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The public production of medicines in Brazil

A produção pública de medicamentos no Brasil

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Abstract *The paper aims to contribute as a reflection on the public production of medicines in Brazil. Public producers present themselves as strategic in Brazil, either as price regulators, in meeting the demands of the Ministry of Health (MoH) on neglected products and those at risk of shortage to SUS. The study used the official bases of the MoH, National Health Surveillance Agency (ANVISA) and Website of Official Pharmaceutical Laboratories (OPL). Thirty-three OPL were identified, 16 with active production of drug registration at ANVISA. For the remaining 17 LFOs, no one identified active portfolio in the bases surveyed. There are 80% of the OPL portfolio concentrated in the first level of the Anatomical Therapeutic Chemical Classification, such as alimentary tract and metabolism, blood and blood forming organs, cardiovascular system, anti-infective for systemic use and nervous system. The OPL participation in the health complex is 48.6% of its portfolio dedicated to the strategic component, 30.6% for primary care and 20.7% for the specialized. It concludes the relevance of the OPL for the Brazilian health policy, with the better realignment of their potential in the face of technological advancement, health legislation, drug dependence and new treatment protocols.*

Key words *Official laboratory, Pharmaceutical industry, Public health, Knowledge management, Public-private sector partnerships*

Resumo *O artigo objetiva contribuir como reflexão sobre a produção pública de medicamentos no Brasil. Os produtores públicos se apresentam como estratégicos, seja como reguladores de preço ou em atendimento às demandas do Sistema Único de Saúde. O estudo utilizou as bases oficiais do Ministério da Saúde, Agência Nacional de Vigilância Sanitária (ANVISA) e dos Laboratórios Farmacêuticos Oficiais (LFO). Foram identificados 33 LFO, sendo 16 com produção ativa de registro de medicamentos na ANVISA. Para os 17 LFO restantes não foram identificados portfólio ativo nas bases pesquisadas. Identificou-se que 80% do portfólio dos LFO estão concentrados no primeiro nível da "Anatomical Therapeutic Chemical Classification", como: alimentary tract and metabolism, blood and blood forming organs, cardiovascular system, anti-infective for systemic use and nervous system. A participação dos LFO no complexo da saúde é de 48,6% de seu portfólio dedicado ao componente estratégico, 30,6% para atenção básica e 20,7% para o especializado. Conclui-se que os LFO têm relevância para a política de saúde brasileira, com melhor realinhamento da potencialidade dos mesmos frente ao avanço tecnológico, à legislação sanitária, à dependência de fármacos e aos novos protocolos de tratamento.*

Palavras-chave *Laboratório oficial, Indústria farmacêutica, Saúde pública, Gestão do conhecimento, Parcerias público-privadas*

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Introduction

The public production of medicines by Official Pharmaceutical Laboratories (OPL) is an important objective of Brazilian Policy of Medicines (1998), in order to ensure adequate access for the general population[1].

Brazil has a long history of investments in the self-sufficient public production of priority medicines and vaccines for public health, and some public laboratories appeared in the 50's. Certain policies encouraged the national production of healthcare products, such as the creation of the Executive Group of the Pharmaceutical Industry (Geifar) in 1962, the Medicines Center (Ceme) in 1971 and the Medicines Master Plan of 1973[2]. However, Ceme was the first initiative to establish a national medicines policy, involving both public and private production to promote access to essential medicines. Ceme had an important coordinating role with the network of OPL, controlling their production and distribution. Despite the efforts of the Ministry of Health (MoH), the Ceme ended its operations in 1990 and the OPL lost a central coordination that managed the purchase of medicines[3].

The OPL aims the innovation, development and production of medicines, vaccines or medical device products for Brazilian Unified Health System (SUS). Therefore, they are considered strategic for research and development (R&D) and as price regulators in the Brazilian pharmaceutical market, as when the MoH in 2005 announced that could produce antiretroviral efavirenz, nelfinavir and lopinavir, and the prices of this medicines decreased 59%, 40% and 46%, respectively[4,5]. The OPL's aim has supported national health policies to combat and control diseases, promote access to medicines and attempt to meet the demands of the Ministry of Health and public health secretariats. Especially the production of medicines for neglected diseases that are not of interest to the private sector, and this is the particularity of OPL production[6,7].

