Public supply of AIDS drugs and the role of Farmanguinhos

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Abstract: This article describes and analyses the part played by the Instituto de Tecnologia em Fármacos (Farmanguinhos) in local production of antiretroviral medicines in Brazil, as well as changes in the pattern of supply, the status of related Production Development Partnerships and the position of Brazilian producers of these medicines. The methodological strategies used were literature review and analysis of official documents and data provided by Farmanguinhos and by the Ministry of Health's Department of Chronic Conditions and Sexually Transmitted Infections, via the Information Access Law. This article shows that, by contributing to the sustainability of Ministry of Health expenditure on medicines, these partnerships have opened new prospects for developing the policy of public supply of antiretrovirals for people living with HIV. Farmanguinhos is the public laboratory that supplies the largest quantities of these products to the Ministry of Health and receives the largest revenues from supplying them. Although the imported medicines supplied to the Ministry of Health account for much larger quantities and revenues, Farmanguinhos continues to be a fundamentally important supplier of locally produced antiretrovirals. Despite the problems found in establishing the partnerships, the gains in antiretroviral production technology competences can broaden the laboratory's technological and production horizons.

➤ **Keywords:** Public health policies. Antiretrovirals. Pharmaceutical industry.

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Received on: 09/08/20
Revised on: 12/08/20
Approved on: 02/22/21

DOI: http://dx.doi.org/10.1590/S0103-73312022320210.en

Introduction

This article describes and analyzes the public supply of medicines for AIDS, with emphasis on the role of the Instituto de Tecnologia em Fármacos (Farmanguinhos) in its production. The changes in the pattern of supply of antiretroviral drugs (ARVs), the status of ARV Productive Development Partnerships (PDPs), and the position of domestic producers are also presented. The policy of universal access to ARVs in Brazil was instituted by Law 9.313 of 1996. The provision of these products, carried out by the Unified Health System (SUS), is responsibility of the federal government. According to data provided by the Department of Chronic Conditions and Sexually Transmitted Infections of the Ministry of Health (DCCI)/MoH), in 2018 the budgetary resources reserved for ARVs for the treatment of about 600,000 people were more than one and a half billion reais. The basket of drugs provided by SUS has a strong predominance of imported and patented drugs, both in the number of pharmaceutical presentations and in the expenditure made. Also, according to the DCCI/MoH, in 2018, the expenditure on imported drugs accounted for more than 70% of the expenditure on ARVs.

There have been different phases in the history of ARV supply policy, from its inception to the present day. The early years were characterized by significant involvement of local laboratories, both official pharmaceutical laboratories (OPLs) and national private ones. In the early 2000s, the panorama changed due to the growing share of transnational companies, which remain the dominant players to this day. Finally, as of the 2010s, the creation of PDPs - involving public and private institutions - sought to nationalize the production of such medications through technology transfer to public laboratories.

Farmanguinhos is a very prominent public laboratory in public provision of ARVs and takes part in PDPs to produce such drugs. Through the analysis undertaken in this study, we hope to better understand the challenges contained in the PDP strategy as an alternative to enable universal access to AIDS treatment in Brazil.

The strategy for this article comprised a literature review on the topic, the examination of official documents provided by Farmanguinhos, and the use of data obtained from the DCCI/MoH via the Information Access Law. This article is part of the results of a larger research project on ARV supply policy in Brazil, which was approved by the Research Ethics Committee of the Escola Nacional de Saúde Pública Sergio Arouca/Fiocruz under number 34783214.0.0000.5240.

The dynamics of public supply of ARVs and the role of Farmanguinhos

In his study, Pimentel (2018) identified 27 OPLs, however, only 11 appeared to have active production lines. OPLs vary in terms of their legal natures, institutional affiliations, size, capacity, labor qualification, and technological capability.

The mission of OPLs is to meet the demands of SUS in such functions as regulating prices in the national market, producing low-cost drugs to increase public access, and producing drugs for neglected and high-cost diseases, such as ARVs. According to Vargas et al. (2016), OPLs jointly account to produce 30% of the medications and 80% of the vaccines used by the SUS. Despite this, they face difficulties such as limited technological capacity (HASENCLEVER et al., 2013), idle production capacity, low labor qualification (VIANA et al., 2016), and limited operational capacity due to dependence on the SUS (CASTANHAR et al., 2005), among others.

