the Pan American Health Organization (Paho)⁴. They carry different characteristics, relations and sizes, being mostly concentrated in the Southeast Region (53%). Most are connected to state governments, four pertain to universities, and five, to federal institutions.

Not all manufacture their own production. Most work on two fronts: supply of drugs produced internally, being the holder of the registration or manufacturing location; or production by third parties, as is the case of PDPs during the technology transfer period⁷. According to data extracted from the Anvisa¹³ website, there were 290 medicines with valid licensing (*graph 1*), among which stands out the Foundation for Popular Medicine (Furp), responsible for 33% of the total, followed by Farmanguinhos and Funed. Of the 20 public laboratories, 14 (70%) produce drugs approved by Anvisa. Of these drugs, 86% are chemically synthesized and only 8% are products of biological origin. A valid license does not mean that the drug is actually being produced, but indicates that the LFO is authorized to produce if the drug is demanded¹⁴.

Graph 1. Medicines under valid licensing by LFO



Source: elaborated by the authors based on information extracted from the Anvisa⁶ website in May 2021

It should be noted that LFOs do not work for, and it would not be rational to work for, the entire Rename. The list, created in 1975, is revised every two years, and the last update released by the SUS in the 2020 edition counts 916 items¹⁵. Therefore, it is the government responsibility, through public policies, to prioritize the medicines to be produced by public producers¹⁶, avoiding competition with national and multinational private companies and creating conditions for the production of medicines of higher added value, which are strategic for SUS.

In addition to the producing activity, LFOs are intended to subsidize the formulation of public policies and to participate in the generation and dissemination of knowledge in health,

having as activities research and technological development.

PRODUCTS

LFOs offer to SUS a broad portfolio of products aimed at the needs of the population, including vaccines, serums, synthetic and biological medicines and health products (*table 1*), covering around 30% of the medicines¹⁷, 70% of the vaccines and 100% of the serums offered by SUS¹⁸. Their products include several therapeutic classes, such as: antibiotics, anxiolytics, antiparasitic, antiulcer agents, anticonvulsants, anthelmintics, antimalarials and antivirals. Some also produce herbal medicines and cosmetics⁴.

Table 1. List of LFOs per region and product types

Region	State	Institute	Types of products
Southeast	MG	Fundação Ezequiel Dias (Funed)	Medicines, serums and vaccine
	RJ	Instituto Vital Brazil (IVB)	Serums and medicines
	RJ	Instituto de Tecnologia em Imunobiológicos (Bio-Manguinhos)	Bacterial and viral vaccines, diagnostic kits and biopharmaceutical drugs
	RJ	Instituto de Tecnologia em Fármacos (Farmanguinhos)	Medicines
	RJ	Laboratório Químico Farmacêutico da Aeronáutica (LAQFA)	Medicines
	RJ	Laboratório Farmacêutico da Marinha (LFM)	Medicines
	RJ	Laboratório Químico Farmacêutico do Exército (LQFEX)	Medicines
	RJ	Fundação Atauilpho de Paiva (FAP)	Vaccine and immunobiologicals
	SP	Fundação para o Remédio Popular (Furp)	Medicines
	SP	Instituto Butantan	Serums and vaccines
Northeast	BA	Fundação Baiana de Pesquisa Científica e Desenvolvimento Tecnológico, Fornecimento e Distribuição de Medicamentos (Bahiafarma)	Immunobiologicals and diagnostic kit
	PB	Laboratório Industrial Farmacêutico do Estado da Paraíba (Lifesa)	Medicines
	PB	Instituto de Pesquisa em Fármacos e Medicamentos (Ipefarm)	Medicines and pharmaceutical input
	PB	Laboratório de Avaliação e Desenvolvimento de Biomateriais do Nordeste (Certbio)	Biomaterials development and evaluation
	PE	Laboratório Farmacêutico do Estado de Pernambuco S.A (Lafepe)	Medicines
	RN	Núcleo de Pesquisa em alimentos e Medicamentos (Nuclam)	Medicines
South	PR	Centro de Produção e Pesquisa de Imunobiológicos (CPPi)	Serums, supplies and antigens
	PR	Instituto de Tecnologia do Paraná (Tecpar)	Vaccine, supplies and medicines
Midwest	DF	Empresa Brasileira de Hemoderivados e Biotecnologia (Hemobrás)	Blood products
	GO	Indústria Química do Estado do Goiás (Iquego)	Medicine and glucometer

Source: elaborated by the authors from Alfob¹³ and laboratories websites.