In 2007, there were the priorities of government agenda in the industrial policy resulted in the inclusion of the Health Industrial Complex (Complexo Industrial da Saúde – CIS) as a planning component of the MoH. The Health Industrial Complex is a concept in which health care incorporates industrial activities (chemicals, biotechnology and medical/hospital equipment manufacturing – and services). It is also considered both as a structural element of the social welfare system and strategic sector for the accumulation of capital, evidencing the multiplicity of relations that exist between health care and development[8]. Over the last decade, a set of public policies has been created in Brazil with the objective of overcoming the vulnerability of the health care productive base while mitigating its effects on the sustainability of the health care system[8]. In this sense, the public production of medicines becomes the subject of incentives, including Partnership for Productive Development (PDP). It was launched in May of 2008 as part of the government's Productive Development Policy and incorporated into the priorities of the Major Brazil Plan in 2011, the National Health Care Plan of 2012-2015 and the Development of the Health Industrial Complex Program (PROCIS)[3,9,10].

PDP are partnerships that involve cooperation, through an agreement, between three institutions to guarantee the production and absorption of technology: 1) OPL for medicines and vaccines responsible for absorption and production of technology; 2) national private producer of active pharmaceutical ingredients and; 3) private entities holding the patent or that development the technology, responsible for transferring the technology. The private entities can be national or multinational[11]. In order to set priorities for the PDP project proposals, a list of strategic medicines for the CIS is created and promulgated by MoH[12].

In general, until PDP started, OPL had portfolios focusing in lower-cost medicines. The portfolios were similar and they compete with each other and with the private sector for the public market. However, with new industrial policy, the CIS strategy directs the composition of the OPL´s portfolios[3]. This paper aims to present an overview of the public production of medicines in Brazil. This approach includes a literature review about the public production of medicines, especially after the creation of PDP and analyze of how many and which are OPL exist in Brazil describe them production, according to the pharmaceutical services financing and government's Productive Development Policy and PDP.

Methods

This exploratory study used the public data and also is composed by a narrative review of the literature.

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Data sources

For the narrative review of the literature, a search of the scientific literature was carried out with the electronic databases MEDLINE, LILACS, Capes Platform and the legislation evolved in the public production of medicines. In addition, a manual search of publications based on the relevant bibliographic references listed in the identified articles was performed.

The search strategy used as descriptors the following Portuguese expressions: "laboratórios farmacêuticos oficiais brasileiros", "laboratórios farmacêuticos oficiais", "produção pública de medicamentos" and "gestão de ciência, tecnologia e inovação em saúde". The period of research was between February to July 2019 and were selected the studies published between 1997 and 2018 that analyzed the public production of medicines in Brazil.

For the exploratory study, two data sources were used to OLP identification: (1) The official website of the Brazilian Ministry of Health (http://portalms.saude.gov.br/) and (2) the portal of the Association of Official Pharmaceutical Laboratories of Brazil (ALFOB) (http://alfob.org.br/laboratorios-associados/).

For medicines identification, it was used two data sources also: (1) The online electronic portfolios of OPL identified and (2) the registers of medicines in the database of the National Sanitary Surveillance Agency (Anvisa – Brazilian term) (http: /portal.anvisa.gov.br/ – field "consulta a registros de medicamentos e produtos para Saúde"). It was necessary use the database of Anvisa became some OPL have not them online electronic portfolios or they have not updated their websites.

It was used the official website of the Brazilian Ministry of Health (http://portalms.saude.gov.br/) for the identification of the medicines with PDP, according to phase.

The data of the surveyed between the periods from September 2017 to August 2018.

Analysis plan

The classification of medicinal products according to their Anatomical Therapeutic Chemical (ATC) classification[13] and compared to Brazilian Essential Medicines List (Rename) 2018 and the list of PDP signed.

Results and discussion

The OPL make up the 33 according to the databases consulted. However, it is important to highlight that the official sources about Official Pharmaceutical Laboratories presents different data. The website of MoH has two areas that present public production of medicines: Pharmaceutical Services and Health Economic-Industrial Complex. The pharmaceutical service area presents 21 OPL and the Health Economic-Industrial Complex area presents 31 OPL[14,15]. This difference occurs in the same website. In contradiction, the Association of Official Pharmaceutical Laboratories of Brazil (ALFOB)[16] presents 21 OPL.

Chart 1 presents the 33 OPL selected according type of products, sources and state in Brazil. The majority (60.6%) of OPL have as source federal or state government, 30.3% are in the universities and 9.1% are military. For 17 (51%) of the OPL selected, the portfolio was not identified neither the medicines registration in validity. Therefore, it was not possible say the type of products.