Farmanguinhos is a federal OPL, linked to the Ministry of Health (MoH). It is defined as an institute of technology and not just a factory, and its institutional mission is broad, including research, development, innovation, and education, in addition to producing drugs to meet strategic programs of the MoH. The therapeutic classes produced in 2017 were: ARVs (35%); immunosuppressants (26%); antivirals (15%); antihypertensive (10%); vitamins and mineral supplements (7.2%) and other classes (13%). ARVs are one of its productive vocations and this laboratory is one of the main public suppliers for the Brazilian AIDS program.

Despite its leading role in the supply of medicines for SUS, Farmanguinhos has seen a substantial decline in its production. The decentralization of Primary Care in 2005 assigned states and municipalities to purchase basic medicines directly from pharmaceutical companies, redirecting part of the demand to Farmanguinhos. These changes coincided with an expressive increase in its capacity through investments by the federal government in the acquisition of research and technological development facilities for the new campus in Jacarepaguá (FIOCRUZ, 2010). In 2016, only 60.5 million units of drugs were produced in comparison to the annual production capacity of 6 billion units (FIOCRUZ, 2018). Low-capacity utilization was generated by the decline in the supply of medicines to the MoH, which includes other medicines in the portfolio, but mainly affected ARVs, with efavirenz and lamivudine+zidovudine being the ones with the highest volume. In addition, the production of lamivudine

was replaced by the acquisition of the drug tenofovir+lamivudine from the national private laboratory Blanver, a partner in PDP. (BRAZIL, 2016).

A relevant factor in the decline of its production was the withdrawal of the ARV efavirenz as a monodrug from the SUS basket in 2016, when it was produced by Farmanguinhos on a large scale. This drug started to be formulated in a combined fixed dose (more than one drug in a single pill) called "3 in 1", composed of lamivudine+tenofovir+efavirenz. This change was aimed at increasing treatment adherence by users, since it significantly reduces the number of pills ingested. The production of the "3-in-1" became one of the PDPs in which Farmanguinhos came to engage, as will be seen below. However, the sudden halting of purchases of efavirenz monodrug by SUS led to a drop in laboratory production and signaled the need for coordination between the management of Farmanguinhos and the MoH AIDS program in terms of planning for product substitution.

To compensate for the losses, Farmanguinhos has been promoting a reorientation of its production profile toward products with higher added value and strategic interest. PDPs were the path through which the laboratory started to seek portfolio diversification, greater market penetration, and financial margin to invest in equipment, research, and development to reduce its technological weaknesses (FERNANDES, 2019).

Chart 1. Antiretroviral drugs produced in Brazil (2018)

Efavirenz (EFZ) 600mg [1]	Farmanguinhos
Efavirenz (EFZ) 600mg [2]	Farmanguinhos
Efavirenz (EFZ) solução oral 30mg/ml	Cristália
Lamivudine (3TC) 150mg [1]	FURP e Farmanguinhos
Lamivudine (3TC) 150mg [2]	Farmanguinhos
Lamivudine (3TC) 150mg [3]	FURP
Lamivudine (3TC) solução oral 10mg/ml	Cristália
Nevirapine (NVP) 200mg	Farmanguinhos
Ritonavir (RTV) 100mg	Lafepe
Tenofovir (TDF) 300mg	Blanver
Tenofovir (TDF) 300mg + Lamivudina (3TC) 300mg (2 em 1)	Farmanguinhos

continue...

Zidovudine (AZT) 100mg	Farmanguinhos
Zidovudine (AZT) solução injetável 10mg/ml	Cristália
Zidovudine (AZT) xarope 10mg/ml	Lafepe
Zidovudine 300mg + Lamivudina 150mg (AZT+3TC) [1]	FURP, Farmanguinhos e Lafepe
Zidovudine 300mg + Lamivudina 150mg (AZT+3TC) [2]	FURP e Lafepe

Source: Prepared by the authors based on data provided by the Department of Chronic Conditions and Sexually Transmitted Infections (DCCI) of the Ministry of Health.

The OPLs that currently supply ARVs are Farmanguinhos, FURP (under the São Paulo government), and Lafepe (under the Pernambuco government), which have specialized in these drugs since the beginning of this policy. As shown in the chart, they supply ARVs in an independent way or in consortium.

Among the national private companies, Cristália and Blanver produce ARVs for the MoH. Cristália has verticalized production capacity and was the only Brazilian private pharmaceutical company to market ARVs until the mid-2010s. Blanver had its production verticalized after the purchase of CYGBiotech, a pharmochemical company, in 2016 (BLANVER, 2019). These and other private Brazilian laboratories produce the active pharmaceutical ingredients (API) for the public laboratories and are part of the PDPs of ARVs.

