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*** Original article**

The Official pharmaceutical laboratories and their relevance to Brazil's public health

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Jorge Lima de Magalh_es
School of Chemistry, Federal University of Rio de Janeiro - EQ/UFRJ; Pharmaceutical Technology Institute of the Oswaldo Cruz Foundation - Farmanguinhos/Fiocruz. Rio de Janeiro, Brazil.
jorgelim@far.fiocruz.br

Adelaide Maria de Souza Antunes
School of Chemistry, Federal University of Rio de Janeiro - EQ/UFRJ; National Institute of Industrial Property - INPI. Rio de Janeiro, Brazil.
adelaide@eq.ufrj.br

N_bia Boechat
Pharmaceutical Technology Institute of the Oswaldo Cruz Foundation- Farmanguinhos/Fiocruz. Rio de Janeiro, Brazil
boechat@far.fiocruz.br

Abstract
This paper identifies the current portfolio of the Brazilian Network for the Public Production of Medicines (RBPPM) and evaluates the modernization and expansion of the Official Pharmaceutical Laboratories (OPLs) production capacity in the last seven years. Investments of about R$ 300 million have been made to expand the annual installed capacity from 5 to 16.6 billion Pharmaceutical Units**1** (PUs). The work consisted of interviews, literature searches and queries to the database of the Official Laboratories Association, National Health Surveillance Agency (ANVISA), Ministry of Health (MS) and Ministry of Science and Technology (MCT). According to the RBPPM portfolio, 99% are similar drugs and the majority of the registers address hypertension and analgesia treatments. The laboratories structure can be considered national property, not only because they produce drugs neglected by the private industry but also because they serve as price regulators and have the potential to develop new pharmaceutical products and formulations. The leading Official Pharmaceutical Laboratories are skilled and competent both in human resources and infrastructure, causing OPLs to be strategic to the MH, thus contributing to the relevance in healthcare.

Keywords:
Official Pharmaceutical Laboratories; Public Production of Medicines; Public Health; Pharmaceutical Industry

Introduction

The improvement of mankind's life quality has contributed to healthier aging and longer life expectancy. Among other factors, such rise in the population age results from the availability of new drugs for treatment of several chronic diseases like diabetes, hypertension, dyslipidemia, etc. (ACHILLADELIS *et al.*, 2001; IBGE, 2000).

The global pharmaceutical industry has grown significantly, generating 773.1 billion US dollars in the year of 2008. This outcome represents 4.8% of growth in relation to the previous year and an average of 6.6% per year, if compared with the evolution since 2003. The leaders of this industry are the following nations: U.S.A., Japan, France, Germany, China, Italy, Spain and United Kingdom (IMS, 2009, 2010).

A *IMS Health* study in 2010 reports an unprecedented expansion of the "Pharmerging" market. This term refers to the new classification adopted by the *Intercontinental Marketing Services Health Inc* (IMS) to determine the 17 emerging markets with high potential of growth in the period of 2009 to 2013, in which Brazil is included. It is expected that the revenues increase in the pharmaceutical market worldwide reaches 90 billion US dollars, which would enable an annual growth of 48% in the global economy in 2013, much higher than the 37% reported in 2009. The same study reports significant changes in the economic overall and health market, including an increased level of access to healthcare and funding.

Brazil has a significant presence in this market due to a growth of 10 billion US dollars/year. With his background, the country occupies the 9th position in the world ranking in revenues, surpassing economies like Canada, Russia and India (MAGALHÃES *et al*., 2008b; IMS, 2010).

This scenario has partially been built by public policies, aiming at the population's access to essential medicines. Studies conducted by the Brazilian Institute of Geography and Statistics (IBGE) point out that 15–20% of the country's population have no access to medicines and 51% earn up to 4 minimum wages. To cope with this situation, the Ministry of Health, through its Unified Health System (SUS), has increased the free supply of the pharmaceutical products indicated in the National List of Essential Drugs (RENAME) (MAGALHÃES *et al.*, 2008a). Considering all pharmaceuticals distributed by SUS (basic care**2**, AIDS etc.), the financial amount achieved reaches R$ 6.8 billion. According to the Ministry of Health, spending on exceptional (or very expensive) drugs increased from R$ 516 million in 2006 to R$ 2.3 billion in 2009 (BRASIL, 2008a).

