Health innovation and social justice in Brazil

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General introduction : Health innovation and social justice in Brazil

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Brazil has entered a period of acute crisis characterized by a slump in industrial production, including pharmaceutical production in 2015, as well as a crisis in the Unified Health System (SUS) which faces cost cutting as growing unemployment and a decline in the use of private insurance is increasing the demand for care in the public sector[1]. Yet the systems introduced from the mid-1990s to encourage the nationalization of foreign technologies, local pharmaceutical production and access to treatment are still active. This is evidenced in the following: in December 2016 the Brazilian government and leading firms agreed on a new programme consisting of Product Development Partnerships (PDP) to acquire new health technologies and produce "strategic" medication for the SUS; in January 2017 Brazil's National Institute of Industrial Property (NIIP) dismissed Gilead's application for a patent on Truvada, a therapeutic combination for the prophylactic treatment of HIV/Aids, and in so doing authorized the production of a Brazilian generic; and the consortium formed in May 2016 by three private-sector laboratories and Fiocruz is still investing in the production of a generic sofosbuvir to supply the government's hepatitis C programme.

The past twenty years have been characterized by the revival and growth of Brazilian health industries under the combined effects of: the local medication production policy to treat the Aids epidemic from the early 1990s, initiated by private- and public-sector laboratories; the enactment of the law on generic medicines and the creation of the National Health Surveillance Agency in 1999[2]; and the policy and funding of the National Social and Economic Development Bank (BNDES) to develop the "health industrial complex", from 2003. In January 2001 the New York Times held Brazilian policy up as a model[3].

The research team that has authored this book has studied and in some cases participated directly in the progressive invention of what now resembles a full-blown innovation system, consisting of: 1) numerous technological and industrial partnerships between science, government and industry; 2) regulatory and industrial property institutions, including the National Institute of Industrial Property, the National Health Surveillance Agency, inter-ministerial groups, and civil society organizations, notably patient and citizen associations; and 3) mechanisms for the evaluation and certification of medicines, with the Health Surveillance Agency and a network of bio-equivalence centres in universities and in Contract Research Organizations (CROs).

While our first research papers published in 2003 concerned the reverse engineering work of chemists in public- and private-sector laboratories[4], who were seeking to develop techniques for the analysis, synthesis and formulation of antiretroviral drugs for HIV/Aids, this volume focuses on a subsequent phase characterized by the proliferation of collective invention structures and industrial partnerships during the 2000s and 2010s, in the form of

[1] "Brazil's health system woes worsen in economic crisis", Jonathan Watts, The Lancet, 16 April 2016.

[2] ANVISA: *Agencia Nacional de Vigilancia Sanitaria*

[3] Tina Rosenberg, "Look at Brazil", *The New York Times Magazine*, January 28, 2001.

[4] Cassier M, Correa M, 2003 "Patents, Innovation and Public Health: Brazilian Public-Sector Laboratories' Experience in Copying AIDS Drugs" in *Economics of Aids Aid and Access in Developing countries*, Edited by Moatti and al., ANRS, p 89-107.

national and international consortiums, Productive Development Partnerships (PDP)[5], and contracts and alliances between university laboratories, pharmaceutical firms and start-ups created around scientific institutions. These industrial partnerships and technological consortiums continue to spread, despite the unfavourable economic and industrial climate since 2012 and especially since 2014. The number of PDP grew from 11 in 2009 to 104 in 2013. In 2014 and 2015, 20 new PDP were set up. They are either between national public- and private-sector laboratories, to duplicate technologies, or between Brazilian laboratories and international firms that own or have licences for transferred technologies. Their scope extends beyond anti-retrovirals for HIV/Aids, to recombinant insulin provided by an Indian firm and a Ukrainian laboratory, and a vaccine transferred by Glaxo, for example. We note that Brazil's PDP policy is a target of strong opposition by the US pharmaceutical industry syndicate, which is concerned about the emergence of an autonomous industrial policy in the field of medicinal drugs, and about the preference given in these partnerships to firms that produce in Brazil: "Brazil: Productive Development Partnerships (PDPs) and government purchasing: … It remains unclear how the current PDP model might limit competition or how Brazil will apply the government purchasing program that offers preferences to locally manufactured products and services in public biddings. For these reasons, PhRMA requests that Brazil be placed on the Priority Watch List for the 2016 Special 301 Report" (The Pharmaceutical Research and Manufacturers of America (PhRMA), special 301 submission 2016).

The current economic and budgetary crisis could lead to reduced funding for these operations, but could also be an incentive to maintain or strengthen them, as a means both to boost investments (cf. the announcement of BNDES funding in 2015 and 2016 to finance the health industry complex) and to reduce the health product trade deficit that worsened in the 2000s and is weighing on Brazil's health economy. We need to remember that the financial crisis that hit Brazil in the early 1980s was a driver of the policy to support local production of active principles through a reverse engineering programme undertaken by Codetec, the R&D firm of Campinas University, with funds from CEME, the Medicines Centre (Central de Medicamentos). In October 2015 the Ministry of Health announced nine new PDP, highlighting their economic advantages for the government[6]. At the beginning of that year the Brazilian development bank (BNDES) had announced an investment programme for the health industry complex, justified by the related reduction of the health trade deficit[7]. The acquisition of new technologies and the growth of the health industries were thus seen as strategic answers to the economic crisis. For example, in September 2015, in the field of interest to us here, the BNDES granted an essentially non-refundable loan for the development of new therapeutic and diagnostic technologies to treat so-called neglected diseases (Chagas, leishmaniasis, tuberculosis) by the Oswaldo Cruz Foundation, in partnership with Drugs for Neglected Diseases (DNDI), a foundation created by MSF (Médecins Sans Frontières) to coordinate R&D projects. At the same time, strong tension was

[5] Law 742, Ministry of Health, November 2007; Laws 374 and 375, February 2008; Presidential Decree, 12 May 2008; list of strategic products that justify the creation of the health industrial complex, 16 May 2008.