Phases of the public supply

From the outset, the provision of ARVs has undergone circumstances that have threatened the financial sustainability of the policy and altered the participation of public producers, starting with the normative conflict in the launching of its legal bases. In the same year of 1996, both Law 9.313, which established the free distribution of ARVs to people living with HIV and AIDS, and Law 9.279, which became known as the Intellectual Property Law (IPL), were instituted. This law, which represents the country's adhesion to TRIPS (Trade-Related Aspects of Intellectual Property Rights), regulates rights and obligations relating to industrial property and established patent protection, with strong impact on the local productive sector. The serious technological and production dependence puts the proposal of universal access to health in check and affects not only ARVs. According to GADELHA (2020), 96% of the drugs used in Brazil are imported.

The policy of acquiring ARVs based on local production was configured in four phases:

Phase 1: Local production without patent protection (first half of the 1990s)

The MoH started offering antiretroviral therapy in the public health system in 1991 (BRASIL, 1999). The first drug offered was the imported zidovudine, which remained the only treatment option until 1996. In 1992 the private Brazilian company Microbiológica started producing the raw material and the drug locally, with an average vial cost 50% cheaper than the imported product (ANTUNES et al., 2013). Lafepe and FURP started their zidovudine production in 1994 and 1996, respectively. This period was characterized by the possibility of free copying of imported products since Brazil had not yet adopted the patent protection system.

Phase 2: IPL and its initial effects (1996 to mid-2000s)

Although the IPL was enacted in 1996, the financial burden of patents began to escalate in the 2000s, when spending rose substantially due to the need to purchase new, second- or third-line drugs that were patented, imported, and expensive (GRANGEIRO et al., 2006).

Moreover, the organizational difficulties of OPLs have jeopardized their share in the national production of ARVs. In the period from 2001 to 2006, the percentage participation of official laboratories compared to private companies in the quantity of ARVs supplied fell from 56% to 45%. The amount paid by the MoH also decreased, falling from 34.5% to 19% (LAGO; COSTA, 2009).

Farmanguinhos was the most affected, as the state-run laboratories absorbed a large portion of its supply of ARVs for the AIDS program. Their participation in quantities supplied fell from 34% to 10% and the revenues from the program went from 25% to 4% (LAGO and COSTA, 2009).

Phase 3: The worsening conditions of financial sustainability of ARV provisioning (mid-2000s to 2010)

This phase takes place at a time when the effects of the IPL are already fully perceived. In 2005, the transition period for developing countries to adapt their industrial facilities to the adoption of TRIPS expired (HASENCLEVER et al., 2013).

In addition, in that same year, third line ARVs were introduced in the SUS basket, which further increased the burden of imports in expenses (POSSAS et al., 2013).

In early 2007, when negotiations to reduce the price of the drug efavirenz failed, the federal government decided to use one of the flexibilities in the IPL and decree compulsory licensing. The API started to be imported from Indian laboratories and Farmanguinhos became responsible for the national part of the production.

This licensing marked a turning point in policy and was reflected in the national and international media, strengthening the federal government's position in subsequent price negotiations with transnational companies (MAGALHÃES et al., 2008). However, the acute dependence on imported products remained.

Phase 4: The production of ARVs through tripartite agreements in the PDP (2010 onwards)

PDPs were an initiative of the federal government with the goals of expanding access to medicines; encouraging local productive and technological development; contributing to the technological and economic sustainability of the SUS; and stimulating the development of a public production network (BRASIL, 2019a). They relied heavily on the purchasing power of the federal government and were conceived as a key element in building systemic innovation policies for healthcare (VARGAS et al., 2016). The first partnerships were established in 2009.

These partnerships are inserted in the broader context of technological development and innovation policies established since the 2000s. From this perspective, health is recognized as an important economic space for development, composed of a productive system and an innovation system, called the Health Economic and Industrial Complex (CEIS) (GADELHA et al., 2019). The institutional framework of PDPs is composed of an extensive list of norms, especially MOH ordinances.

Although there are variations, the standard configuration of PDPs foresees the participation of a public laboratory, which will internalize the technology, a national private laboratory, which will develop the API locally to supply the public laboratory, and a foreign private laboratory, which will own the technology of the product to be incorporated.

The approved PDPs concern mostly medicines, vaccines, and blood products. In this category, by the beginning of 2019, there were 85 PDPs in effect (among these, 15 had been suspended) and 36 were extinct. The PDPs for other types of products

(diagnostic kits, materials, and equipment, among others) comprised only 12: six active (of which 3 were suspended) and six were extinct (BRASIL, 2019a).