Among their products, there are medicines and supplies aimed at the treatment of neglected diseases, which currently mainly affect developing countries. Those diseases are less considered for Research and Development (R&D) by Big Pharmas,

as they are related to poverty and do not generate financial returns¹⁰. At this point, it is worth to emphasize the strategic role of the mentioned institutes is to be emphasized, because, even minorly, they act directly or in partnerships, usually with

non-governmental or non-profit institutions, such as the Drugs for Neglected Diseases (DNDi) initiative, in the carrying on of research for the production of medicines and drugs, new or improved ones, for the treatment of those diseases. With emphasis for tuberculosis, those diseases are responsible for 11.4% of the global load, although only 1.3% of the 1,556 new drugs licensed between 1975 and 2004 were addressed specifically for them, causing together 500,000 to one million deaths annually¹⁹.

On the other hand, some LFOs, including Butantan, Bio-Manguinhos and Farmanguinhos, have been involved in the development and/or production of more complex products, such as biological medicines, appearing as Ceis instruments of economic and technological development. Industrial policy incentives have helped LFOs contribute to reduce the price of these drugs and their impact on the public budget. That new approach has already brought positive results for some LFOs, such as increased revenue and greater participation in the distribution of specialized and strategic medicines to SUS^{7,20,21}.

R&D AND EDUCATION

LFOs carry out a large part of their R&D activities in a shared operation, adopting strategic alliances with other pharmaceutical laboratories, universities and national and international research centers, and making their facilities, equipment, materials and human resources available. That effort to innovate can be seen in numbers. A survey carried out by Alfob in 2019⁶ involving its 18 associated Institutes found that LFOs invest, on average, 6% of their revenue in R&D, a minor percentage compared to the world pharmaceutical industry average of approximately 17% of total sales, but higher than the 4.8% average of the Brazilian pharmaceutical industry²². There were ten pre-clinical research projects under progress,

three clinical research projects, and 44 patent applications in the Brazilian National Institute of Industrial Property (INPI)⁶.

As for the teaching area, the study noted the role of some LFOs – e Funed, Nuplam, Farmanguinhos, Bio-Manguinhos, Butantan – in the training of professionals for the transfer of knowledge. Among those, Farmanguinhos stands out, which has a vice-directory of Education, Research and Innovation aimed at filling breaches of the National Health Innovation System (SNIS), especially with regard to the development of drugs and medicines, offering updating courses, and specialization, master and doctorate degrees²³.

Despite the initiatives, because their origins are not related to R&D but with pharmaceutical assistance and coverage of breaches of the national production of vaccines and essential medicines, it appears that LFOs still have minor participation in the SNIS when compared to universities and research institutions²⁴. It is necessary that those institutions progress in activities that involve innovation, making use, if necessary, of incremental trajectories of institutional innovation²⁰.

HUMAN RESOURCES

Regarding human resources, the comparison between two studies carried out in 2004²⁴ and 2019⁶ showed that LFOs have invested in hiring personnel and improving the training of employees. During that period, the number of employees increased by 40%, from approximately five thousand to 8,352 people, while the percentage of master and doctor degrees rose from 3.6% to 12.72%, evincing greater attention on science.

ACTIVE PHARMACEUTICAL INPUTS

As for Active Pharmaceutical Ingredients (API), a survey carried out by Abifina and Abiquifi on APIs manufactured in Brazil

by their members, it was possible to ascertain that of the 124 APIs identified, 15 (12%) are listed in the PDP²⁵. The numbers, although small, show the participation of LFOs in the State's effort to reduce dependence on inputs and to strengthen national pharmaco-chemistry.