[6] "Ministerio da Saude anuncia novas PDP destinadas a fabricaçao de medicamentos e equipamento de saúde", INVESTE SAO PAULO, 8 octobre 2015.

[7] The BNDES has a special programme, Profarma, for funding the pharmaceutical industry.

running throughout the public health system, evidenced by demonstrations in June 2013 and 2014 demanding "hospitals rather than stadiums"[8].

Copying and social medicine

A crucial characteristic of this Brazilian experience of rebuilding the country's health industries from the early 1990s is that it took place in direct relation to the constitutional right to health, which was enshrined in the new Constitution of 1988[9]. The demands of HIV/Aids patients and the first initiatives to distribute AZT played a major role in mobilizing both this legal instrument and the pharmaceutical laboratories that could duplicate the only molecule available at the time. The Director of Microbiologica, the first firm to copy AZT, saw the firm's engagement as the outcome of a technological opportunity: the laboratory's expertise in small molecule chemistry. It was a response to the Aids movements' demands for access to treatment: "Many people died at the time. But these people started these ONGs, non-governmental organizations, and these started to make, to organize pressure immediately. So when it appeared, we decided we'd produce AZT in Brazil … And AZT is a nucleoside and the experience and competence of this company is in nucleic acid chemistry. So for us it's like manna from heaven"[10]. In 1996 the Ministry of Health decided to set up a national copying programme, while the President of Brazil issued a decree that organized the universal and free distribution of medicines to treat the Aids epidemic. The Ministry summoned the Director of the federal pharmaceutical laboratory, Eloan Pinheiro, and gave her the list of antiretrovirals that it was purchasing at a high price from multinational firms: "And then they called me and said: you need to develop drugs for Aids. And I said let's go"[11]. Pinheiro compared this list to the list of medicines not under patent in Brazil and decided: "we'll try to reproduce these medicines here in Brazil". This programme was launched in a context of epidemic urgency and the fear of being swamped by the number of treatments to distribute: "the evaluation of the WHO was so bad they supposed that by 2000 Brazil would have one million people [with HIV/Aids], and the prices of the international companies were very high" (Eloan Pinheiro).

While the Farmanguinhos federal laboratory started to supply the Health Ministry for the distribution of free generic ARVs to Brazilian patients, Eloan Pinheiro was also involved in an international movement initiated by Médecins Sans Frontières, to revive therapeutic innovation for a set of pathologies known as "neglected diseases" that barely benefited from new molecules put on the market[12]. In 1999, MSF created the DND Working Group, consisting of experts who had been working for a long time on tropical diseases at the WHO, the Walter Reed Army Institute of Research, the Harvard School of Public Health, as well as

[8] A synthesis report on Brazil, published by the OECD in November 2015, highlighted both the progress made in access to treatment, with the implementation of the unified health system (SUS) in 1988, and the persistent insufficiency of public spending on health (OECD Economic Surveys, Brazil, synthesis, 51 pages).

[9] Relations between pharmaceutical production and health policy in Brazil have been studied by several authors: Galvao J., 2002, "Access to antiretroviral drugs in Brazil", *The Lancet*, volume 360, Issue 9348, 1862-1865; Amy Nunn, 2009, *The Politics and History of Aids Treatment in Brazil*, Springer, 186 pages; Matthew Flynn, 2015, *Pharmaceutical Autonomy and Public Health in Latin America: State, Society and Industry in Brazil's AIDS Program*, Routledge, 230 pages.

[10] Interview with Jaime Rabi, April 2003.

[11] Interview with Eloan Pinheiro, April 2005.

[12] Pécoul, Chirac, Trouiller, Pinel, 1999, "Access to essential drugs in poor countries: a lost battle?", *JAMA*, January 27, 1999; vol 281, n°4.

several experts at scientific or pharmaceutical institutions in developing countries, including Mahidol University in Malaya and the Oswaldo Cruz Foundation. Pinheiro who had just launched several generic ARVs, was invited by MSF to participate in this working group: "At the time, we had huge visibility because we had produced all the generics for HIV (the antiretrovirals). It was the first time that a developing country managed to develop seven formulae for Aids medication. And these medicines were put on the market and this gave us huge visibility, so Farmanguinhos was invited to this meeting in Paris in 1999". The Oswaldo Cruz Foundation was a founding member of the Drugs for Neglected Diseases Initiative (DNDI) in 2003, and the Farmanguinhos Institute was a stakeholder in an international consortium set up to develop the formulae of two new artemisinin-based combinations (FACT)[13]. DNDI established its regional office for Latin America in Rio, and now runs many research projects on neglected diseases (leishmaniosis, Chagas disease, tuberculosis) with Oswaldo Cruz Foundation laboratories. A chapter of this book, written by Mady Barbeitas, is devoted to collaborative R&D projects on leishmaniasis, involving the Ministry of Health, the Oswaldo Cruz Foundation, and the DNDI Foundation.

Industrial policy was integrated with health policy. The Health Industrial Complex policy, proposed by economist Carlos Gadelha[14], was designed to acquire and invent new technologies and to industrialize them in Brazil in order to supply the public health system, which gradually has to meet the population's needs despite the current lack of public spending on health (OMS, 2012, OCDE 2015)[15]. We could talk of a neo-developmentalist policy since the aim is to promote local innovation and production, with a view to reducing dependence on foreign imports, from a technological, commercial and health point of view. The public-sector laboratories are these industrial partners' obligatory points of passage. An example is the industrial consortium set up in 2007 to produce a generic version of Merck's efavirenz, and which was organized and controlled by the Health Ministry's Farmanguinhos laboratory (cf. Chapter 2 in this book).