Among the challenges faced by OPLs and pointed out by the literature are the productive and technological precariousness of public laboratories - which limits their engagement in partnerships - and the predominance of technology transfer processes for patent-expired drugs, to the detriment of innovative products (GUIMARÃES et al., 2019). Other problems pointed out are the large number of terminations, suspensions, and delays in the development of Partnerships, especially in the more advanced stages, in which there was a large investment of time and resources. A major risk in the delays that affect PDPs is that of transferring technologies that are already obsolete at the end of the processes (OLIVEIRA JUNIOR, 2016).

Some of the advantages pointed out by the literature include the increase in the public laboratories' revenues and the increase in the population's access to needed medicines (REZENDE, 2013). As for the economy, data from the MoH indicate that the savings generated by the acquisition of products from PDPs in the period from 2011 to May 2017 was over 4.6 billion reais (BRASIL, 2017a) when comparing the prices offered by the PDP as the prices charged before its implementation.

Status of the antiretroviral basket offered by SUS

The free and universal provision of ARVs by the state is part of the Brazilian response to HIV/AIDS control. It resulted in a decline of about 70% in mortality and 80% in hospital admissions for AIDS-related conditions from 1996 to 2002 (POSSAS et al., 2013). In 2018 the MoH expenditures on ARVs were R$1.57 billion reais for the care of 593,000 people. The decline in deaths and the entry of new patients means that the number of individuals on treatment increases every year. In the same year, more than 69,000 new patients started treatment (BRASIL, 2019b).

Between 2005 and 2010, spending on third line ARVs rose from 4.5% to 29% of the amount spent on all ARVs, with these drugs being used by only 3% of patients. After that, spending on ARVs, although high, remained relatively stable until 2016. One explanatory hypothesis would be the incorporation of few drugs and the reduction of treatment costs, both by public production and by lowering the prices of older drugs. However, the new spending cap and the recent currency devaluation could impose serious restrictions on spending on medicines, increasing competition for resources (VIEIRA, 2018).

As of 2017, the SUS basket was renewed and old ARVs were replaced by new ones or new presentation forms, due to lower toxicity, fewer associated adverse events, and reduction in the number of daily pills (BRASIL, 2017b; 2017c). The incorporation of dolutegravir (imported) resulted from the combination of two strategies: price negotiation and portfolio reorganization with the exclusion of old drugs and change in prescription indications for second-line drugs. This considerably limited the increase in spending on ARVs (BATISTA, 2018), but not enough to change the burden of imports in the basket, as indicated in the following table.

Table 1. ARV supplier by quantity purchased and spending, 2018

Supplier	Quantity	Percentage	Expenditure (R$)	Percentage
Private Transnational	211,943,890	30.96%	983,114,153.04	62.30%
Private Indian	116,564,599	17.03%	90,390,217.45	5.73%
Private Domestic	8,502,661	1.24%	13,294,176.63	0.84%
Official Laboratories*	158,078,923	23.09%	157,051,268.06	9.95%
Farmanguinhos	189,554,380	27.69%	334,215,021.80	21.18%
Total	684,644,453	100.00%	1,578,064,836.98	100.00%

Source: Prepared by the authors based on data provided by the Department of Chronic Conditions and Sexually Transmitted Infections (DCCI) of the Ministry of Health.

*Includes Farmanguinhos in the production of lamivudine (3TC) 150mg in a consortium with the FURP laboratory, and of zidovudine 300mg + lamivudine150mg (AZT+3TC) with FURP and Lafepe.

As can be seen, imported drugs currently account for almost half of the total quantities purchased and almost 70% of the expenditures. Among national suppliers, Farmanguinhos, alone, maintains a strong position: it is second both in quantities and in expenditures in MoH purchases. Its production (27.69%) exceeds that of the other two national laboratories combined (23.09%), as well as its share in expenditures. This indicates the resumption of its prominence after the decline experienced between 2001 and 2006 (LAGO; COSTA, 2009).

The current scenario also indicates a decrease in the number of national public players compared to the 2000s. The laboratories Iquego/GO, Funed/MG and Lifal/AL have stopped producing ARVs. It is possible that the greater complexity of the

new ARVs has pushed OPLs with poorer technological capacity out of production. But this does not explain the case of OPLs that take part in the PDPs for ARVs, but no longer produce the drugs. Private national companies, such as Cristália and Blanver, also showed little relevance in production, although they were both present in the PDPs, as will be seen later.