The mission of ALFOB is strength all OPL and valorize them in the formulation and implementation of public policies, especially in the areas of health and socioeconomic development. It also seeks to promote access to strategic technologies for the health system and contribute significantly to national development[16]. At the same time, ALFOB is an association, which partly explains the fact that 63% of the OPLs are associated with it.

Figure 1 presents the OPL´s geographical distribution in Brazil map. The color intensity shows the states with the highest number of OPL. Among the 33 OPL, 16 are in green because it was possible to identify the production and 17 are in the red because they don't have medicines valid registration or whose them portfolio was not found.

It is important to highlight the management aspect of the OPL. Although these laboratories have been upgraded according to the health legislation, now they have appropriate technical conditions, but their commercial and managerial development did not advance so much. In 2005, the MoH established the Brazilian Network of Public Medicines Production with the purpose of coordinating the public laboratories.

It is worth noting the concentration of the existing OPL in the Southeast. This region for decades has presented since the beginning colonization as the one that receives the most investments.

Chart 1. Official Pharmaceutical Laboratories according to official data source.

Official Pharmaceutical Laboratory (in Brazilian term)	Type of products	Source	State
Centro de Pesquisa e Produção de Medicamentos do Amazonas (CEPRAM)	-	University	Amazonas
Centro de Produção e Pesquisa de Imunobiológicos (CPPI)	Physiological serum	State	Paraná
Centro de Tecnologia e Geociências (UFPE)	-	University	Pernambuco
Empresa Brasileira de Hemoderivados e Biotecnologia (Hemobras)	Blood products	Federal	Brasília (DF)
Faculdade de Farmácia, Odontologia e Enfermagem (UFC)	-	University	Ceará
Fundação Ataulpho de Paiva (FAP)	Vaccine	Federal	Rio de Janeiro
Fundação Baiana de Pesquisa Científica e Desenvolvimento Tecnológico, Fornecimento e Distribuição de Medicamentos (Bahiafarma)	Medicines and diagnostic tests	State	Bahia
Fundação Ezequiel Dias (FUNED)	Vaccines, medicines and physiological serum	State	Minas Gerais
Fundação para o Remédio Popular (FURP)	Medicines	State	São Paulo
Industria Química do Estado de Goiás (IQUEGO)	Medicines and medical devices produced	State	Goiás
Instituto Butantan	Vaccines and physiological serum	State	São Paulo
Instituto Carlos Chagas (ICC FIOCRUZ)	-	Federal	Rio de Janeiro
Instituto de Biologia molecular do Paraná (IBMP)	-	Federal and state	Paraná
Instituto de Pesquisa em Fármacos e Medicamentos (IPeFarM)	-	University	Paraíba
Instituto de Tecnologia do Paraná (TECPAR)	-	State	Paraná
Instituto de Tecnologia em Fármacos (Farmanguinhos)	Medicines	Federal	Rio de Janeiro
Instituto de Tecnologia em Imunobiológicos (Bio-Manguinhos)	Vaccines, diagnostic tests and biologicals	Federal	Rio de Janeiro
Instituto Vital Brasil (IVB)	Vaccines and physiological serum	State	Rio de Janeiro
Laboratório de Avaliação e Desenvolvimento de Biomateriais do Nordeste (CERTBIO)	-	University	Paraíba
Laboratório de Produção de Medicamentos (LPM)	-	University	Paraná
Laboratório de Tecnologia Farmacêutica (UFPB)	-	University	Paraíba
Laboratório Farmacêutico da Marinha (LFM)	Medicines	Military	Rio de Janeiro
Laboratório Farmacêutico do Estado de Pernambuco Governador Miguel Arraes (LAFEPE)	Medicines	State	Pernambuco

it continues

Chart 1. Official Pharmaceutical Laboratories according to official data source.