Local production and technology creation

Copying is an integral part of R&D and tends to fuel innovation[16]. Most importantly, the duplication of antiretroviral medicines cannot be reduced to the copying of old technologies as they were recorded in patents when registered by the owner. Jaime Rabi, who was the first in Brazil to copy AZT in the early 1990s, explains this clearly: "From the technology viewpoint it was for us a big challenge. It was not simple to make AZT at the time. It was not simple. A lot of technology had to be developed. It was not a case of reverse engineering anymore. There was a lot of innovative work being done here to produce AZT… the AZT we produced at Microbiologica in the early '90s was different in specifications to the AZT being produced by Welcome at the time … we knew that we were making AZT by a different process, by a better process" (Jaime Rabi, 2003). Brazilian chemists could not be content simply to reproduce the already known synthesis methods, which were often not yet stabilized at the time the patents were written and filed. They had to bridge the gap with new techniques and improve the processes. This was the case of the reproduction of efavirenz

[13] FACT: Fixed-Dose Artemisinin Combination Therapy.
[14] Gadelha, C., "The health care economic-industrial complex: Concepts and general characteristics", C Gadelha, *Health*, 2013.
[15] http://www.who.int/gho/publications/world_health_statistics/FR_WHS2012_Full.pdf, p 131.
[16] Samuelson P., Scotchmer S., 2001, "The law and economics of reverse engineering", Research paper, University of California at Berkeley, 78 p, http://people.ischool.berkeley.edu/~pam/papers/l&e%20reveng5.pdf.

patented by Merck and put under compulsory license in Brazil in May 2007. The synthesis routes that were eventually implemented by Brazilian laboratories were not those indicated by Merck in its patent, simply because many improvements had been made: "What I know is that what Merck protected, first, has changed a lot: no one practices that, it's too expensive, it's harmful, there are a lot of bad things in this synthesis; today there are more practical syntheses, more direct, safer, less expensive; a lot of improvements. After that patent different processes were developed, much more efficient ones, and safer … our synthesis is different from Merck's" (Cristalia Laboratory, 2011). The differences between the efavirenz syntheses used now in Brazil and the one described in Merck's patent are so big that in 2012 the Brazilian government even considered not renewing the compulsory license decree issued in 2007 for five years to foster the production of generics in Brazil![17] In other words, because they had changed the process, Brazilian producers no longer encroached on the first patent in any way.

The connections between reproduction and innovation come in various forms. Brazilian manufacturers developed many improvements to the ARV synthesis routes, to make them more reliable or to improve their productivity and thus their competitiveness with the products of Indian or Chinese laboratories: "in the patents, they use 4kg of raw material to produce 1kg of stavudine. Here, we use 1.9kg for 1kg. We like this new way" (Labogen, 2004). These process improvements are generally kept secret so as not to alert Indian or Chinese generics producers. Formulation innovations are often patented (three Brazilian laboratories have filed patents on new anti-retroviral formulae for HIV/Aids treatment). Copying has also led to product innovations in the form of derived or hybrid molecules. For instance, the Farmanguinhos federal laboratory developed a molecule derived from efavirenz, which it did not patent. Brazilian laboratories also take advantage of the fact that some molecules used for HIV/Aids treatment or malaria are in the public domain, in order to produce new fixed-dose combinations. The federal laboratory has thus developed new combinations in collaboration with Médecins Sans Frontières and the DNDI. Although it patented a fixed-dose combination for HIV/Aids in 2002, at MSF's request it did not patent the artesunate and mefloquine fixed-dose combination.

The private-sector laboratories have increased their patent portfolio significantly since the early 2000s. In 2011 Cristalia, which has a large R&D laboratory, had no fewer than 139 patents. Laboratories in both sectors draw on the expertise of many PhDs whom they recruit to orientate their work towards similar or more radical product innovations. One of the most remarkable examples of copying linked to innovation is the firm Microbiologica. While this laboratory introduced AZT into Brazil in the early 1990s, it also joined innovation networks in the USA and Europe, to work on the invention of new antivirals used in treating hepatitis B and C. At the beginning of the 2000s the CEO, Jaime Rabi, collaborated with Idenix and Pharmasset, two renowned pharmaceutical R&D companies that were spin-offs of Emory University. Microbiologica participated actively in the invention of this new therapeutic class that is now often in the news because of its prices and the patent wars around it[18]. In 2016 the firm was at the head of a consortium of Brazilian laboratories working on a generic version of sofosbuvir. Their aim is not to copy or to transfer the technologies that Microbiologica initially helped to develop with the US start-ups, but simply to lift the patent barrier (cf. chapter 5 of this book).

[17] The federal government did finally renew the compulsory license decree for the remainder of the process patent's validity, until 2014.

[18] Our interviews with Jaime Rabi in March 2003, November 2014 and December 2016. Jaime Rabi sat on the Pharmasset Board in the late 1990s.

An economic study published in 2010 showed the increase of R&D expenditures within Brazilian national firms that had benefited from the growth of the generics market over the previous ten years, when spending had been cut in the local branches of multinationals: "The rates of innovation for the Brazilian firms increased, like the amounts invested in internal R&D and total of innovation, and we found yet that these Brazilian firms invested little more in R&D than the multinational industries in Brazil … For the initial period of analysis, domestic firms would spend less than foreign firms. Innovative domestic firms would spend only 66% of the amount spent by multinationals. The result is inverted in 2005, when domestic firms spent 107% of the amount spent by foreign firms. The expenses of domestic firms increased whereas the ones of foreign firms declined"[19]. Not only did the R&D spending of Brazilian generics producers increase, but also the level of training of their employees, measured in terms of the number who had PhDs, Master's, and other higher education degrees. In other words, the copy of technologies and the production of generic medicines boost R&D and innovation. This conclusion, based on research in Brazilian firms since 2000 (PINTEC survey) is consistent with the conclusions of our first surveys in public- and private-sector laboratories engaged in the copying of antiretrovirals for Aids (Cassier, Correa 2003)[20].