The PDPs for ARV production, the Official Pharmaceutical Laboratories and Farmanguinhos

The establishment of a PDP comprises several steps. Initially, the MoH publishes, by ordinance, a list of strategic products for the SUS, which contains the products eligible for PDP proposals. Briefly, in Phase I, the proposal is submitted and evaluated. If approved, a Term of Commitment is signed between the MoH and the public institution. In Phase II the absorption and transfer of technology begins, still without the acquisition of the product by the MOH. In phase III the process of technology absorption and transfer continues and the product is acquired by the MOH. Phase IV is the technology internalization phase, in which the public institution is considered capable of producing the product in the country without the participation of private partnerships (BRASIL, 2019a).

The lists of strategic products were criticized for having dispersed objectives and little transparency in their elaboration process, which would have made them susceptible to being taken over by production sector interests to the detriment of health policies (OSÓRIO-DE-CASTRO, 2017). The current version (08 March 2017) is strongly oriented towards biotech drugs, which directs capacity building efforts towards the biotech route and consequently towards PDP (PARANHOS et al., 2019). Of the 56 PDP-eligible drugs there were seven ARVs, a relevant amount for a single therapeutic class. The chart below shows the ARVs in PDPs in effect in 2019.

Chart 2. Antiretrovirals in PDP by presentation and participants - PDPs in force, 2019

Antirretroviral Drug	Presentation	Proposing OPL	Technology holder or developer	Private partner entity	Year of submission of the Term of Commitment	PDP phase
Atazanavir	Capsule (200mg; 300mg)	Farmanguinhos	Bristol-Myers Squibb	Nortec	2011	III
Darunavir	Coated pill (75mg; 150mg; 600mg)	LAFEPE	Janssen-Cilag	Nortec	2018	II
		LAQFA	Cristália	Globe	2018	II
Dolutegravir	Coated pill (50mg)	LAQFA	Cristália	Cristália	2017	I
		LAFEPE	Blanver	Nortec	2018	II
Entricitabine + Tenofovir	Coated pill (200mg+300mg)	Farmanguinhos	Blanver	CYG Biotech e Nortec	2018	II
		NUPLAM	GILEAD representada por GILEAD do Brasil	Nortec	2018	II
Ritonavir Thermostable	Pill (100mg)	LAFEPE	Cristália	Cristália	2010	III
Tenofovir	Pill (300mg)	FUNED	Blanver	Nortec	2009	IV
		LAFEPE	Cristália	Cristália	2009	IV
Tenofovir + Lamivudine (2 em 1)	Coated pill (300mg+300mg)	LAFEPE	Cristália	Cristália	2012	II
		Farmanguinhos	Blanver	Globe, Nortec e CYG Biotech	2012	III
Tenofovir + Lamivudine + Efavirenz (3 em 1)	Coated pill (300mg+300mg+ 600mg)	Farmanguinhos	Blanver	Globe, Nortec e CYG Biotech	2012	II

Source: Prepared by the authors based on Brazil, 2019a.

Therefore, 13 PDPs oversaw the production of eight ARVs. This number corresponds to 15% of the 85 drug PDPs in force, a significant portion for the same therapeutic class. Of the 14 participating official laboratories, 5 are involved with ARVs, which points to the little variability of the national participants, reinforcing the argument of technological specialization and pointing to limits to the expansion of the portfolio. If, on the one hand, this increase could reduce the

dependence on a single product and include other advantageous products, on the other hand, should the new drugs have routes very different from the one adopted, the investment would be excessively high, and could generate delays or jeopardize the completion of the process.

Of the 13 PDPs in effect, six were formalized as of 2017, evidence that these drugs remain attractive. It is worth noting that domestic private companies are also interested in ARV production since they are in four of the six partnerships.

Considering the drug substitutions foreseen in clinical protocols with ARVs (BRASIL, 2019b), it is anticipated that the use of some products in PDP will decline, as is the case of atazanavir. The same will happen with tenofovir monodrug since its use in fixed dose combined with other ARVs is therapeutically superior. As with efavirenz, demand for this drug will be dramatically reduced. For these reasons, the PDPs for atazanavir and tenofovir may be outdated and their continuation should be reconsidered or scaled back.