As shown by Barata (1997, p.531-74), achievements like the right to health, as established in the 1988 Brazilian Constitution, Article 196, section II, and the establishment of SUS by Law nº 8080 (Sept 19, 1990), have contributed to change the country's epidemiological profile. Therefore, we might conclude that Brazil has emerged as a changing society that seeks to cope with the issues of pharmaceutical assistance and healthcare with emphasis on Health Promotion and Prevention (ABIQUIF, 2007; BARROS, 2004).

According to Monteiro (2003), poverty is directly related to the non-satisfaction of the basic human needs, among them healthcare. Records contained in a study conducted by the Ministry of Health (BRASIL, 2006F) corroborate this fact by showing a decrease of 50% to 5.2% of deaths by infectious or parasitic diseases in the years of 1930 to 2003. This fact is motivated by Public Health policies and actions, among them the access to MH programs, such as AIDS, malaria, tuberculosis, leprosy, etc.

In this approach, one of the Brazilian government's actions regarding healthcare is the incentive to public production of medicaments to diminish the country's dependence. The producers, the Official Pharmaceutical Laboratories (OPL), act not only in manufacturing, but they are strategic as policy inducers, in the development of new formulations and drugs as well as prices regulators in the domestic market. This can be confirmed by an experience in 2005: when the MH announced to have technological capability to produce the antiretroviral drugs Efavirenz, Nelfinavir and Lopinavir, the prices of private laboratories dropped 59%, 40% and 46%, respectively (ANTUNES *et al.*, 2008).

Thus, this paper shows the evolution of OPLs with respect to infrastructure increase over the years and the relevance of these laboratories for the Unified Health System (SUS), both in developing competences and providing management tools to the Brazilian government.

Methodology

Literature searches were made in databases indexed by Scielo, Medline, Lilacs and ScienceDirect. Regarding the field survey, this was made in four federal OPLs located in Rio de Janeiro, and the others by means of telephone interviews and questionnaires sent by e-mail or fax.

The survey was made by invitation to all OPLs that are members of the Brazilian Association of Official Pharmaceutical Laboratories (ALFOB**3**) and in the MH website, besides inquiries to the database of ANVISA (National Health Surveillance Agency) for confirmation of their portfolios.

The information and data obtained were processed by Excel (Microsoft *Office* 2003) and produced tables and charts, and the indicators obtained were used for the analyses and assertions contained in this work.

For reasons of reliability and ethics, the OPLs will be referred as to A-L in this study. However, regarding the portfolios and installed capacity, the names are disclosed.

The Official Pharmaceutical Laboratories and the Brazilian Network of Public Production of Medicines

Twenty-three active OPLs**4** were identified. They are located in the Northeast, Mid-West, Southeast and South regions and comprise the Public Production of Medicines (RBPPM) and the majority belongs to ALFOB. Figure 1 shows the geographic arrangement of the OPLs, and those marked with stars are the states where laboratories are being implemented.

Figure 1: Geographical distribution of OPLs

Source: Adapted from ANTUNES and MAGALHÃES, 2008.

Responses to the survey represented 65% of the OPLs; however, the remaining 35% were considered irrelevant for the present purpose, because they did not represent 1% of the installed capacity.

ALFOB has the objective of serving as a management tool for the 20 member laboratories and also aims to encourage improvements on pharmaceutical production under government (MAGALHÃES *et al.*, 2008a).

In 2005, the Ministry of Health, with the purpose of organizing and optimizing management and the initiatives of promotion and technological development of the OPLs, created the BNPDP (BRASIL, 2005b). Joining the network is institutional and the focus is on the development of actions that aim at the reorganization of the official system for producing drugs, raw materials and inputs. Thus, it seeks to supply SUS' demands in a regular and appropriate manner, particularly to meet the public healthcare programs, such as AIDS, tuberculosis and focal endemics, for which the OPL's output is unique and strategic.

Of the 21 member OPLs, 13 are held by state governments, 4 to universities and 4 are federal units (3 belong to the Armed Forces: Navy, Army and Air Force, and 1 directly to the Ministry of Health – Farmanguinhos). Also, there are 2 official laboratories that are not members of ALFOP: the Center of Pharmaceutical Technology of the State of Piauí (NTF), belonging to the Federal University of Piauí (UFPI) and the Pharmaceutical Laboratory of the State of Santa Catarina (LAFESC) (ANTUNES *et al.*, 2008). Seven additional laboratories are being implemented: Foundation of the University of Amazonas (FUAM), Pharmaceutical Laboratory of Sobral (LAFAS), State University of Feira de Santana (UEFSFARMA), Clinical Laboratory and

Food Science of the Federal University of Ceará (LACT), Pharmaceutical Laboratory of Tocantins (FARMATINS), Municipal Laboratory of Manipulation and Herbal Medicine - Itatiaia, Pharmaceutical Industrial Laboratory – University of Alfenas (UFE) (BERMUDES *et al.*, 2006).