Collective Invention

This book highlights the collective dimension of technology development in the reproduction of inventions, as well as their improvement or radical modification. The justifications for this cooperation are multiple: the necessity to pool the complementary skills and know-how of scientific and industrial institutions, and of the producers of active principles and those of final medicines; the wish to combine similar knowledge and assets, to share information and advance faster, to validate technologies, and to secure several supply sources; and finally the adoption of a collective learning strategy with a view to bringing together the participants in the network. The collectives in question may be formed spontaneously around know-how trading, or may be R&D or production consortiums coordinated by contracts governing the division of work and the allocation of resources between the parties. Collective invention, as the economist Allen understands it[21], characterizes the case of Brazil, where it reinforces clusters of public- and private-sector laboratories with a view to building a national technological and industrial base. Partnerships between small or medium-sized laboratories, whose R&D capacities are modest compared to those of multinationals, constitutes their strength.

[19] "Structure and innovation in pharmaceutical industry in Brazil: the impact of generics drugs", Thiago Caliari and Ricardo Ruiz, 2010, 16 pages. These authors took into account the following indicators to measure the innovation rate: 1- product innovations; 2- process innovations; 3- patent applications filed at the national patent office; 4- ongoing R&D activity; 5- employees' above-average education; 6- the firm's exports; 7- the firm exports and get a premium price.

[20] The results of a survey of 16 biotechnology and pharmaceutical firms in 2008 likewise indicated the positive impact of the ARV copying programme on innovation: "Another recent example includes the partnerships between public pharmaceutical laboratories and private national pharmo-chemical firms for the national production of anti-retroviral medication to supply the national program to care for AIDS patients. Partnerships of this sort show the importance of joint action by system players to promote innovation and development in the country", *Innovation in Brazil: Public policies and business strategies*, Ricardo Sennes, 46 pages.

[21] Allen, R, 1983, "Collective Invention", *Journal of Economic Behavior and Organization*, 4, p 1-24

Forms of know-how trading (Von Hippel)[22] appeared between public and private producers of generic medicines engaged in the copying of ARVs for HIV/Aids when this collaboration enabled them to enhance and to validate their technological developments. The sharing of information between imitators compensated in a sense for the absence of interaction with the inventor and owner of the technologies which, as we know, is crucial in the duplication of new technologies (Collins). Thus, for instance, chemists at the private-sector laboratory Nortec used their firm's highly specialized equipment to help chemists at Farmanguinhos solve problems in characterizing the indinavir molecule, and in return received analysis methods developed at the federal laboratory. Additionally, when the latter compared samples of active principles provided by producers in the private sector, it freely and confidentially shared the results of its tests with them. It gave each of them advice on improving their processes and products. The analytical chemistry department at Farmanguinhos learned a great deal from working with chemists at Microbiologica, which is an expert in small molecule chemistry. Likewise, they benefited significantly from the free assistance of chemists at the federal university who had developed new syntheses and who transferred knowledge on new classes of anti-retroviral molecules. Private-sector laboratories could also agree ad hoc to share copying between themselves, as for instance Cristalia and Nortec did in 2006 to duplicate tenofovir.

One of the most successful forms of this pooling of research and knowledge was the consortium set up in 2007 to produce a generic of Merck's efavirenz that was under compulsory license. This consortium, headed by the Oswaldo Cruz Foundation, brought together three laboratories producing active principles, and the Farmanguinhos federal laboratory that produced the final medicine. While the private-sector laboratories in the consortium initially developed their synthesis process separately, they were gradually led to join forces and to cooperate in order to solve certain problems: "we discussed this with other companies that used to make efavirenz" (Cristalia, 2011).

The consortiums' importance grew during the 2000s, both nationally and internationally, in the reproduction of existing technologies and the invention of new pharmaceutical or diagnostic technologies. These were industrial consortiums or PDP, consisting of public laboratories and private pharmaceutical chemicals firms, and that were formed to combine the production of APIs and the formulation of final medicines. There were several types of PDP, oriented either towards the copying of existing technologies – tenofovir[23], ritonavir, kaletra and raltegravir –, or towards the invention of new medicine formulations or biological tests, as in the case of the PDP set up between the Oswaldo Cruz Foundation and Lifemed to develop a miniaturized multiplex test. While most PDP consisted of Brazilian scientific and technological institutions and firms, others were organized with transnational firms for the acquisition of existing technologies, such as the PDP formed between Farmanguinhos and Bristol Myers Squibb for the local production of atazanavir, the PDP between Merck for Raltegravir, the one formed with the Canadian Apotex for Darunavir, and the one concluded with Chembio Diagnostics for the acquisition of a diagnostic platform.

In several chapters we analyse different types of consortium set up on a national and international scale. The research carried out to acquire the technology for thermostable

[22] Von Hippel E, 1987, "Cooperation between rivals: informal know how trading", *Research Policy*, 16, 291-302.

[23] "Making Tenofovir accessible in the Brazilian public health system: patent conflicts and generic production", J. Veras, *Developing World Bioethics*, volume 14, number 2014, p 92-100.

molecules [24] for ritonavir was set within a national consortium between public-sector pharmaceutical laboratories, the private firm Cristalia, the National Technological Institute (NTI), and an international consortium, the Technological Cooperation Network on HIV/AIDS, in which the Chinese firm Desano played an essential role as supplier of Ritanovir raw material samples to develop a thermostable formulation. The FACT consortium set up in 2003 to develop new artemisinin-based therapeutic combinations to treat malaria involved both French universities and start-ups, and the Farmanguinhos federal laboratory. In particular, the latter benefited from the contribution of recording methods provided by the French research company Catalent [25]. In October 2015 the Centre for Information Technologies (CIT) at the Ministry of Science and Technology, announced the forthcoming arrival of a new portable diagnostic platform for Chagas and other tropical diseases, which had been developed by an international consortium set up in 2011 with the European Union. The consortium consisted of five Brazilian laboratories and six European ones (French, German, Italian and Portuguese) and was jointly funded by the Brazilian government research agency CNPQ and the European Union[26].