In the case of ARVs, radical innovations have been scarce and fixed-dose combinations of drugs have had a successful horizon. An example of this is the establishment of PDPs to produce unprecedented combinations of antiretroviral drugs in the country, such as the "2 in 1" used by more than 300 thousand people and the "3 in 1", in use by about 200 thousand. This effort was successful in the PDP for the "2 in 1" between Farmanguinhos/Blanver/Globe, Nortec-CYGBiotech, which reached phase III, i.e., the stage in which the effective technology transfer takes place. However, the second consortium for "2 in 1"(LAFEPE/Cristália) and the "3 in 1" (Farmanguinhos/Blanver/Globe-Nortec-CYGBiotech) stalled at phase II because they could not overcome the technological risk involved in developing the combinations (PIMENTEL, 2018). The "3-in-1" is being purchased from Indian laboratories through the Pan American Health Organization (PAHO).

The ritonavir tablet has been delivered by Lafepe on a PDP basis for over a year and represents an important innovation. Its previous presentation, in soft capsules, required refrigeration, which posed challenges for distribution and preservation. Finally, darunavir and dolutegravir are drugs that are expected to see increasing use and their PDPs remain important for AIDS policy.

Chart 3 shows the PDPs of ARVs that have been terminated. Unfortunately, the Ministry of Health does not provide information about the stage of production at which these PDPs were terminated, which would allow us to infer the hardships

they experienced. However, it is known that three out of five were terminated after 4-5 years from the signing of the term of commitment, which is a long period, considering the maximum term of 10 years for a PDP. In the case of drugs like darunavir and "3 in 1" the claim of "demand reduction" for the extinction is not justified since these drugs are still widely used and are also the subject of other current Partnerships.

Chart 3. Antiretrovirals in PDP by participants, year of signing the Term of Commitment, year and reason for termination, 2019

Antirretroviral	Proposing OPL	Private partner entity	Year of signing the Term of Commitment	Year of termination	Reason
Darunavir	Farmanguinhos	ApotexPharmchem, NT Pharm and Globe	2013	2015	Project failures
Lopinavir + Ritonavir	Farmanguinhos, FURP and IQUEGO	Cristália	2012	2017	Production not relevant due to reduced demand by the final area
Raltegravir	LAFEPE	MSD and Nortec	2011	2015	Production not relevant due to reduced demand by the final area
Ritonavir (soft caps.)	LAFEPE	Cristália	2012	2015	Excessively high investment due to the need to adapt the manufacturing area and equipment acquisition
Tenofovir + Lamivudine + Efavirenz (3 em 1)	LAFEPE	Cristália	2012	2017	Production not relevant due to reduced demand by the final area

Source: Prepared by the authors based on Brazil, 2019a.

There are two cases in which the justification for extinction is adequate. Lopinavir+ritonavir was removed from the SUS basket and raltegravir suffered a drop in demand due to the expansion of its replacement by dolutegravir. The justification

for the cancellation was the reduction in demand by the final area, which is consistent with the decrease in the use of these products. Such examples illustrate the importance that market research capabilities and interaction with the AIDS program play in preventing the entering into PDPs with obsolescence potential.

Although the PDP policy seeks to nationalize production to cheapen access to products, there are situations such as that of tenofovir, which is produced by Gilead - manufacturer of the branded product and sole supplier to the Brazilian government that present important challenges. During the 2000s, this drug was subject to price negotiations and measures to address the patent barrier until its production by PDP was announced in 2009. That same year, the patent application for this product, applied for by Gilead, was definitively rejected by the National Institute of Industrial Property (INPI) after a long process, during which there were several challenges to the company's application. The following year, faced with the prospect of local production and the loss of the monopoly, Gilead reduced the unit price of its drug by 40% (CHAVES, 2018). Gilead's response can be considered a dumping action, in which the company that lost market position makes the reduction as a way to maintain access to the public market and delegitimize the PDP (TEMPORÃO; GADELHA 2018).

The price issue deserves further examination. Before PDPs, it was already possible to find generic versions of tenofovir in the international market. Some researchers estimate that the local product, while cheaper than the price paid before the PDP, cost ten times more than the available international generic (CHAVES, 2018). Therefore, price regulation in environments of limited competition cannot be based solely on the development of local production, but also needs to articulate strategies such as tackling patent protection and monitoring the product in the international market. However, Temporão and Gadelha (2018) suggest analyzing prices considering the long-term effects, otherwise it mistakenly discredits PDPs and corroborates the position of pharmaceutical oligopolies - precisely what these partnerships seek to minimize.

Another consequence of the price reduction made by Gilead was the decrease in the price paid by the MoH to the OPL participating in the PDP. This measure brought savings to the national treasury, but harmed the policy, since it generated legal uncertainty and decreased the revenue of the public laboratory, also reducing the payback margin to be used for investments (PIMENTEL, 2018).