The established OPLs have varying sizes and different technical, administrative and financial characteristics, and their main mission is to produce RENAME medicaments to meet SUS' demands. It is worth noting that these OPLs offer qualification programs in management, chemistry, pharmacy, engineering and production (HASENCLEVER, 2002; BRASIL, 2006e; MDIC, 2006).

Some laboratories have stood out over the years, like Farmanguinhos, associated to Fiocruz and located in Rio de Janeiro. In 2004, Farmanguinhos expanded its technological facilities five times with the acquisition of the former pharmaceutical manufacturing plant of GlaxoSmithKline in Jacarepaguá. Other examples are FURP – Foundation for Popular Medicine in the state of São Paulo, with its third industrial plant, LAFEPE – Pharmaceutical Laboratory of the State of Pernambuco, FUNED – Ezequiel Dias Foundation in the state of Minas Gerais and IQUEGO – Indústria Química do Estado de Goiás S/A.

This BNPDP productive public complex serves the Ministry of Health by producing drugs in the most diverse pharmaceutical forms (tablets, liquids, ointments, etc) and different therapeutic classes (pain killers, antiretroviral and antihypertensive drugs, antibiotics, vaccines, etc.) (TEMPORÃO *et al.,* 2005).

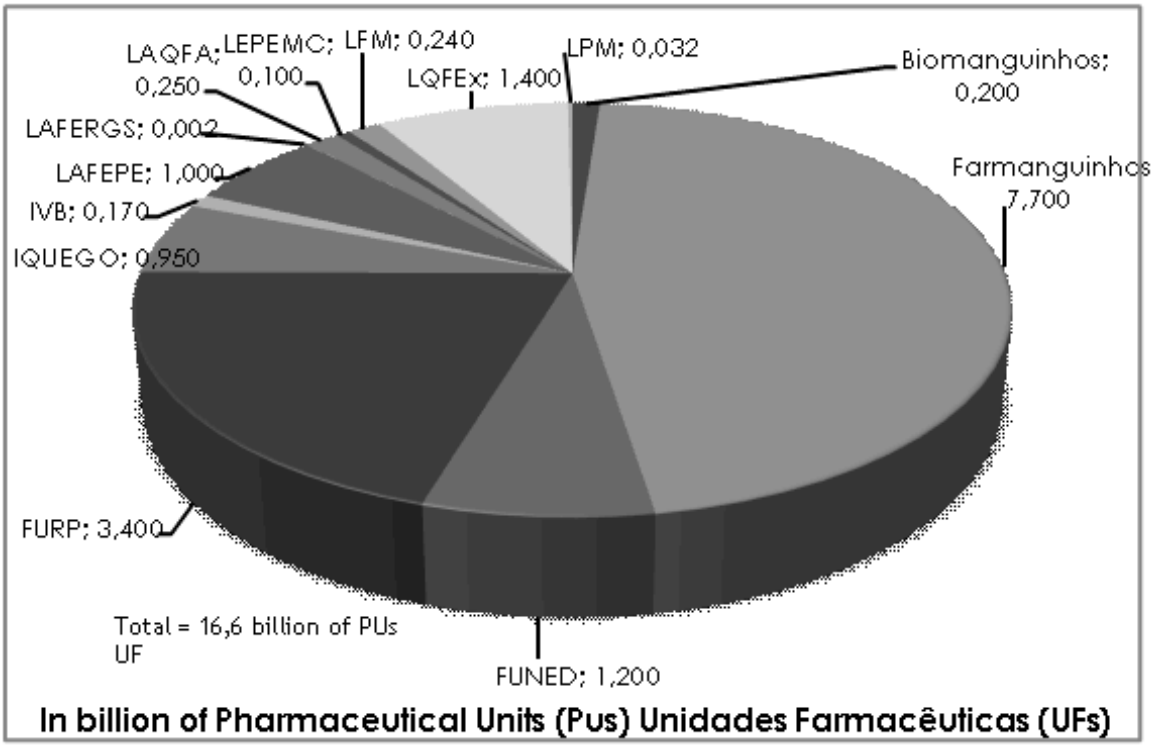
The State seeks to stimulate innovation among the productive complex**5**, health services and the educational/research institutions (GADELHA *et al.*, 2003; GADELHA, 2005). Therefore, investments have been made in the modernization and expansion of OPLs' manufacturing facilities over the last years (more than R$ 271.5 million), particularly in the leading public laboratories like Farmanguinhos, FURP, LAFEPE, FUNED and IQUEGO (MDIC, 2006). However, the analysis suggests that even with financial supports, these OPLs are still lagging behind the private sector, both in technology and processes and products as well.