In his chapter devoted to new diagnostic methods, Koichi Kameda shows multiple cooperative projects currently existing between the Fiocruz Biomanguinhos laboratory, university laboratories, Brazilian start-ups, and the creation of hybrid technological institutions such as the IBMP, the Institute of Molecular Biology of Paraná, spawned by the partnership between the Oswaldo Cruz Foundation and the Department of Science, Technology and Graduates of the State of Parana, which set up a test production factory. The proliferation of these collective invention structures, involving science, government and industry, and which largely transcend the framework of PDP governed by the Ministry of Health, attest to the emergence of a system of innovation in Brazil's health industries, and the diffusion of what Henry Etzkowitz and his colleagues, in 2005, called the "incubator" form involving universities, industrial syndicates, cooperatives, and NGOs[27].

Instituting government and civil society regulation of intellectual property

The regulation of intellectual property needs to find the right balance between allowing the copying of essential medicines for public health, and encouraging and protecting the inventions of national laboratories. Public-sector laboratories as well as private Brazilian firms started in the early 2000s to file patent applications, both at the Brazilian patent office and internationally, and this tendency is growing. Is it possible to allow both the nationalization and copying of foreign technologies considered by the Health Ministry to be strategic, and the stimulation of local innovations ?

One of the most original devices and also one of the most controversial ones,

[24] In this volume, see the chapter by Cristina D'Almeida: "Knowledge generation and laboratory capacity building in the fight against HIV/AIDS in Brazil: Experiences on the development of a heat-stable formulation comprising Ritonavir".

[25] « Needs driven versus market driven pharmaceutical innovation : the consortium for the development of a new medicine against malaria in Brazil », K Kameda, Developing World Bioethics, 2014, p 101-108.

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[26] http://www.poditrodi.org.

[27] "Towards meta-innovation in Brazil: the evolution of the incubator and the emergence of a triple helix", Henry Etzkowitz, José Manoel Carvalho de Melho, Mariza Almeida, *Research Policy*, 34, 2005, p 411-424.

experimented with in Brazil since 2001, is the authorization given to the National Health Surveillance Agency, ANVISA, to examine the granting of pharmaceutical patents. In Brazil this process therefore falls under the joint authority of the National Institute of Industrial Property, and of ANVISA. The latter has recruited chemists and specialists in biotechnology to create a division specially for examining drug patents. This special regulation of pharmaceutical patents by ANVISA, which results in a substantially lower acceptance rate than that of the patent office's examiners, is cited in a manual published by the WHO to help developing countries apply industrial property rights by taking sides with public health[28]. This approach has been strongly challenged by the pharmaceutical multinationals through various court cases. In his chapter on "prior consent" of the National Health Surveillance Agency, Edouardo Guimaraes presents the results of an ethnographic survey that he carried out at the ANVISA examination division.

The second chapter, co-signed by Jacqueline Soares and Eduardo Guimaraes, describes a controversy over the patentability of polymorph molecules, involving a wide diversity of actors, from the chemists at the Oswaldo Cruz Foundation, to the chemicals and pharmaceuticals industries, the National Institute of Industrial Property, the National Health Surveillance Agency, the Inter-ministerial Group on Intellectual Property, and even Parliament. Some molecules are indeed able to exist in several crystalline forms, which can influence the molecule's properties (bio availability, stability, efficacy). To what extent can the process of obtaining polymorphs be patented? Some see polymorphs as existing in nature and therefore as not being patentable. The prohibition on the patentability of polymorphs would also prevent the ever-greening of patents from which the multinationals benefit. The Health Ministry and the ANVISA patent examination division, wanting to limit the extension of the patentability of pharmaceutical molecules, were against patents on polymorphs. The patent office, wanting to encourage incremental innovations, was in favour of them. The two authors show the phenomenon of learning on the occasion of two years of public debates, in 2007 and 2008. We see that Brazil's National Institute of Industrial Property is more severe than its US and European counterparts, and that patents previously granted would no longer be approved today, due to an elevation in the standards of patentability. This highly technical subject has become a matter of public debate involving science, industry, the State and civil society.

The chapter by Pedro Villela introduces new actors into the pharmaceutical patent regulation field: international NGOs such as MSF, and patent organizations in Brazil. We can follow these organizations' learning curve with regard to intellectual property law, through their interaction with academic legal experts (e.g. Carlos Correa from the University of Buenos Aires); patent experts at the Farmanguinhos federal pharmaceutical laboratory (e.g. Wanise Barroso); the patent examination division at ANVISA; and international experts such as James Love of the Consumer Project of Technology, and Tahir Amin at I-Mak[29] during training seminars or battles for obtaining compulsory licences or the cancellation of certain patents. The organizations have used the law as a weapon to obtain the suspension (efavirenz) or cancellation (tenofovir) of patents on certain drugs, the molecules of which are then nationalized by Brazilian firms. They recruit their own legal experts to fight these legal

[28] Carlos Correa: *Guidelines for the examination of pharmaceutical patents: developing a public health perspective*. Geneva: World Health Organization, 2007.

[29] "I'MAK is a team of lawyers and scientists increasing access to affordable medicines by making sure the patent system works" (I-MAK).

battles. Where relevant, they cooperate with organizations in other countries of the South, for example India, to challenge certain patents such as those of Gilead on tenofovir and, more recently, on sufosbuvir.

We thus see that in Brazil there is public and citizen regulation of pharmaceutical patents, with the intervention of the Health Surveillance Agency in the granting of patents, the patient organizations, which monitor the patent examination procedure or even to oppose it, the Ministry of Health, which fights for years for a compulsory licence, or the Farmanguinhos federal laboratory which in 2006 opposed Gilead's patent on tenofovir, until finally the molecule fell into the public domain.