PRICE ADJUSTMENT

The role of those laboratories in regulating prices in the national market is also to be noted. Raw materials overpricing and abuses in drug prices have evinced the State regulatory role as for the pharmaceutical industry¹⁰, and the LFOs are instruments of this policy. An example of this statement was the experience that took place in 2005: when the MS announced that they had technological competence to produce the antiretroviral drugs Efavirenz, Nelfinavir and Lopinavir, private laboratories reduced the prices of these drugs by approximately 50%⁴.

They also aim to save money in the acquisition of medicines and strategic products by SUS, especially those of high cost, previously purchased from private companies, many of them foreign ones. Doing so, they help the reduction of the deficit in the health trade, which raised from US\$3 billion to US\$ 12 billion in the last 20 years, a period of full construction of SUS²⁵, revealing the country's strong external dependence on health products and Ceis' great technological vulnerability.

STATUS AND PDP IMPACT

The PDPs, MS-funded agreements to transfer technology from a private company to a national LFO, have largely added to the change in the profile of official laboratories. Those

partnerships represent, among other factors, the country's effort to develop the public drug industry and reduce dependence on foreign inputs, since the PDP model involves, in addition to manufacturing the product by an LFO, the API production by a national pharmaco-chemistry, aiming at the Brazilian self-sufficiency in strategic inputs²⁰.

Despite all the political and management challenges faced to conclude those partnerships, it appears that, in general, they have provided for the modernization or creation of technological platforms and for the improvement in the professionals training at those institutes, making them able to add more and more to the national R&D, following SUS needs^{6,7,21}. They also favored the incorporation of biological medicines for some LFOs, as was the case of Bio-Manguinhos, which, by means of the PDP, is no longer a laboratory specialized solely in vaccines, but, rather, a producer of biological medicines employing mature technologies²⁷.

According to MS data issued September 2020²⁸, there are 91 PDP in force. Most of the drugs listed (42) are already licensed at Anvisa and distributed to SUS (phases III and IV). Below, it follows detailed information on the participating institutions, numbers, types of products, technological platform and percentage of PDP by phase (*table 2*), as well as the total number of partnerships, broken down by LFO and execution phase (*table 3*). It appears that LFOs carrying the largest number of PDP contracts – Bio-Manguinhos, Farmanguinhos, Butantan and Lafepe – hold together 50% of the total of contracts, indicating that, although the number of participating LFOs is large, most of the contracts is concentrated in a small number of laboratories.

Table 2. Summary of current PDPs, as per Sep 2020

Participating Institutions	18 Public institutions (14 LFO, 2 Universities, 2 Research Institutes) 32 private partners
Quantity	91 in force, being 85 drugs-vaccines-blood derivatives and 6 health products
Types de Products	53 medicines, 4 vaccines, 6 health products and 1 blood product
Technological platform	58% synthetic products and 30% biological products
Percentage per phase	Phase I 9% / Phase II 45% Phase III 32% / Phase IV 14%

Source: elaborated by the authors based on tables retrieved from the MS website, as for September 2020²⁷.

Table 3. PDP in force by LFO, Phase and Product Type, as per September 2020

Total of PDP in force per IP	Public Institution (IP)	Number of PDP per Phase		Type of product
		(I, II, III or IV)		
13	Farmanguinhos	4	II	Synthetic
		6	III	Synthetic
		3	IV	Synthetic
13	Bio-Manguinhos	1	I	Biotechnological
		6	II	
		4	III	Biotechnological
		1		Vaccine
10	Butantan	1	IV	Biotechnological
		7	II	Biotechnological
		3	III	Vaccine
10	Lafepe	1	I	Synthetic
		4	II	Synthetic
		1	III	Synthetic
		4	IV	Synthetic
6	LFM	2	I	Synthetic
		3	III	Synthetic
		1	IV	Synthetic
6	IVB	4	II	Synthetic
		2	IV	Synthetic
6	Tecpar	5	II	Biotechnological
		1	III	Biotechnological
5	Bahiafarma	1	I	Health product
		1		Synthetic
		1	III	Synthetic
		1		Biotechnological
		1	IV	Synthetic
4	Furp	2	II	Synthetic
		1	III	Synthetic
		1	III	Health product

Table 3. (cont.)