The government has made efforts to keep the OPLs as a national patrimony. For this purpose, three ministerial ordinances were enacted (BRASIL, 2008c; 2008d; 2008e) emphasizing their importance to the country's technological sovereignty and assurance of national security**6**. The OPLs thus take a bolder approach as Brazil's inducers to increase its innovation capacity and also to enlarge their market shares beyond the national borders.

Portfolio of the Official Pharmaceutical Laboratories and production to the Unified Health System (SUS)

As shown in Graph 1, the installed capacity of BNPDP represents a potential of 16.6 billion of Pharmaceutical Units/year. FARMANGUINHOS, FURP, LAQFex, FUNED and LAFEPE are the leaders with larger production capabilities, representing 80% of the total capacity of the Network. The graph should be in grayscale.

Graph 1: Potential of the OPLs' installed capacity for drugs production



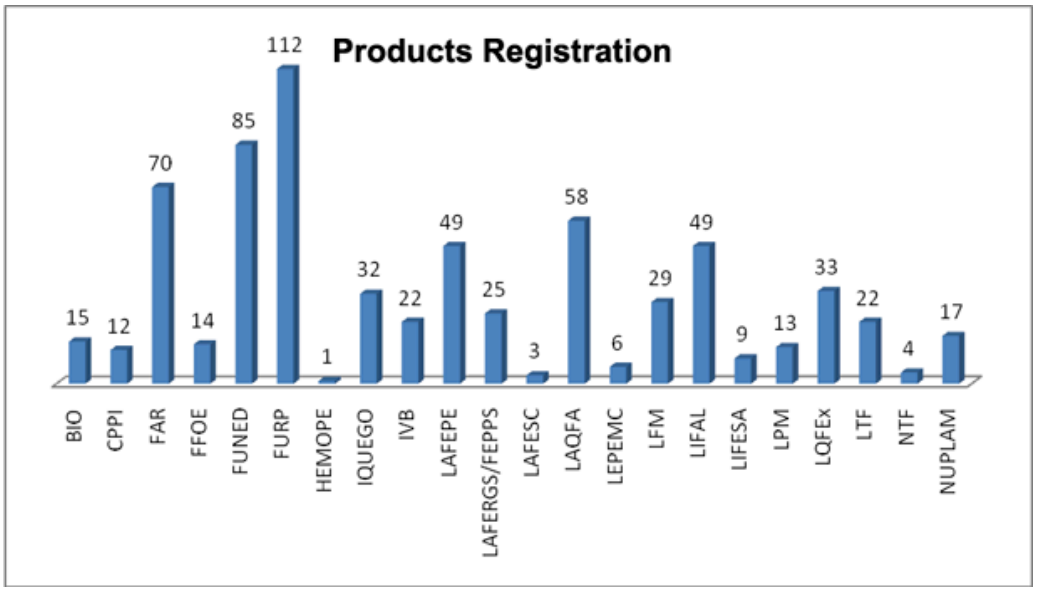
Source: Prepared by the author based on the field survey

Even with this potential, the demand of the Ministry of Health is not supported by the OPLs to meet the entire scope of RENAME, as well as the lists of medicines of the state and city governments. Created in 1975, this list is revised periodically, resulting in gaps in the OPLs' portfolios. The capacity of the OPLs to respond with the development and register of new products is estimated to take three years**7**, because this involve the development of pharmaceutical technologies for the formulations, processes and analytical methods and finally the register of the new products with ANVISA and thus obtain authorization for commercialization (MAGALHÃES *et al.*, 2008a).

One of the factors that contribute to RENAME's continuing review is the scientific evolution in discovering new pharmaceuticals and the pressure of nonprofit organizations to use these drugs. Also important are the fabulous campaigns promoted by private laboratories, always claiming to have higher efficiency in their new associations and/or formulation than usual. Therefore, the gap between RENAME and the OPLs portfolios tends to increase, and the State is compelled to include new drugs to the list, even if they still do not show resistance to the conventional treatment (BERMUDEZ, 2004; 2006).