There are ongoing discussions among industrial property experts, both in industry and among economists, on the impact of these interventions on the innovation economy that the government would like to have. Kenneth Shadlen, a British economist, highlights the potentially negative effects on innovation of certain rules upheld by ANVISA, on the non-patentability of polymorph molecules or the second therapeutic use of an already-known molecule. Here, ANVISA's action could penalize the incremental innovations of Brazilian laboratories [30]. In response, the Agency has pointed out that ever-greening is essentially of pharmaceutical multinationals' doing, and that a less rigorous examination would mean to catch at shadows and to reinforce the international laboratories' power. We have found that the universities and the public- and private-sector pharmaceutical laboratories are registering more and more patents on molecules derived from those that they duplicate. Examples are Farmanguinhos' patents on molecules derived from artesunate, used for malaria, on new combinations of molecules, even a patent granted in 2001 on a new family of molecules used for HIV/Aids treatment, jointly owned by Farmanguinhos and the Federal University of Rio de Janeiro. Cristalia, one of the most innovative firms in Brazil, has benefited from the compulsory licence on efavirenz to produce the generic API and the medicine, since 2007. It has simultaneously accumulated a portfolio of 139 patents since the early 2000s. The director of industrial property at the Farmanguinhos laboratory drafted the opposition statement that caused Gilead's patent to fall into the public domain in 2008, and on a daily basis draws up the patent applications filed by the laboratory's chemists to govern the exploitation of their inventions. The delicate fine-tuning of patent management is intended to protect and control Brazilian firms' and universities' inventions, while nonetheless preserving a public domain in which access to treatment is facilitated.

Constructing and regulating the generic drug market

Our book also considers another dimension of the innovation system: the regulation of generic medicines that was set up from 1999. The chapter written by Marilena Correa, Maurice Cassier & Maria Andrea Loyola, shows the formation, expansion and regulation of the similar and generic medicines' markets since the 1990's. In particular, it explores the diffusion of bio-equivalence tests for the copy of both similar and generic medicines. The bio-equivalence tests carried out in centres authorized by ANVISA measure the quality of copies to guarantee their inter-changeability with first medicines.

[30] Shadlen, Kenneth. "The political contradictions of incremental innovation: lessons from pharmaceutical patent examination in Brazil", *Politics & Society*, v. 39, n. 2, pp. 143-174, 2011 ; SHADLEN Kenneth, The politics of patents and drugs in Brazil and Mexico : the industrial bases of health policies, in Intellectual Property, Pharmaceuticals and Public Health, Access to Drugs in Developing Countries, Edited by K Shadlen, S Guennif, A Guzman, N Lalitha, p 178-201.

The laboratories engaged in the copying of antiretrovirals for treating HIV/Aids started very early, even before the adoption of the generics law and the creation of ANVISA in 1999, to test their medicines for bio-equivalence. Their intention at the time was to be able to defend themselves against accusations by patent owners, that Brazilian copies were of poor quality.

A noteworthy article published by the University of Recife Bio-equivalence centre, in May 2002, in the *Anais da Academia Brasileira de Ciências* (Annals of the Brazilian Academy of Sciences), traced bio-equivalence testing on similar drugs in Brazil back to 1995: "our research group started clinical trials and bioequivalence studies, with the collaboration of the public pharmaceutical laboratory of Pernambuco State (LAFEPE), the Brazilian official company to pioneer the development of medicines for AIDS and herpes virus treatment, between 1995 and 1998, even before the establishment of generic policy in Brazil"[31]. The article then gave the results of bio-equivalence for AZT, Ganiclovir, didanosine, lamivudine and zalcitabine, and for a LAFEPE fixed-dose combination "similar to the reference medicine". A report by the Ministry of Health in February 2001, titled "National Drug Policy"[32], also listed the Brazilian copies produced by the federal laboratory in Rio that had passed the bio-equivalence tests: "Six Far-Manguinhos-produced drugs – zidovudine, didanosine, lamivudine, zidovudine+lamivudine and zalcitabine – have been approved in bioequivalence tests and thus are eligible for licensing as a generic drug. The bioequivalence testing of indinavir and nevirapine is in its final phases". The report pointed out that from then on, all medicines bought by the Ministry of Health had to pass bio-equivalence tests: "Bioequivalence tests, proving the interchangeability of the drugs, are a recent achievement of the Brazilian National Drug Policy, guaranteed by the 1999 Generic Drugs Bill" (National Drug Policy, February 2001). We also identified several articles by the laboratory of Campinas University, one of the oldest and largest bio-equivalence centres in the country, which disclosed the bio-equivalence results of private laboratories' copies. In August 2000, the director of the bio-equivalence centre, Gilberto de Nucci, evoked these tests with other international scientists: "we routinely use healthy volunteers for bioequivalence drugs (protease inhibitors or transcriptase reverse inhibitors). We generally perform single dose administration of the two formulations". In February 2002, de Nucci's team published the bio-equivalence results of the copy of nevirapine in the *Journal of Mass Spectrometry*: "this method was employed in a bioequivalence study of two nevirapine tablet formulations (Nevirapina from Far-Manguinhos, Brazil, as a test formulation, and Viramune from Boehringer Ingelheim do Brasil Quimica e Famaceutica, as a reference formulation"[33]. The bio-equivalence measurements were applied to so-called "similar" medicines even before they became a legal requirement in 2003 and 2004.

The growth of the bio-equivalence test market and the extension of the network of bio-equivalence centres approved by the Health Surveillance Agency is a keystone in the construction of the pharmaceutical innovation system. In 2000, the national bio-equivalence centres performed only 27% of all bio-equivalence tests, whereas in 2010 they performed 87% of them. In the meantime, ANVISA had funded the creation of bio-equivalence centres in universities. In 2010, 27 analysis centres, with a public or private status, had been approved

[31] Antonio J. Alves, "Clinical Studies-Generic Medicines", *An Acad Bras Cienc*, 2002, 74, 3, p 552.
[32] "National Drug Policy", Ministry of Health, Brazil, February 2001, 21 pages.
[33] "Nevirapine quantification in human plasma by high-performance liquid chromatography coupled to electrospray tandem mass spectrometry. Application to bioequivalence study", Laurito TL1, Santagada V, Caliendo G, Oliveira CH, Barrientos-Astigarraga RE, De Nucci G, *J Mass Spectrom.* 2002 Apr.; 37(4):434-41.

and integrated into REBLAS, the national network supervised by ANVISA. The last chapter of our book describes the current map of bio-equivalence centres in Brazil supporting therapeutic regulation and innovation.