Total of PDP in force per IP	Public Institution (IP)	Number of PDP per Phase		Type of product
		(I, II, III or IV)		
4	Nuplam	3	II	Synthetic
		1	III	Synthetic
3	Funed	1	II	Biotechnological
		1	III	Synthetic
		1	IV	Synthetic
		1	I	Synthetic
3	LAQFA	2	II	Synthetic
		1	I	Synthetic
2	LQFEX	1	III	Synthetic
		1	I	Synthetic
2	UEPB	2	III	Health product
1	Hemobrás	1	III	Hemoderivado
1	ICC-Fiocruz/IBMP	1	II	Health product
1	Nuplam LAQFA	1	II	Synthetic
1	UFPE	1	II	Health product
91	Total	91		

Source: elaborated by the authors based on spreadsheets retrieved from SCTIE/MS, available in the MS website, as per 09/21/2020²⁵.

Despite the advances, threats are being faced for the continuity of PDPs. As factors external to the LFO, the following can be identified: the lack of stability in the State policies involving the agreements; the exchange rate instability present in recent years, which directly impacts on the prices; and, more recently, in 2019, the MS abeyance of partnerships with seven LFO²⁹, affecting the production of 19 medicines distributed by SUS.

WEAKNESSES AND CHALLENGES

Despite the strategic role LFOs play for SUS, they carry weaknesses that often lead to the facility underproduction and slow response to demands. Studies indicate concerns such as the lack of qualified personnel for more complex activities like technology transfer, demanding greater work on personnel qualification towards innovation strategies.

Other challenges are organizational rigidity, insufficient planning, political interference, obstacles imposed by the bureaucracy of the public procurement legislation (Laws No. 8.666/93 and 10.520/02), structure limitations, among others^{20,21}.

Also, difficulties such as investment cutback and budget reducing, caused by the stoppage of the spend increasing imposed by Constitutional Amendment No. 95 and by the current fiscal and financial crisis of the Brazilian State. So, changes in legislation and agreements, changes in government personnel, reduction of public demands, unfair competition with foreign suppliers and by lack of prospects for new public bids increased the vulnerability related to Covid-19 and universal access to healthcare. In addition, changes brought about by the 4th Technological Revolution, i.e., big data, data mining, internet of things etc., engendering accelerated technological and scientific development, bring

additional challenges to the institutes, forcing them to review their skills and their traditional data management systems so to sustain their competitiveness and sustainability^{7,19,30,31}.

Ceis' vulnerabilities, as the external dependence on inputs, intermediate products and exchange rate fluctuations, together with the setbacks brought by the pandemic, such as the protectionist barriers imposed by countries that produce inputs and medicines like India and China; the growing prices of imported products used in production and research due to the world demand increasing and the national currency devaluation; and international logistics difficulties as consequence of the rise in freight prices and the reduction in the number of routes, evince the difficult current scenario that impact LFOs responsiveness in dealing with the pandemic^{25,31}.

Advances in the pandemic - most relevant actions

During the pandemic, efforts to fight the disease while maintaining daily activities have been carried out by LFOs. As examples of actions developed by some of them, were retrieved from their websites: production and distribution of alcohol gel to health professionals, purchase of protective material to supply health units, carrying out of diagnostic tests, development of virus-resistant mask, production increase of drugs under study for Covid-19 treatment and development of serums.

Butantan, Bio-Manguinhos and Farmanguinhos have stood out in the fight against the pandemic, coordinating studies and clinical trials and creating partnerships in innovative projects and research on vaccines and medicines.