Official Pharmaceutical Laboratory (in Brazilian term)	Type of products	Source	State
Laboratório Farmacêutico do Estado de Santa Catarina (LAFESC)	-	State	Santa Catarina
Laboratório Farmacêutico do Estado do Rio Grande do Sul (LAFERGS)	-	State	Rio Grande do Sul
Laboratório Industrial Farmacêutico de Alagoas (LIFAL)	Medicines	State	Alagoas
Laboratório Industrial Farmacêutico do Estado da Paraíba (LIFESA)	-	State	Paraíba
Laboratório Químico Farmacêutico do Exército (LQFEX)	-	Military	Rio de Janeiro
Laboratório Químico-Farmacêutico da Aeronáutica (LAQFA)	-	Military	Rio de Janeiro
Núcleo de Pesquisa em Alimentos e Medicamentos (NUPLAM)	-	Federal	Rio Grande do Norte
Núcleo de Tecnologia Farmacêutica (NTF/UFPI)	-	University	Piauí
Núcleo de Tecnologias Estratégicas em Saúde (NUTES/UEPB)	Health equipment	University	Paraíba
Unidade de Produção de Medicamentos (LEPEMC/UEM)	-	University	Paraná

Source: Authors' elaboration.

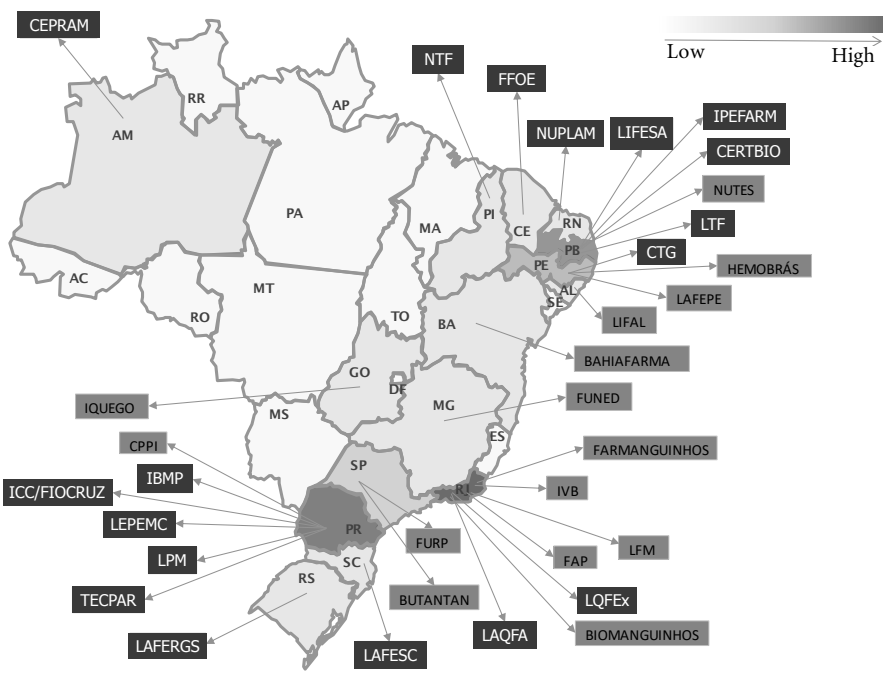

Figure 1. Geographical distribution of OPL in Brazil map.

Source: Authors' elaboration.

This is because it was the capital of the country from the 18th century until the year 1961. Nevertheless, the commercial and tourist evolution of the city, with infrastructure, where the MoH was

in place until the 1970s, established the Pharmaceutical laboratories of the armed forces (Navy, Army and Aeronautics). Likewise, the Oswaldo Cruz Foundation, part of the MoH, with its headquarters in Rio de Janeiro, is part of the largest public laboratory in the federal scope, the Institute of Technology in Drugs, called Farmanguinhos. This conglomerate of public production comes to integrating to the other OPLs of other Brazilian regions. Over the following decades, the Federal and State Governments have promoted investments to increase OPL capacity in other states[18].

OPL present an expensive production, often a reflection of the ineffective machine, so it is necessary an open discussion about the selection these medicines to production by these laboratories including a methodology that combines technical (public health) with economic criteria. These criteria should be clear and, if possible, quantifiable. Moreover, it is important that instruments such as PDP to evaluate as a methodology including performance and effectiveness indicators. Another point to consider, are constantly updating of new production technologies, as well as the need to comply with the sanitary legislation of the medicines. It refers to the renewal of registration (similar, generic, etc.), the OPL face a series of difficulties, such as legislation, such as the certification of suppliers of active pharmaceutical ingredients (API) and pharmaceutical bioequivalence tests in light of the reference medicine. For medicinal products where there is no interest for the pharmaceutical industry, such as medicines for neglected diseases (malaria, tuberculosis, etc.), there are no "reference medicines" on the market. In this context, there are a number of challenges to be faced in maintaining the registration of medicines. Combined with the lack of financial investments and human resources on a constant basis, as well as in the endogenous technology development efforts, it contributes to the promotion of the maintenance of medicines registration and the insertion of new medicines available in the SUS.