An innovation system in the making[34]

The innovation system that we define here combines diverse collective invention structures, measures to regulate industrial property – designed to achieve a balance between innovation policy and public health policy –, and standards and systems to measure the bio-equivalence and the therapeutic efficacy of medicines. At the same time, the studies published here draw a map of the main actors and obligatory points of passage of this innovation system in the making. One of the most noteworthy aspects is the multiple roles of the public-sector pharmaceutical laboratories: the Farmanguinhos lab and the LAFEPE in Recife, as well as the official laboratories of several States, for instance Fiocruz in Parana, known for its diagnostic methods. The federal laboratory and the Oswaldo Cruz Foundation supervising it are involved in the creation of technologies, in their dissemination in industry, and in the regulation of industrial property through the patents that they own or the oppositions or demands for compulsory licences that they institute. Public-sector laboratories are necessarily involved in the hundreds of PDP created since 2009[35].

Our book also highlights a group of private-sector laboratories involved in many PDP to develop and produce the active principles of medicines. The Ministry of Health asks them to develop the production of a particular medicine on the list of strategic products. From the late 1990s Cristalia in the State of Sao Paulo, one of the most active of these laboratories, embarked on the reverse engineering of antiretrovirals for HIV/Aids treatment and from 2002 signed R&D agreements with the Farmanguinhos laboratory and the Federal University of Rio de Janeiro. It headed the industrial consortium that produced efavirenz, put under compulsory license in 2007, and increased its industrial investments to support the growth of the PDP in the 2010s. Cristalia is also very active in the industrial property domain, where it patents its own inventions and opposes certain patents. Nortec, a spin-off of the federal laboratory in the State of Rio de Janeiro, entered the field of antiretrovirals in the 2000s, at the request of the government that was a 20% shareholder in the firm. Nortec regularly has R&D partnerships with the federal laboratory and with its chemistry department. Microbiologica, a spin-off of the Federal University of Rio, founded in the 1980s, is an R&D firm producing medicines. It was the first laboratory to embark on the copying of AZT in the very early 1990s. In the early 2000s it participated in innovation networks based primarily in the US and Europe, which developed the new generation of antiretrovirals for treating hepatitis B and C. In particular, it provided the synthesis processes of these antivirals – processes that it patented and licensed. Apart from these firms created in the 1980s and 1990s, this book discusses the

[34] The recent report "The Brazilian Innovation System: a mission-oriented Policy Proposal", Marianna Mazzucato, Caetano Penna, 2016, *Cgee*, 114 pages, also highlights the emergence of an innovation sub-system in the health sector, p. 12 and p. 82.

[35] Waldemiro Francisco Sorte Junior: "The production and R&D structure of the Brazilian pharmaceutical industry: the role of public procurement and public drug production", *Global Public Health*, Vol. 7, No. 10, December 2012, 1062-1079; Matthew Flynn, "Public Production of Anti-Retroviral Medicines in Brazil, 1990–2007", *Development and Change*, volume 39, Issue 4, 2008, pp. 513-536.

arrival of new start-ups, especially in the fields of diagnostic methods and medical devices[36].

Brazilian universities are likewise participants in this health industry innovation system. Diverse forms of collaboration exist between university laboratories and pharmaceutical firms, through: R&D contracts to develop technologies for producing generic medicines or new molecules; consultancy agreements with academic researchers who sit on the Boards of scientific firms; and patents owned jointly by universities and private firms. Research statistics show a growth in the number of patents registered by Brazilian universities in the field of health during the 2000s[37], even though there are also studies showing the problems involved in their industrialization[38]. Universities moreover host many bio-equivalence and clinical trial centres, although the feeling in industry is that there are not enough of certain phases of clinical studies.

The National Health Surveillance Agency (ANVISA), created in 1999, is a key player in this innovation system[39]. Its intervention in the regulation of pharmaceutical patents and the fact that it has kept this role despite recurrent clashes with the National Institute of Industrial Property and the international pharmaceutical industry, are both remarkable and controversial. ANVISA also funded the network of bio-equivalence centres to foster a system of measurement and certification of copied medicines. Not only does it issue certificates of good production practice or certificates of approval for bio-equivalence centres, it also advises laboratories with a view to raising the standards and the quality of health products. In the early 2000s ANVISA funded the Farmanguinhos federal laboratory's research and monographic studies on standards for antiretrovirals.

The Ministry of Health strongly supported the emergence of this innovation system: it propelled the ARV copying programme in 1996 and encouraged the public laboratories as well as private firms to participate in it. It has also been heavily involved in the regulation of industrial property rights in several ways: by creating the prior consent device for medicine patents, under the authority of ANVISA; by preparing the compulsory licence decision on efavirenz in March 2004; and by acting within the Inter-Ministerial Group on Industrial Property (IGIP) to limit the extension of pharmaceutical patents and their ever-greening. The Ministry of Health has moreover been responsible for the health industry complex, and

[36] See the WHO study "Local Production and Technology Transfer to increase Access to medical Devices. Addressing the barriers and challenges in low and middle-income countries", 2012, on the development of new technological firms in Brazil, p. 34.