Butantan is the main national producer of immuno-biologicals and a large manufacturer of hyperimmune serums and vaccine antigens³²; Bio-Manguinhos is responsible for the self-sufficiency of MS essential vaccines,

and a large producer of reagents and biopharmaceuticals³³; and Farmanguinhos is the SUS' largest public producer of antiretroviral drugs³⁴, holding the largest number of licensed PDP by MS²¹. In the midst of the pandemic, the three laboratories intensified their activities and deliveries, formed new international alliances and kept essential MS programs, such as Vaccination and STD/Aids Program, in addition to fulfilling important stages of their PDP^{30,34,35}.

BIO-MANGUINHOS AND BUTANTAN

Bio-Manguinhos and Butantan ensured the production of vaccines to meet the PNI during the 2020 Multi-vaccination Campaign, with emphasis to the campaign against measles. The triple viral vaccine, i.e., measles, mumps and rubella, is produced by Bio-Manguinhos, while the vaccine against the Influenza virus, including H1N1 flu, is produced by Butantan^{32,35}.

Regarding the vaccine, great steps have already been taken towards strengthening the national science and technology, and ensuring autonomy against the disease. In July 2021, 18 national vaccines were under development by universities and Institutes of Science and Technology (ICT), five of which coming from LFO – two from Bio-Manguinhos and three from Butantan³⁵. *Table 4* summarizes the types of vaccine and their stages. If approved, they will represent a milestone in technological innovation for the country, since, to date, there has never been a fully national vaccine due to various obstacles. Those are the insufficiency of policies regarding innovation; bureaucratic legislation; difficulty in partnering private companies caused, in part, by the process risk, and, mainly, by the fragility of national vaccine producers in terms of technological capacity for innovation, that is, the capacity to carry out disruptive and not just incremental innovations^{7,37}.

Table 4. National vaccines against Sars-CoV-2 under development as per Public Pharmaceutical Institute, Platform and Development phase, July 2021

IFP developer	Technological Platform and Type of vaccine	Developing Phase
Bio-Manguinhos	Synthetic vaccine	Pre-clinic
Bio-Manguinhos	Vaccine based on protein subunit	Pre-clinic
Butantan/ Dynavax / PATH	Inactivated Virus Vaccine	Phase I/II
Butantan	Outer membrane vesicles on multi-antigen platform	
Pre-clinic	Vacina baseada em partículas semelhantes a vírus (VLP)	Pré-clínica

Source: CGPCLIN/Decit/SCTIE/MS³⁵.

In addition to the endogenous development of vaccines, other measures have been adopted by those LFOs to fight the pandemic and protect the health of the population.

Butantan, a property of the state of São Paulo, is developing studies of a serum from horse plasma and a product compounded of neutralizing monoclonal antibodies^{38,39}.

As the most relevant action, Butantan has coordinated the Proviscov clinical study, which is related to the safety and efficacy of the vaccine produced by Chinese pharmaceutical Sinovac Biotech. The study involved twelve research centers and 9,000 volunteers, all of whom were frontline health-care professionals caring for patients with Covid-19. In September 2020, they signed a contract with Sinovac for the transfer of vaccine technology so to provide 46 million doses of the immunizing agent in a full national production, in case Anvisa approved the clinical study tests. In January 2021, the emergency use of CoronaVac was approved^{36,40}.

Since the beginning of the pandemic, Bio-Manguinhos have been working to restrain and prevent the disease. In partnership with the Paraná Institute of Molecular Biology (IBMP) and supported by the Oswaldo Cruz Institute (IOC/Fiocruz), the laboratory developed in record time the Sars-CoV-2 Molecular Kit. The distribution to Central Laboratories of Public Health (Lacen) and to

reference laboratories began in early March. They also obtained the Anvisa licensing to the TR DPP Kit, result of a partnership with Chembio (USA), which, unlike molecular testing, does not require a laboratory structure and can be used in outpatient clinics and primary health care units⁴¹.