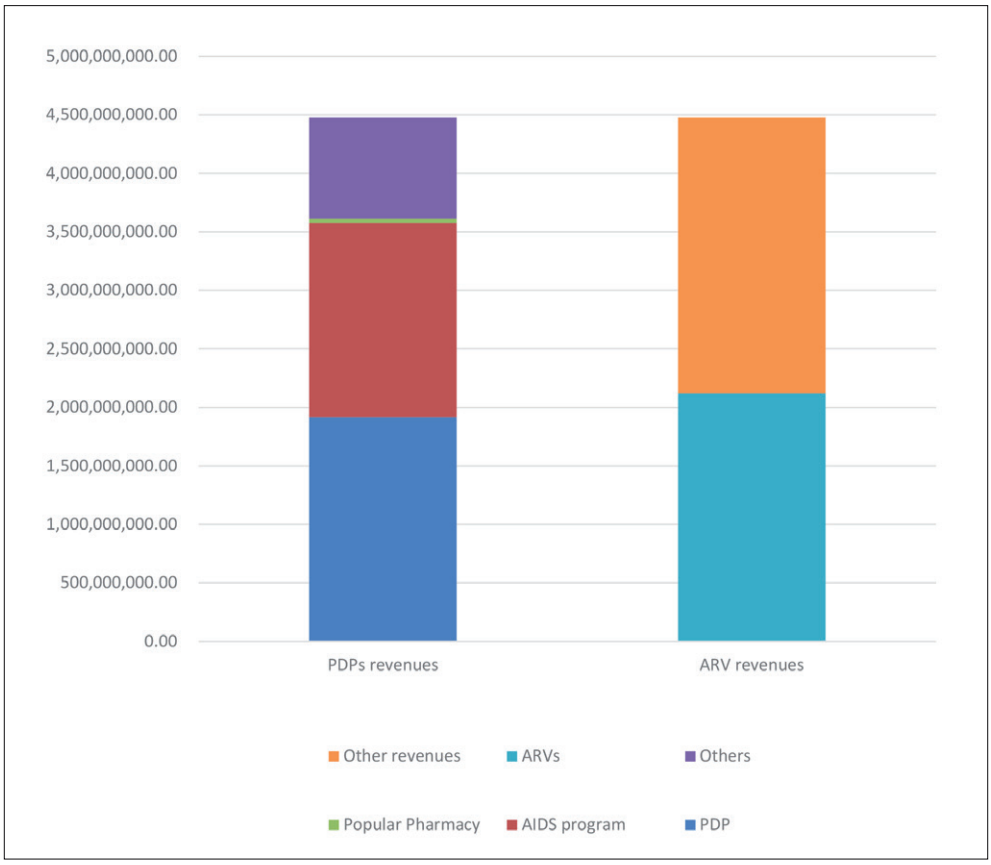
As for Farmanguinhos' participation in PDPs, it was the public laboratory with the highest number of partnerships already approved by the MoH. Since the beginning of the program in 2009, 23 were approved, 22 of them for medicines and one for Research and Development (R&D). Ten years later, 11 were still in effect (of which 3 were suspended) and 11 had been extinguished (BRASIL, 2019a). Among the active ones, ARVs predominated (4), which is consistent with the laboratory's production tradition. The other PDPs were antivirals (2, 1 of which was suspended); antineoplastics (2, 1 of which was suspended); immunosuppressant (1); tuberculostatic (1), and antiparkinsonian (1, suspended). As can be noted, all of them were intended for high-cost drugs for the SUS and/or with heavy dependence on imports, except for only one, which was focused on the treatment of tuberculosis (BRASIL, 2019a).

Portfolio expansion is one of the major interests of this laboratory, but it presents other risks. For example, the partnerships that lacked affinity with the original Farmanguinhos portfolio faced more complex, costly, and time-consuming trajectories. Most of the cancelled partnerships fit this situation. As of 2017, choosing products that had greater adherence to existing lines corrected this problem (FERNANDES, 2019).

Some difficulties identified in the Farmanguinhos PDPs were the high average time for completing phase II - which delayed selling the product to the MoH - and phase III after the first supply to the MoH, especially in the transfer of API technology. In two partnerships, phase III was extended without starting commercial production of the drugs. In such a case, the MoH is exempted from the purchase exclusivity and the laboratory is obliged to resort to other financial sources to complete the internalization of the technology. The two-phase III partnerships (atazanavir and "2-in-1") that were delayed in 2018 had already started their shipments to the MoH, and one of them had internalized the API of "2-in-1" by Blanver, a Brazilian private partner, and the other (atazanavir) was still producing with imported API (FERNANDES, 2019).