There were 152 different medicines produced in total by 16 OPL. Among the 152 medicines, 33 (21.7%) have not valid medicines registration, highlighting to 18 of Lafepe. Therefore, for this study, it was considered 121 medicines produced by OPL, containing 110 (90.9%) from Rename 2017, and the remaining (9.1%) had been present in earlier versions of Rename or there are oncology medicines. Anti-infective for systemic use was the most frequent group (39.7%), followed by nervous system (14.0%) and alimentary tract metabolism, cardiovascular system, blood and blood forming organs and antineoplastic and immunomodulating agents (7.4%) (Table 1).

Anti-infective for systemic use medicines produced by OPL were, most frequently, antiviral and vaccines. These results are reflection of the strong aid policy in Brazil and the National Immunization Program (PNI). This program is part of the Strategic Component of Pharmaceutical Services whereupon MoH concentrates management.

The antineoplastic and immunomodulating agents divide in antineoplastic agents, monoclonal antibodies, interferons and TNF-α inhibitors. Also nine medicines of antineoplastic and immunomodulating agents group: five have PDP active (imatinib, interferon beta-1a, leflunomide, infliximab and tacrolimus). Until PDP, no OPL produces anticancer medicines, most likely because their production requires a differentiated manufacturing structure[19]. The large number of medicines intended for cancer treatment and from selected biological source questions whether the current OPL are qualified to absorb these technologies, specifically regarding the production of anticancer medicines. The current structure of the OPL would not support such produc-

Table 1. Number and percentage of medicines according to the first level of Anatomical Therapeutic Chemical (ATC) classification in Official Pharmaceutical Laboratories (OPL) portfolio.

ATC classification (1st level)	n	%
A – Alimentary tract and metabolism	9	7.4
B – Blood and blood forming organs	9	7.4
C – Cardiovascular system	9	7.4
D – Dermatological	3	2.5
G – Genitourinary system and sex hormones	4	3.3
H – Systemic hormonal preparations (exclusive sex hormones and insulins)	1	0.8
J – Anti-infective for systemic use	48	39.7
L – Antineoplastic and immunomodulating agents	9	7.4
M – Musculoskeletal system	1	0.8
N – Nervous system	17	14.0
P – Antiparasitic products, insecticides and repellents	6	5.0
R – Respiratory system	3	2.5
V – Various	2	1.7

Source: Authors' elaboration.

tion, requiring the construction of new facilities and the expansion of existing ones in order to meet the regulatory requirements to produce this type of medicine[3].

The medicines for nervous system were, in most frequent, for psychiatric diseases as schizophrenia and depression and analgesics and antipyretics. And the medicines for alimentary tract metabolism and cardiovascular system were medicines to treat diabetes and hypertension. These results confirm that until PDP started, OPL had a portfolio focusing in lower-cost medicines and presented in the basic component of pharmaceutical services.

Until 2007, the federal government (MoH) centralized all funding of the Brazilian Pharmaceutical Policies. However, with the decentralization of Pharmaceutical Services, both the financing and transfer of federal financial resources started to be regulated by local (states and municipalities) health activities and services. In the same way, as well as their monitoring and control[20]. Like this, the new policy was to create the components of pharmaceutical services (basic, strategic, and specialized).

Basic Component intends purchase of medicines and supplies related to the diseases and health programs of primary health care and dedicated to meet both the individual and collective basic needs of the population. The three spheres of SUS management (federal, state, and municipal) are responsible for the funding, but the procurement and management of medicines supply are the responsibility of municipal. In some cases, the procurement of medicines of basic component can be responsibilities of federal and state management, according to a decision by the bipartite and tripartite commissions[20-22].

The Strategic Component has medicines for treatment of diseases with an endemic profile, such as HIV/AIDS, malaria, Chagas disease, leishmaniosis, tuberculosis, Rocky Mountain spotted fever, nutritional deficiencies and vaccines, whose control and treatment have guidelines and policies that have a socio-economic impact. MoH is responsible for funding, procurement and management of medicines supply[20-22].

At last, the Specialized Component of Pharmaceutical Services is a strategy that aims to create access to high-cost medicines, based on paths of care expressed in Clinical Protocols and Therapeutic Guidelines (PCDT) published by the MoH[12]. The medicines of this component are divided in three groups, and this division determines which sphere will finance, purchase and manage[20-22].