Another initiative has been the evaluation and discussion of different partnership models with the world's leading developers for production and clinical development in their facilities⁴². As a result, they signed a technology acquisition agreement with pharmaceutical company AstraZeneca in September 2020 ensuring access to 100.4 million doses of the ChAdOx1 vaccine, developed by the University of Oxford. Similar to what happened to Butantan, the emergency use of the vaccine was approved in January 2021, being the definitive licensing released in March 2021. So, Bio-Manguinhos became the holder of the first license of a Covid-19 vaccine produced in the country. In June 2021, they signed a contract with AstraZeneca for a 100% nationalized production of the immunizing agent, a milestone for the production of the vaccine in Brazil. The agreement with AstraZeneca will allow, in addition to the technological incorporation of that vaccine, the domain of a platform for the development of immunization agents to prevent other diseases, such as malaria^{36,42,43}.

FARMANGUINHOS

As for drugs, the fastest possible strategy for science to help fight Covid-19 is the analysis of drugs already approved for other uses⁴⁴.

Farmanguinhos has supported research development for Covid-19 treatment with the supply of drugs and placebos. Two of their medicines were tested for effectiveness. Regarding studies on the antimalarial chloroquine, they collaborated for the Solidarity clinical trial, provided by the World Health Organization (WHO), coordinated by Fiocruz with the participation of Bio-Manguinhos; and for the CloroCOVID-19 study, developed by Dr. Heitor Vieira Dourado Tropical Medicine Foundation, in Manaus (AM)⁴⁵. As for the antiretroviral drug Atazanavir, they have participated in the study coordinated by the Center for Technological Development in Health (CDTS) by means of the involvement of Fiocruz scientists, D'Or Institute for Research and Education, Iguaçú University⁴⁶, and the entitled Covid-19 Brazil Coalition IX, in partnership with pharmaceutical company Blaxter and Hospital of the Heart (HCor). It should be noted that none of those medicines has shown promise so far. However, the LFO has also been studying the feasibility of researching and developing new drugs while looking for partnerships for other products⁴⁷.

Conclusions

The LFOs, both as for stated initiatives and prospective actions, have proved their competences towards the economic and technological development of Ceis, competences arisen during the fight against the pandemic. Their activities demonstrate the effort to integrate public health and industrial policies, also as at the federal as the state levels. The change in profile moved by the need for competitiveness and strengthening of scientific and productive capacity made many of them migrate from a

purely industrial model to a more strategic one, enhancing the ICT role.

Due to their activities and strategies during the pandemic identified in the study, a broader perspective analysis made possible to recognize the great role those institutes play for maintaining the various MS programs and reducing Ceis' vulnerabilities. Taking this scenario under consideration, it is worth to reinforce the importance of expanding the State's role so to maintain and sustain an environment that favors the health innovation system, essential for the country's economic development and the sustainability of its pharmaceutical industry.

In times of ongoing transformation brought about by the 4th Technological Revolution, an agenda for change is imposed on those institutes. In order to achieve sustainability and long-term development, they must invest ceaselessly in cooperation with public and private institutions, in the qualification of their professionals, and in the incorporation of new management models and technologies. The commitment to the production of essential medicines and health products for SUS, ranging from the most basic to those of greater complexity and added value, as well as the increase in activities associated to innovation, are fundamental measures to strengthen the Ceis public strategic arm and to provide greater support to SUS, given its enormous challenge of ensuring universal access to health.

Collaborators

Fernandes DRA (0000-0002-0969-2707)* contributed to the conception, planning, data collection, interpretation of results and writing of the manuscript. Gadelha CAG (0000-0002-9148-8819)* contributed to the supervision of the study, analysis, interpretation of results and critical review of the manuscript. Maldonado JMSV (0000-0002-0815-1765)* contributed to the analysis, interpretation of results and critical review of the manuscript. ■

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Received on 06/10/2021

Approved on 10/12/2021

Conflict of interest: non-existent

Financial support: Project 'Desafios para o Sistema Único de Saúde no contexto nacional e global de transformações sociais, econômicas e tecnológicas - CEIS 4.0'