The number of products available by each OPL is shown in Graph 2. Even with a lagging portfolio, we can see the significant presence of FURP with 112 registrations, followed by FUNED with 85 registrations, and FARMANGUINHOS, 70.

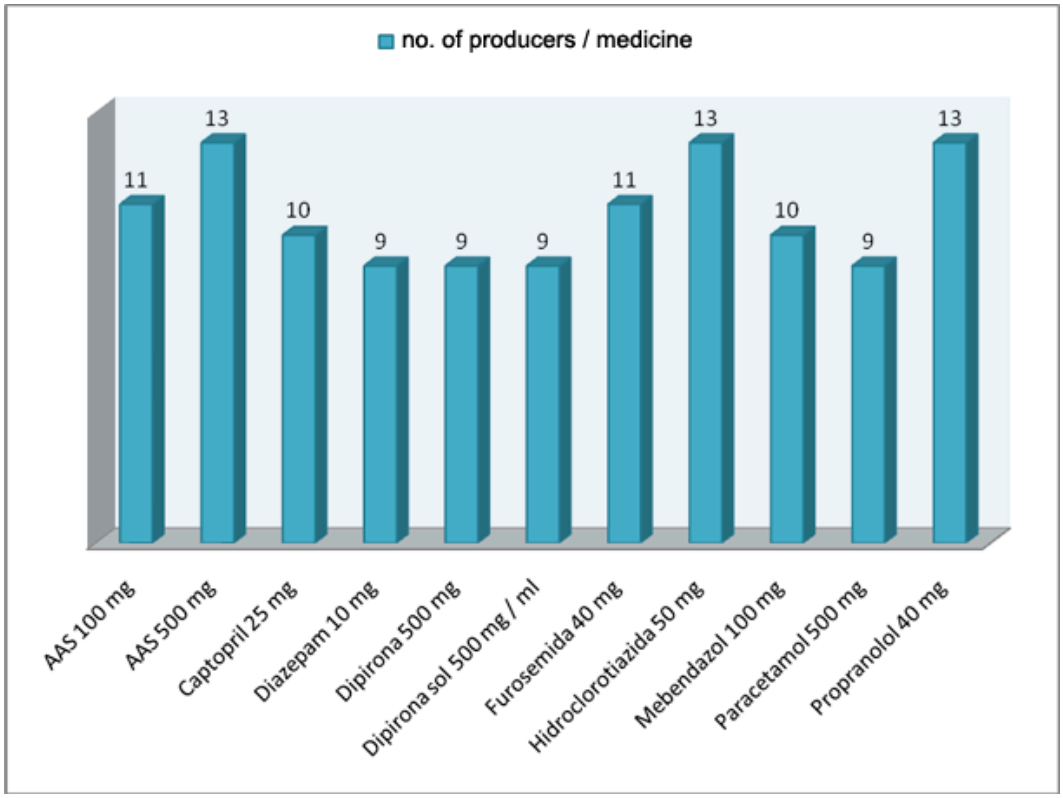
Graph 2: Amount of products fabricated by the official pharmaceutical laboratories



Source: Prepared by the author based on the field survey

In BNPDP there are 309 entries, from which 9% are for hypertension and diabetes treatment and analgesics, which are represented in the type of drugs produced by 65% of the total OPLs. Graph 3 shows the eleven drugs with the largest number of manufacturers.

Graph 3: Drugs with the largest number of official producers - OPL



Source: Prepared by the authors based on the field survey

The products available in the BNPDP include the following therapeutic classes: antibiotics, tranquilizers, antiparasites, antiulcers, anticonvulsants, antihelminthics, antimalarials and antiviral drugs. Some also produce fitotherapic medicines and cosmetics.

The entries are too numerous to be shown in this paper; however, for a better understanding of the methodology used in the survey, the antiviral-producing OPLs**8** were extracted from the list as shown in Table 1. In 2009, these drugs moved more than R$ 1 billion and began to be available in the public network in the early 1990s. The first antiretroviral (ARV) produced by a LFO was AZT (Zidovudine), the pioneers being LAFEPE, FURP and Farmanguinhos in 1993, 1997 and 1998, respectively. Currently LAFEPE has 19 registrations of ARV, followed by FARMANGUINHOS with 14 registrations, and IQUEGO with 12.

