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### ► **To cite this version:**

Maurice Cassier, Marilena Correa. Nationalizing efavirenz : compulsory licence, collective invention and neo-developmentalism in Brazil. Cassier Maurice, Correa Marilena. Health Innovation and Social Justice in Brazil, Palgrave Macmillan, p 59-90, 2019, 978-3-319-76833-5. <10.1007/978-3-319-76834-2\_3>. <halshs-03975575>

**HAL Id: halshs-03975575**

**<https://shs.hal.science/halshs-03975575v1>**

Submitted on 6 Feb 2023

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## Chapter 2 : Nationalizing efavirenz : compulsory licence, collective invention and neo-developmentalism in Brazil

**Maurice Cassier and Marilena Correa**

### **Introduction**

In May 2007, the President of Brazil signed a compulsory licence decree to authorize the use of two patents belonging to Merck, on efavirenz, a medicine used extensively in tritherapy for treating HIV/Aids<sup>1</sup>. The decree specifies that this compulsory licence is to be granted non-exclusively for the production of generic medicine for “non-commercial public use”, in order to supply Brazil’s National AIDS Programme which provides this type of medicine to patients for free (Article 1 of the 4 May 2007 compulsory licence decree)<sup>2</sup>. This decision put a lot of pressure on national laboratories, both private ones, for the synthesis of the active principle, and public ones, for the formulation of the medicine, insofar as the information contained in Merck’s patents was incomplete and that the preparation of the molecule in question was “complex and highly specialized”, as Merck themselves put it<sup>3</sup>. In light of the difficulties surrounding the replication and production of the molecule, the compulsory licence decree provided for the possibility of importing the generic medicine if it was not possible to produce it in Brazil straight away (Article 5 of the decree). Thus, for almost two years the Brazilian Ministry of Health imported a generic efavirenz purchased from an Indian laboratory, Aurobindo, until national production gradually took over.

In February 2009, the Brazilian Ministry of Health inaugurated the first batches of efavirenz nationally produced by the Farmanguinhos federal laboratory in Rio de Janeiro. In September 2011, we visited the federal laboratory’s factory and were able to follow the efavirenz production line from the delivery of the pharmaceutical raw material from three private Brazilian laboratories, to the drums of efavirenz powder, to the packaging of the final medicine capsules. Efavirenz has now become a national generic medicine certified by the National Health Surveillance Agency, ANVISA, having undergone the necessary tests on healthy volunteers that confirmed its bioequivalence with the proprietary medicine.

Since the turn of the century, this singular medicine’s evolution in Brazil has simultaneously contributed to the development of pharmaceutical patent law, to the reconfiguration of the way the national pharmaceutical industry is organized, and to the changes in the regulation of medicines – rise of generic medicines certified with ANVISA’s “G” stamp on the packaging. The patenting of efavirenz was set against a background of ongoing tension between intellectual property and public health: Brazil’s National Institute of Industrial Property – the INPI – issued this patent in 1999, in line with the new 1996 patent law which introduced pharmaceutical patents in a country that had not had any since 1945. From then onwards, the Ministry of Health had to purchase from Merck this new

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<sup>1</sup> A compulsory licence authorizes the exploitation of a patent without the authorization of the patent holder, who maintains ownership of the patent and receives royalties for the licence. The Brazilian decree set a rate of remuneration of 1.5% of the price paid by the Ministry of Health (Article 2). About this compulsory licence decision, see Flynn 2007, Nunn & al, 2007, D’Almeida, 2008, Possas, 2008, Chaves G, Viera M, Reis R, 2008, Horisch, 2010, Rosenberg 2014.

<sup>2</sup> Decreto nº 6.108, de 4 de maio de 2007. Concede licenciamento compulsório, por interesse público, de patentes referentes ao Efavirenz, para fins de uso público não-comercial.