[37] Thiago Caliari, Roberto Mazzoleni and Luciano Martins Costa Povoa (2013) point out the growing role of Brazilian universities and public research organizations in patenting, and their importance in the chemicals, biotechnology and pharmaceutical sectors : "Innovation in the pharmaceutical industry in Brazil post-TRIPS" in "TRIPS Compliance, National Patent Regimes and Innovation", Edited by Sunil Mani and Richard R Nelson, Edward Elgar, p. 29-30 ; see also "University and Patenting in Brazil", Ana Lucia Vitale Torkomian, Marli Elisabeth Ritter dos Santo, Helice, volume 2, 2013, Issue 1 ; Rosana Ceron di Georgio : "From University to industry : Technology Transfer at Unicamp in Brazil", Handbook of best practices, 2007, p 1747- 1752 ; OECD 2008, Science and Innovation Outlook, country notes, p 164.

[38] Gustavo Dalmarco, Mariana de Freitas Dewes, Paulo Antonio Zawislak, Antonio Domingos Padula, "Universities' Intellectual Property: Path for Innovation or Patent Competition?", J. Technol. Manag. Innov. 2011, Volume 6, Issue 3.

[39] Matthew Flynn and Egléubia Andrade de Oliveira have studied ANVISA, in particular: "Regulatory Capitalism in Emerging Markets: an Institutionnal Analysis of Brazil Health's Surveillance Agency (ANVISA)", 2008, Paper presented at the annual meeting of the American Sociological Association Annual Meeting, Hilton San Francisco, San Francisco.

approves PDP. It has continually worked with networks of patient organizations, notably in the field of HIV/Aids.

The patient organizations and NGOs have also asserted themselves as actors in this innovation system. Over time, they have become protagonists that monitor and regulate medicine patents. From 2006 they engaged in petitioning the Institute of Industrial Property to refuse or cancel certain patents, particularly the one on tenofovir, and in 2015 Gilead's patent on Sofosbuvir. They have supported the local production of generic medicines, and are currently critical of the high prices of Brazilian generics[40]. In 2006 they demanded an audit of Brazil's industrial capabilities[41]. Patient organizations and NGOs have also developed collaboration with the Oswaldo Cruz Foundation for the development of new medicines for HIV/Aids and neglected diseases. Today they are calling for more transparency in the PDP, from which they feel excluded.

The map of health industry innovation networks has thus become denser since the late 1990s, even though shortcomings persist: the lack of investment in the production of chemical intermediates and active principles for pharmaceuticals; the fact that joint R&D efforts between private-sector firms are likely to be impeded by inadequacies in the cooperative strategies of firms; and the priority given to the short term. The technological content of PDP needs to be evaluated, as well as the setting of prices, which are often deemed to be too high.

Sociology in action

The research reported in this book is about science, technology and law in the making, as shown in the field studies that were carried out in university chemistry laboratories, in industrial pharmaceutical laboratories in both the public and private sectors, and at the patent examination divisions of ANVISA (the Health Surveillance Agency) and the National Institute of Industrial Property. We examine the work of chemists, of patent experts and of pharmacologists at the bio-equivalence centres, thus reconstructing the research and knowledge creation involved in the duplication of medicines, in the adaptation of technologies, and in the development of secondary inventions. This furthermore enables us to monitor the patent examiners' interpretations, as well as discussions on the scope of patentability or of the public domain, both in Parliament and at ANVISA. This research, started in 2002 on the reverse engineering of HIV/Aids medications, is still underway in broader fields: antivirals for hepatitis, diagnostic methods, therapeutic innovations for treating neglected diseases (malaria, Chagas, leishmaniasis, tuberculosis). We have thus explored the strengthening of laboratories' R&D capabilities and the multiplication of technological and industrial partnerships, at the same time as the dissemination and standardization of bio-equivalence tests for copied medicines.

Most of the authors of this book are specialized in more than one discipline, for example in law and in sociology or pharmaceuticals, or in medicine and in sociology or economics. Cristina d'Almeida presents an analysis of the consortium working on thermostable drug technologies that she studied from the inside when she was at the Farmanguinhos federal laboratory and then at the Ministry of Health. Jacqueline Soares, a

[40] Amy Nunn, Elize M Fonseca, Francisco Bastos, Sofia Gruskin, Joshua Salomon, "Evolution of Antiretroviral Drug Costs in Brazil in the Context of Free and Universal Access to AIDS Treatment", *Plos Medicine*, November 2007, p 1804-1816.

[41] Joseph Fortunak and Octavio Antunes, 2006, "ARV Production in Brazil: an evaluation", Report for the Brazilian Interdisciplinary AIDS Association (ABIA) and MSF Brazil.

chemist and patent examiner at the Institute of Industrial Property, analyses discussions on the patentability of polymorph molecules. Mady Barbeitas, a veterinarian and sociologist, has spent an 18-month internship at the regional branch of the DNDI Foundation in Rio de Janeiro, which enabled her to observe innovation projects concerning leishmaniasis treatment. Koichi Kameda, a lawyer, did internships in the legal services of the Institute of Molecular Biology of Parana and at the Biomanguinhos Institute in Rio, to study R&D projects and the production of new diagnostic methods for detecting infectious pathologies. Eduardo Gumaraes completed an internship as an observer at the patent examination division of ANVISA to study the routine implementation of the prior consent procedure. Pedro Villela carried out an ethnographic study of the health-related activism of Médecins Sans Frontières and HIV/Aids patient organizations. For the past 15 years, Maurice Cassier and Marilena Correa have been following the work of chemists and experts in industrial property working on the duplication of anti-retrovirals used in Aids treatment and today in producing direct-action antivirals for hepatitis. The anthropologist Maria Andrea Loyola had studied the genesis of generic medicine policy in the 1980s.

Several authors of this book have been engaged in actions concerning intellectual property regulation, ranging from patent examination at the Institute of Industrial Property or ANVISA (Jacqueline Soares), to the negotiation of technology transfer agreements for the Farmanguinhos public-sector laboratory (Cristina d'Almeida), the initiation of opposition to the tenofovir patent (Maurice Cassier and Marilena Correa, along with Wanise Barroso in charge of intellectual property at Fiocruz), or campaigns for the decision on a compulsory licence on efavirenz in 2007. Some of them, like Jacqueline Soares at Microbiologica, have participated directly in reverse engineering.