Table 1: Antiviral-producing OPLs in 2009

PRODUCT	QUANTITY OF AV AND ARV PRODUCERS									N_ OF PRODUCERS OF THE DRUG
	FAR	FUNED	FURP	IQUEGO	IVB	LAFEPE	LFM	LAQFA	LIFAL	
Aciclovir 200 mg tabs						■				1
Aciclovir 400 mg tabs						■				1
Aciclovir 250 mg inj.sol.						■				1
Didanosine 25 mg tabs	■	■	■	■	■	■	■	■	■	9
Didanosine 50 mg tabs	■	■	■	■					■	5
Didanosine 100 mg tabs	■	■	■	■	■	■	■	■	■	9
Didanosine 100 mg powder		■				■			■	3
Didanosine 4 g powder						■				1
Efavirenz 600 mg tabs	■					■				2
Stavudine 15 mg CPS					■		■	■		3
Stavudine 20 mg CPS	■		■	■	■	■	■	■		7
Stavudine 30 mg CPS	■		■		■	■	■	■		6
Stavudine 40 mg CPS	■		■	■	■	■	■	■		7
Stavudine 1 mg/mL						■				1
Indinavir 400 mg CPS	■		■	■		■			■	5
Lamivudine 150 mg tabs	■	■	■	■	■	■		■		7
Lamivudine 10 mg / mL				■				■		2
Lamivudine + Zidovudine 150 mg + 300 mg tabs	■	■	■	■	■	■	■			7
Lamivudine + Zidovudine + Nevirapine 150 mg + 300 mg + 200 mg tabs		■								1
Nevirapine 200 mg tabs	■	■		■					■	4
Oseltamivir 75 mg CPS	■									1
Ribavirin 250 mg CPS	■									1

Ritonavir 100 mg CPS											1
Tenofovir 300 mg											1
Zidovudine 100 mg CPS											6
Zidovudine 250 mg CPS											4
Zidovudine 10 mg/200 mL											3
Total of 27 entries	Entries per OPL	14	11	11	12	8	19	9	8	7	

Note: OPLs not producing ARV: Biomanguinhos, CPPI, FFOE, Hemope, LAFERGS/Fepps, LAFESC, LEPEMC, LIFESA, LPM, LQFEx, LTF, NTF and NUPLAN.

Source: Prepared by the authors based on the field survey

The overall percentage of official resources allocated to the purchase of all of medicines included in the public network is approximately 20%, while in the private sector is 80%, due to the existing diversification and the presence of many drugs under patent and, therefore, not produced by the OPLs (BOECHAT, 2003; BNDES, 2006).

Thus, the existing disparities between the purchase of medicines in the private and public sectors are evident, with two existing markets, public and private, acting concurrently and not competing with each other.

The OPLs production is primarily destined to people lacking resources. Looking at the data of IBGE (BRASIL, 2006g), they show that ¾ of the Brazilian population are users of the SUS system and earn up to four minimum wages, accounting for 16% of the market consumption of medicines. As a result, as the demand of SUS is available free by the MH, the OPLs fill an essential gap.

Evaluation of the competences and infrastructure of the Official Pharmaceutical Laboratories

In this section, our concern was to demonstrate the OPLs' human resources and facilities existing until 2007. It was observed that the composition of the technical staff is distributed in a very variable form. These specialists are assigned according to diverse areas of knowledge, and the capabilities and size of each OPL.

It was identified that the network has 5130 collaborators**9** distributed throughout the organization, with educational degrees ranging from high school to masters and doctors. The OPLs that have the five largest work forces are (in ascending order): FUNED, LAFEPE, FARMANGUINHOS, LIFAL and FURP (HASENCLEVER, 2002). Of note is the number of masters and doctors in Farmanguinhos.

Graduated professionals correspond to an average of 40% and researchers with master and doctor degrees are fewer in number. On the other hand, professionals with junior and senior high school degrees represent 60% of the work force.

In the team's composition, the OPLs seek for professionals with over 10 years of knowledge. However, when comparing to the total employees, the predominant time varied from 6 to10 years. Still in this regard, seven laboratories reported having less than 30% of professionals with up to 5 years of experience. In contrast, 70% of the work force of the "E" and "K" laboratories has more than 10 years of experience and only the "E" laboratory has 70% of professionals with less than 5 years of experience.

When the OPLs were questioned about the percentage of turnover invested on training, the "A" laboratory reported using 10%, "B" 5%, and the others from 0.12% to 0.5%.
With respect to the technology prevailing in BNPDP, the existing technology is for the production of tablets (plain and coated), followed by (less intensive) oral liquids, serums, injectables, capsules, creams and ointments, salts and powders.