<sup>3</sup> Proceedings of the Merck/Farmanguinhos trial, 18 February 2005.

antiretroviral medicine which is part of tritherapies provided to patients free of charge by the government, in line with the 13 November 1996 law. In 2003, Efavirenz was administered to 53,000 patients: one third of all the patients treated. In 2002, it was classified as an essential medicine in Brazil. This generated strong tension between the status of efavirenz as a patented medicine, and as an essential medicine given out as a public good to a large number of patients. The Ministry of Health asked the federal laboratory in Rio de Janeiro to carry out reverse engineering work to be able, if possible, to produce the medicine locally as a generic medicine. This copying work precipitated the lawsuit between Merck and the Farmanguinhos laboratory between 2004 and 2006, which was to produce remarkable jurisprudence, authorizing the reverse engineering of a patented molecule to record the generic medicine with ANVISA so as to avoid any delays in the medicine reaching patients. The legal decision, taken in December 2006, paved the way for the May 2007 decree, which was the first pharmaceutical compulsory licence issued in Brazil and was to have a considerable international impact. Efavirenz appeared as a creator of legal acts that carried the molecule into the public domain. Its duplication became legal. Following the application of the compulsory licence an industrial consortium was formed, associating three private laboratories. The laboratories were in charge of developing the technology needed to synthesize the active principle, which was to be delivered to two public laboratories for the formulation of the final medicine. Efavirenz thereby contributed to reconfigure the industrial organization of the Brazilian medicine industry by promoting principles of cooperation and pooling of technology and production in a mixed economy, both public and private.

The efavirenz consortium set up in 2007 also inaugurated a policy of technological development partnerships that aimed both to supply Brazil with so-called “strategic” medicine (law 978 of 28 May 2008) and to broaden the technological and industrial capacities of local laboratories. Laws enacted in 2008 and 2010 allowed the State to free itself from the rules of standard public markets to enter into “service contracts” and “technological development partnerships” with local laboratories. The idea was to promote national production, even if the price of Brazilian products was 25% higher than that of foreign products. This price surplus, authorized for a period of five years, was justified with the obligation of creation of wealth in terms of both job creation and tax revenue, as well as with technological innovation and development actions<sup>4</sup>. This can be described as a neo-developmental policy seeking to build an “industrial health complex” (November 2007 and February and May 2008 laws)<sup>5</sup>. The efavirenz compulsory licence was thus the trigger event and testing ground for these measures and this policy. In all these domains, whether the regulation of intellectual property – compulsory licence decree –, the forms of industrial organization – consortium set up at the initiative and under the watch of the federal laboratory and the Ministry of Health – or the creation of local technology – the recent programme of Product Development Partnerships –, State governance played a major role. This governance by the State should moreover be seen as the product of these decisions and interventions in the field of health and medicine, namely with regards to efavirenz, which we examine here.

In this paper we analyse the legal, technological and industrial challenges of the process of nationalization of efavirenz, from the early days of the reverse engineering work carried out by the federal laboratory in 2001 to the now routine production of the certified generic medicine. We draw on two types of source. The first consists of interviews held from 2002 in the industrial laboratories involved in the reverse engineering of the molecule, and surveys carried out in 2009, 2010 and 2011 with the managers of the laboratories that belong

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<sup>4</sup> Article 6 of Law 12349 of December 2010.

<sup>5</sup> Law 742 of the Ministry of Health of November 2007, Laws 374 and 375 of February 2008, Presidential Decree of 12 May 2008, then the list of strategic products that justify the creation of the health industrial complex, of 16 May 2008.

to the efavirenz consortium to produce the generic medicine. The second is made up of legal and regulatory sources, which are particularly dense for this medicine. This namely includes archives from the trial between the patent owner and the federal laboratory between 2004 and 2006, the compulsory licence decree of May 2007, the call for tenders in the Official Gazette to form the industrial consortium, the contractual documents governing the partners' obligations and interactions, and the service contracts for ordering pharmaceutical active principles from the national laboratories. In-depth and repeated interviews with the chemists involved allowed us to compile an inventory of the knowledge, technology, personnel, raw material and pharmaceutical products that were shared amongst the different partners, in other words to depict the actual economy of this industrial collective.