Moreover, each hospital has its own list of medicines that includes oncology medicines. For treatment of cancer, there are centers of treatment and each center has a specific list[23].

For public laboratories, the decentralization of Pharmaceutical Services resulted in loss of market. The procurement and management of medicines supply of Basic Component are by municipal government and they follow the Law No. 8,666/93, which sets out the general rules for bidding procedures and government contracts. According to this law, the decision for the winning bid is made by these criteria: lowest price, best technology or a combination of technology and price. Usually the first criterion is chosen and the private sector wins the sale because offers more competitive prices. According to Zaire et al.[24], that analyzed the acquisition values of purchases of medicines by state and municipal government, the private laboratories presented lower prices than OPL.

As public laboratories, OPL have to follow the Law No. 8,666/93 to buy materials to produce the products and equipment, including active pharmaceutical ingredients (API). The process of acquisition initiates with a description of the material. Therefore, all technical description must be well detailed and exhaustive for the production and quality of medicines. A wrong purchase can cause material and time losses and extra costs. The process of purchase using the Law No. 8,666/93 is a bureaucratic process and consumes a lot of time. Thought, this law allows the standardization of materials, but the process is equally bureaucratic and time-consuming. This combination of factors worsens, making inefficient public sector. OPL have to follow public legislation to buy the material for production, this is more time consuming to produce if compared with pharmaceutical private companies.

Although these public laboratories received financial investments for modernization and expansion, in relation to production capacity, they are still inferior to the private sector in technology, processes and products[4], which results in products with not competitive prices. The Law No. 8,666/93 allows government agencies to procure from OPLs without going through the bidding system, even so, the OPL that produce medicines lost a big part of public market after 2007.

The dependence on SUS as the main buyer leaves the OPL vulnerable to changes in withdrawal and new introductions among the products financed by the health system. The development and production of a medicine or vaccines is not quick, being difficult to follow the speed

of incorporation of products. Furthermore, OPL produce based on a demand from the government. It is worth noting that medicines, demand of MoH is more organized and stable, but the demand from states and the municipalities are different. As there is no regularity on this issue, LGAs are not able to schedule continuous purchases to organize themselves in the management of raw material purchases, in the same way as private pharmaceutical labs.

The production of the OPL is focused (48.6%) on the strategic component, 30.6% of the basic component and 20.7% of the specialized component. These results are different if compared with the portfolios in 2015, whose distribution was 64% of the basic pharmaceutical services component, 29% of the strategic component and 7% of the specialized component[3].

First, the change can be attributed to the definition of strategic medicines for the CIS. The selection of these medicines should consider: 1) the importance of the medicine to the SUS, according to policies and programs of health promotion, prevention and recovery; (2) centraling acquisition of the medicine by the MoH, or the possibility of centralization; and (3) interest in the national production of the medicine and active pharmaceutical ingredients relevant to the health economic-industrial complex. One should additionally consider the high purchase price for the SUS, the import dependency for health care within the context of the SUS for the previous three years, recent medicines incorporated by the SUS and the possibility of it being a neglected medicine with potential shortage risks[3].

The definition of strategic medicines for the CIS explains the increase of medicines on the strategic component and, especially, on specialized component.

In the second place, the difference between the production in 2015 and 2017 can be related to execution of PDP. The most the contracts were signed after 2014 and the PDP have four phases. Only in the phase III, OPL have to show to MoH that there has been progress in the development and transfer of the technology and the application of sanitary registration in OPL´s name. In this phase, there is a limit of five years or ten years to the transfer to be completed. Usually, ten years are accepted for biological medicines[25,26].

There are a large number of OPL and the lack of coordination reflects at their portfolios. The OPL produces similar products and medicines that could be produced at low prices by private national industries and be available in SUS, as paracetamol, ferrous sulfate, folic acid and metformin. Chart 2 shows that 30.6% of them are manufactured by more than one OPL.

It is necessary open discussion about the selection of the medicines to be produced by OPL including a methodology that combines technical (public health) with economic criteria, and that these criteria are clear and, if possible, quantifiable. In addition, that discussion has to occur together with the coordination of OPL and definition which products are strategic for public production, presenting robust criteria for the selection.