For the production of these medicines, the OPLs have equipments of the last generation (imported) and old, national ones. The time of usage is between 6 to 10 years, but the "A", "B", "J" and "L" laboratories claimed having machines with the latest technology, with less than 5 years, while "F" has machines working for more than 20 years.

The equipments require qualification**10**, which is a requirement of the Good Manufacturing Practices (RDC 17 of 19/04/2010 of ANVISA)**11**, and is present in greater or lesser extent in the BNPDP. The equipment qualification program (EQ) was found to be as follows:

- 9 OPLs completed 75%
- 2 laboratories completed 25%
- 1 laboratory completed 50%
- 2 laboratories completed 100%

In this scenario, about 75% of the laboratories claimed to have competence to manage their activities with regard to facilities (infrastructure), production processes, production planning and control. The remaining 25% need qualification in all these areas.
Regarding the potential for Research and Development (R&D) for medicines production, six laboratories claimed to launch an average of 1 to 2 products/year. In 2007, "A", "B", "D", "G", "H" and "J" laboratories reported that they expected to launch 6, 4, 2, 4, 1 and 2 new products, respectively. However, these results were not followed up by the present work.

The scope of development of new drugs by the OPLs is defined according to the health programs existing in the city, state or even in federal level. In other circumstance, "H", "J" and "K" laboratories assured that they define their portfolios to comply with the specific interests of the Ministry of Health to which they are subordinated.

The competences or capabilities that are under development in 90% of the BNPDP are:

- Wet granulation by the single pot**12** system.
- Granules or particles coating
- Suppliers' qualification
- Processes validation
- Cleaning validation
- Equipments validation
- Processes by direct compression
- Development of formulations

Regardless RENAME's demands, the OPLs reported that they would like to develop some kinds of pharmaceutical technologies, among them:

- Nasal medicines and lung sprays
- Biotechnological medicines
- Implementation of R&D for medicines
- Tablets coating
- Development of drugs with long lasting effects.

It is worth noting that some OPLs already have know-how for some of these technologies, such as for tablets coating. The expectation is that when the BNPDP is fully consolidated, sharing of this knowledge becomes a reality among the OPLs.

Production of similar, generics drugs and the quality of chemicals

To meet Law 8666, the OPLs concentrate their production in similar drugs**13**, differently from the private laboratories. This law regulates procurement tenders and contracts in the range of the Public Administration and establishes that all purchases are made at the lowest price. As the private sector is not subject to this law and follows the Generics Law (nº 9.787, 1999), they buy raw materials (RM) from qualified suppliers**14**. This dichotomy exists because the market price of a qualified RM is usually higher in order to ensure the reproducibility of production inputs and the medicine itself. It is also claimed that the Generics Law requires qualification of three suppliers and that the RM be always purchased from one of them, contrary to Law 8666, where it is not possible to direct purchases in the public service.

Notwithstanding the above, "B" and "F" laboratories have already succeeded in producing generics and each one has already registered one product, a result of the evolution in research and partnerships. However, the main difficulty is found in the RM procurement process, particularly when another supplier offers a lower price than that of the qualified supplier. The OPL is not allowed to buy the qualified RM due to the Law 8666 and cannot manufacture the generic drug if it buys the RM with the lowest price.

It is also worth noting that the production of generics can represent an important qualification for the OPLs that wish to export their medicines to developing countries or transfer technology (QUENTAL *et al.*, 2006).
In addition to the production of similar or generic drugs, the "C" was identified as an exception, also acting in the field of cosmeceuticals. Such innovation, explains the laboratory, is to meet a specific health program in their state, where workers who are exposed to sun, such as street sweepers, postmen, among others, need sunscreen.

The OPLs reported many problems, among them difficulties to develop robust, consistent formulations due to the considerable variability of the RM received from their suppliers. The R&D staff reported that the laboratory informs the specifications for the RM in the procurement process. But even if these products are chemically equivalent, they may present peculiarities in their physical characteristics that are not always described in official analytical methodologies. So, the quality of the RM varies according to the supplier and fabrication lot, causing difficulties in the definition of a consistent pharmaceutical formulation.

Farmanguinhos and FURP laboratories reported losses of up to 30% of the final product delivered as a consequence of the lack of standardized RM. This problem could be minimized by purchasing pharmaceutical raw materials from qualified suppliers to avoid the problems with the quality of raw materials that historically (last 10 years) have occurred either with domestic suppliers or imports (Farmanguinhos database, 2005).