Despite the problems listed, in the case of Farmanguinhos, revenues from PDPs have become a significant component of its budget. Between 2009 and 2017, earnings from PDPs were the second largest source, below only those from the AIDS program, as shown in the first column of the graph below (in current values). The second column shows that the total revenue from ARVs, added to the revenue of the AIDS program with the PDPs of these drugs, totaled almost half of the revenue. The high percentage shows the relevance of ARVs in its technological trajectory and in sustaining its portfolio.

Graph 1. Distribution of Farmanguinhos' revenue sources 2009-2017



Source: Prepared by the authors based on data provided by Farmanguinhos (2018)

Final considerations

This article has shown that the establishment of PDPs has opened new perspectives for the development of the policy of universal and free provision of ARVs. Given the heavy expenditure on imported ARVs in the SUS basket, the strategy of nationalizing production is an option to ensure drug treatment for people living with HIV and AIDS, promote greater sustainability of the MoH's financial expenditures on drugs, reduce technological dependence on the local manufacturing sector and, consequently, increase the overall sustainability of the SUS itself.

Therefore, it is not surprising that PDPs have prioritized ARVs. These drugs are very relevant to public health, besides encouraging technological innovation, increased production capacity, and revenue for national public and private producers.

Incorporating technology to produce fixed-dose combinations and presentation forms that facilitate treatment adherence has benefited hundreds of thousands of people living with HIV and AIDS and has generated savings for the public purse.

The main obstacles of the PDP strategy mentioned in the literature were also found among ARVs, such as delays and extinction of partnerships, which generate waste of resources and time. Furthermore, delays may imply the transfer of technologies that are already obsolete at the end of the process.

The international purchase price of ARVs, as in the case of tenofovir, has shown that the availability of cheaper versions of the products should be evaluated and may be an additional possibility to increase access to medicines. However, buying at a lower price as a single strategy does not leverage domestic production or reduce the external dependence of the SUS.

This article also showed that in the public supply of ARVs, Farmanguinhos has regained the leading role in the AIDS program. Currently, it is the OPL that supplies most of these products to the MoH, and it is also the one with the highest revenues. Although imported drugs still predominate in the basket and in the MoH AIDS program budget, Farmanguinhos has had its position as a key provider of local production of ARVs strengthened by the PDP. Despite the difficulties in the implementation of the partnerships, the gains with the incorporation of technological competencies, expansion of the portfolio, and economic sustainability, in view of the increase in revenue, were significant.[1]

Acknowledgements

This research received financial support from CNPq (process 401820/2015-7) and from the Vice-Direction of Research and Innovation/ENSP-Fiocruz.

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Note

[1] R. F. do Lago and A. C. A. de Sousa: conception, data analysis, drafting and approval of the final version.

Resumo

A oferta pública de medicamentos para aids e o papel de Farmanguinhos

Este artigo descreve e analisa a participação do Instituto de Tecnologia em Fármacos (Farmanguinhos) na produção local de medicamentos antirretrovirais no Brasil. São também apresentadas as mudanças no padrão de provimento, a situação das parcerias para o desenvolvimento produtivo e a posição dos produtores nacionais para esses medicamentos. As estratégias metodológicas foram revisão bibliográfica, análise de documentos oficiais e dados fornecidos por Farmanguinhos e pelo Departamento de Condições Crônicas e Infecções Sexualmente Transmissíveis do Ministério da Saúde, via Lei de Acesso à Informação. Este artigo mostra que o estabelecimento das parcerias abriu novas perspectivas para o desenvolvimento da política de oferta pública de antirretrovirais para as pessoas vivendo com HIV, por contribuir para a sustentabilidade das despesas financeiras do Ministério da Saúde com medicamentos. Farmanguinhos é o laboratório público que fornece mais quantidades e recebe os maiores valores provenientes do fornecimento desses produtos ao Ministério da Saúde. Embora os medicamentos importados preponderem largamente em quantidade e valores pagos pelo Ministério da Saúde, Farmanguinhos permanece sendo um provedor fundamental na produção local de antirretrovirais. Apesar dos problemas verificados nas Parcerias, os ganhos nas competências tecnológicas na produção de antirretrovirais podem ampliar o horizonte tecnológico e produtivo do laboratório.

➤ **Palavras-chave:** Políticas públicas de saúde. Antirretrovirais. Indústria farmacêutica.