According to Magalhaes et al.[27], in 2010 there were 23 OPLs in the public drug production network. Comparing with this study, currently there is a 43% increase in the number of OPLs. However, this does not constitute an increase in production and its productive capacity, since when comparing the list of products registered at the last time and at the present time, a reduction of the same is noted. Among 121 medicines produced by OPL considered in this study, 28 (23.14%) medicines had PDP signed, but five that were extinct. The most of medicines focused on the specialized component (56.5%), 30.4% of the strategic component, 8.72% of the basic component and 4.3% is oncology medicine.

PDP have four phases and among 23 medicines with PDP active, one medicine is phase I, one phase II, 17 phase III and four phase IV.

Phase I is the PDP project proposal. From the strategic medicines list, OPL elaborate a PDP project proposal following the MoH model. The proposal must contain the strategic medicine chosen and the other partners (the producer of active pharmaceutical ingredients and the private entity responsible for transfering the technology). The contact with the partners and the MoH is responsibility of the OPL[25,26]. The proposal of PDP is analysed by a Committee of SCTIE of MoH.

The selection of strategic medicines should consider the centralizing acquisition of the medicine by the MoH, or the possibility of centralizing. During the transfer, the OPL buys the medicine from the private partner and sell to MoH. Therefore, the OPL execute the PDP with the profit between the purchase, from private partner and the sale to MoH. Ministry of Health guaranties to the OPL exclusive purchase, based on the lowest price in the global market. During the technology transfer period, the price of the medicine has to be negotiated each year and have to be cheaper 5% for MoH[25,26,28].

There is not an official financing from MoH for PDP because your activity is limited to buy

Chart 2. Medicines of the Official Pharmaceutical Laboratories (OPL) portfolio according to the therapeutic indication and number of public producers.

Products	Therapeutic indications
Paracetamol	Analgesic and antipyretic
Zidovudine and lamivudine	Antiretroviral
Snake venom antiserum	Immune sera
Tetanus antitoxin	Vaccin
Captopril	Antihypertensive
Lamivudine	Antiretroviral
Ferrous sulfate	Antianemic
Nevirapin	Antiretroviral
Rabies serum	Immune sera
Human insulin NPH	Antidiabetic
Human insulin R	Antidiabetic
Infliximab	Immunosuppressant
Folic acid	Antianemic
Amoxicillin	Antibiotic
Atorvastatin	Antilipid agent
Diazepam	Anxiolytics
Phenobarbital	Antiepileptics
Isoniazid	Antimycobacterial
Methyldopa	Antihypertensive
Phenytoin	Antiepileptics
Sulfadiazine and trimethoprim	Antibiotic
Dexamethasone	Corticosteroid
Hydrochlorothiazide	Diuretic
Metamizole sodium	Analgesic and antipyretic
Simvastatin	Antilipid agent
Dapsone	Antimycobacterial
Pyrazinamide	Antimycobacterial
Riluzole	Nervous system medicine
Ziprasidone	Antipsychotic
Dexchlorpheniramine	Antihistamine
Metformin	Antidiabetic
Neomycin and bacitracin	Antibiotic
Sildenafil	Drug used in erectile dysfunction
Tacrolimus	Immunosuppressant
Rifampicin	Antimycobacterial
Rifampicin and isoniazid	Antimycobacterial
Imatinib	Antineoplastic agent

Source: Authors' elaboration.

strategic medicines for CIS exclusivity from OPL. However, the OPL are public laboratories financed by state or federal government, so there is a financing of PDP, even indirect, what makes difficult to control what is actually invested in PDP[25].

Phase II is composed by a contract between MoH, OPL and the others partners. This contract must contain how will be the development, transfer and absorption the technology, rights of intellectual property and the obligations of each one. For MoH, it is necessary to detail the conditions for purchase. For OPL and private entities, they have to invest a minimum percentage in research, development and innovation. And the OPL need to have an industrial manufacturing layout to produce the strategic medicines for CIS selected[11,25]. This contract will guide the MoH in the process for the first purchase process after PDP agreement.

In phase II, the contract is signed and the sanitary registration by Anvisa is published. The sanitary registration can be the private entity or the OPL, because the PDP may be with a private entity that is not the official holder of the patent, so, they will develop the medicine to transfer to the OPL. In this case, the private entity does not have the sanitary registration before phase II. When the product has no patent, there is a privilege of private national laboratories and often times they have to develop the medicine selected as strategic for CIS. Important to say that this phase does not have a limit of period, but a committee inside Anvisa was created to analyse the sanitary registration requirements for PDP[25,26].