One of the usual problems in the acquisition of RM is related to the different suppliers in the R&D and production stages. The first is to obtain the pilot lot, where all tests that will define the specifications that are necessary to obtain the registration with ANVISA are carried out. As the purchase of raw materials is under Law 8666, there is no guarantee that the supplier in future purchases, for the production stage, is the same of the product registration.

Thus, the OPLs try to find ways to encourage the domestic technological development and ensure the full quality of raw materials for the production of drugs, such as, e.g., public-private partnerships (PPP). For this purpose, the domestic RM-producing laboratories should improve their skills and capabilities to meet appropriately the needs of the drugs-producing

laboratories, among other actions, meeting ANVISA Resolutions no. 57 of Nov. 18, 2009, and RDC no. 249, of Sept. 13, 2005.

Final considerations

- The availability of drugs to the Brazilian population is still a huge challenge for the country because of SUS' growing demand. Thus, the State, among other policies, makes efforts to increase public production in an attempt to improve the access to medicines by the population.
- There are 22 Public Laboratories and 7 being established / implemented, the leading ones with common or outstanding technological resources. Thus, each government seeks to integrate, socialize and improve actions to increase the production capacity and technological development.
- The OPLs' installed capacity is a national asset that meets the Ministry of Health's demand for basic healthcare drugs and strategic programs like AIDS, leprosy, tuberculosis, malaria, etc.
- Special thoughts should be given to the OPLs' compliance to Law 8666 and the quality of drugs production regarding the reproducibility of their products and the Generics Law.
- The study showed that the BNPDP is making joint efforts with the competent authorities to enhance the quality and quantity of the domestic production of pharmachemicals. The installed capacity of the country meets only a portion of SUS' demand, not considering all RENAME.
- Finally, this work suggests that the OPLs try to adapt their porfolios to RENAME through a realignment of their R&D capabilities, besides providing bureaucratic means to expedite registrations with the competent offices.

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Notes

1 Capsules, ampoules, creams, pomades, tablets, pills, ointments and other forms.

2 According to the National Medications Policy (PNM), it refers to products necessary to rendering the cast of actions and procedures understood on the basic health attention.

3 Created in 1984, it is a social society, of national scope, non-profitable, designated in abbreviation by the acronym ALFOB. It has administrative, patrimonial and financial autonomy, reigned by statute and legislation applicable. It is headquartered and with jurisdiction in the city of Brasília/DF, with undetermined duration period.

4 There are 30 National Public Laboratories, being 21 associated to ALFOB, 2 do not have association and 7 are under implantation stage.

5 The productive health complex is a sector that drives R$ 160 billion yearly in Brazil, responding by 8% of the national PIB and 10 million jobs. Policies are being promoted using the State purchase power, as well as private-public-partnerships (PPP) (Source MS).

6 In this case, MS is understood as national dominion, the capacity Brazil has to detain technology for the production of drugs and medications in national territory, and thus strengthen its National Defense.

7 Time estimated by the author own experience, from 15 years of services on private initiative (Sanofi-Aventis) and 11 years at Fiocruz/Farmanguinhos.

8 Inside this line, there are antiretrovirals - a subdivision of antivirals.

9 It is understood as work force acting on the laboratory, all public servants, third parties and scholarships.

10 In order for a process to be validated it is necessary that the equipments forming it are qualified for the object to which they are destinated. These, on the other hand, must compose the Validation Master Plan.

11 It replaces RDC 210 by ANVISA.

12 Humid granulation system involving excipients, drugs, etc. in a same vial. This equipment makes the granulation and/or homogenization of powders in humid or dry manner, normalizes (granulates) the mass/powder, dries, and finally mixes (homogenizes). The product is sent to be transformed in the pharmaceutical form chosen (tablets, capsules).

13 They are medicines that have the same composition, concentration, dosage, form or therapeutic indication of the reference product (or brand), but have no bioequivalence with the approved reference medicine.

14 Qualified supplier goes beyond a simple economy on the cost of raw materials, it is a manufacturer or homologated representative of the raw material and must be considered the potential specialist on this subject, being the owner of technology and knowledge enough to guarantee the consumer a quality over any expectation and a permanent technical assistance. He stills provides economy on physical-chemical, microbiological and instrumental analytical controls, and all workmanship involved in the processes. In summary, the supplier must always fulfill what is established on the production program and delivery of raw materials.