The private entity can receive funding from the National Bank for Economic and Social Development (Banco Nacional do Desenvolvimento Econômico e Social – BNDES) to modernize and expand the layout and produce and development strategic medicines for the CIS. BNDES is a public bank, linked to the Ministry of Industry, Foreign Trade and Services. Or the funding can be by Projects and Studies Financer (Financiadora de Estudos e Projetos – FINEP) linked to the Ministry of Science Technology Innovation and Communications[26].

In phase III, OPL have to show to MoH that there has been progress in the development and transfer of the technology and the application of sanitary registration in OPL's name. In this phase, there is a limit of five or ten years to the transfer to be completed. Usually, ten years are accepted for biological medicines. And the phase IV is the internalization of technology, which is when development, transfer and absorption of technology are finished[23,24]. If the OPL didn't absorb the

technology in five or ten years, the MoH stops to buy the medicines exclusivity from them[11].

After phase IV the OPL and the private laboratories (national or international) have the sanitary registration of the medicine and they can compete in the Brazilian pharmaceutical market[11]. Moreover, this scenario takes to the same discussion about how the dependence on SUS as the main buyer leaves the OPL vulnerable.

Final considerations

The Brazilian Policy of Medicines is concerned with the public production of medicines, especially those from the Brazilian Essential Medicines List (Rename), and this production predicts the articulation between different industrial segments (official, national private and transnational). In this proposal, OPL prioritized essential medicines, especially those one included in Basic and Strategic Components. The difference between Health Industrial Complex, which led to the new public production policy, and the National Policy of Medicines is the focus on high-cost medicines, including oncology.

The SUS can act as an engine for national industrial development and this feature linked to the Brazilian legislation for access to treatment, makes the Brazilian public production of medicines differentiated. It is a viable production of pharmaceuticals, once there is a national market and needs to address specific requirements, such as neglected diseases. However, self-sufficiency in pharmaceutical supply is questionable, because most active pharmaceutical ingredients are now sourcing globally.

In the area of pharmaceuticals, the countries that demonstrated the most advanced levels of production were consistently strengthened by technology transfer in addition to having greater coherence in their domestic policies that increased their absorptive capacity (human skills and scientific infrastructure) throughout their growth and expansion. And was in this line, that PDP in CIS policy was construed, however, it is important defines more robust criteria for the selection of strategic medicines for public production.

The biggest barrier to technology transfer, perceived by both technology recipients and donors, is lack of R&D capacity in developing countries. In addition, in OPL is not different. The low investment in R&D reflects on the implementation of the current technology policy transfer through the PDP. The Brazilian Industrial Policy does not detail how would be the technology development cooperation and exchange of knowledge. So, with low capacity in R&D in OPL, low technology capacity and no in-house capacity are developed and/or maintained for independent R&D, it is hard to provide changes in this policy such as the PDP. Furthermore, the investment in R&D is very important too to leads to technological accumulation and strengthens the government's negotiating power, especially in cases of medicines with patent, especially with in cases of PDP.

The new industrial policy aims to promote the technological and economic sustainability of SUS, with the increase of the capacity of production and innovation, reduce the Brazilian external dependence and vulnerability (productive and technological) of strategic products for CIS, and other points, but presents serious problems related to governance. Moreover, the OPL are an important piece of PDP but without coordination, the OPL are participating of PDP more as price regulators in the Brazilian pharmaceutical market them protagonists for reducing the Brazilian external dependence and vulnerability.

In this study, we can observe the large quantity of OPL without production of medicines. This can be explained by the lack of capacity of OPL to adapt to new legislative paradigms (health legislation), such as the renewal of generic medicines registrations in the light of reference medicines. Likewise, the endogenous development of new technologies and the absorption capacity of technologies derived from PDP.

There is a large public productive park available to the MoH to attend the SUS. These are an enormous difference and strategic for the Government, in what concerns to price regulators, performance in the market niche essential to neglected diseases and technological development. However, they did not fully adjust to the new public policies. It is necessary to seek better synergies of technological instruments, partnerships and incentives, for the reorientation of policies for drugs and medicines in Brazil.

Collaborators

TA Figueiredo contributed to the design of the research work's central idea, data collection, database creation, data analysis and writing of this paper; RG Fialho Neto participated in the data collection, database creation and data analysis. JL Magalhães contributed to the design of the research work's central idea, data collection, database creation, writing of this paper and proofreading its final version.

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