### **1) Reverse engineering and legal showdowns (2001-2006)**

Brazilian laboratories, both public and private, began the work on the reverse engineering of efavirenz very early on, from the 2000s (the patents had been issued to Merck by the Brazilian INPI in 1999). The government made strategic use of the reverse engineering work to obtain a rebate from the owner of the molecule. The Ministry of Health called on the Farmanguinhos federal laboratory, but also on private laboratories which it asked to synthesize the active principle: "When the government revealed its intention to break the nelfinavir and efavirenz patents, we also got involved. We even submitted a sample, we developed the process here" (Nortec Head of R&D, May 2004). In fact, the Nortec laboratory developed the synthesis of efavirenz in cooperation with the federal laboratory: "We proposed a joint development mechanism for both nelfinavir and efavirenz" (Head of R&D, op. cit.). Owing to the technology developed by the Brazilian laboratories, if the commercial negotiations failed the Ministry of Health could resort to the threat of a compulsory licence: "once national manufacturers have developed the reverse engineering, they can go to speak with the multinational companies in full confidence: 'if you don't supply me, I have a back-up plan. We have the knowledge and the know-how'" (Head of R&D, Cristalia, April 2004).

This strategy for negotiations with Merck was repeated in 2001 and 2003: "If they negotiate a lower price, we are not going to manufacture it, but if they don't, we want to be prepared" (E. Pinheiro, Head of Farmanguinhos, March 2002). Both in 2001 and in 2003 Merck ultimately agreed to reduce the price of efavirenz and the government withdrew its compulsory licence threat. At the same time, chemists were learning about complex technology and strengthening their industrial knowledge, which could be used, should the government decide to impose a compulsory licence: "In any case it's not wasted technology. And when the patent has expired... In my opinion it's important to work on these molecules" (Head of R&D at Cristalia, op. cit.).

Reverse engineering was a way both to reduce the cost of acquiring the patented medicine and to increase national technological capacity until the medicine could be produced locally, either once the patent had expired or following its suspension with the issuing of a compulsory licence: "we have the technology for lopinavir, nelfinavir, efavirenz; we have developed these technologies, but we cannot produce them: they are patented" (Head of R&D at Cristalia, op. cit.). The private laboratories were dependent on a compulsory licensing decision to recover their R&D investment. "The government had used the threat of a compulsory licence in 2001 and 2003, but had backed down both times: "Last year we worked on patented products: nelfinavir and efavirenz. The government told us it was going to break the patents. It asked us to carry out development work. We spent a lot of money, namely on purchasing raw material. And nothing happened. We carried out this development

right up to the test-run stage: 5kg of nelfinavir and 1kg of efavirenz ... and the government was insisting, they said we were going to do it, we were definitely going to do it!” (CEO of Labogen, April 2004). In 2003, the federal laboratory’s chemists travelled to India and China to visit the manufacturers of the generic medicine, to identify potential suppliers and to collect raw material to make progress with the reverse engineering. This material arrived in Brazil by diplomatic bag to avoid legal conflicts with Merck. The national laboratories thus accumulated knowledge and technology for the production of efavirenz. In March 2004, the public laboratory of the state of Pernambuco, LAFEPE, and two private laboratories, Cristalia and Cellofarm, registered a medicine “similar” to Efavirenz with ANVISA.

At the time, in 2003 and 2004, the Ministry of Health was pursuing a double strategy, negotiating a voluntary licence for efavirenz with Merck, and preparing for a compulsory licence if and when the negotiations were to fail<sup>6</sup>. A technical note from the Ministry of Health in 2004 detailed a compulsory licence scenario which provided for both importing the generic medicine to maintain the supply for the AIDS Programme, and implementing national production. A confidential table listed the Indian laboratories that could potentially supply imports and the national laboratories capable of providing the active principle (Cristalia, Nortec and Labogen – the document told us that the latter had produced pilot batches) and the final medicine (three public laboratories Farmanguinhos, LAFEPE, FURPE, and a private laboratory, Cristalia).

The Brazilian laboratories’ progress in the reverse engineering of efavirenz generated strong opposition from Merck. In 2001, Merck wrote a letter of warning to the Farmanguinhos federal laboratory prohibiting it from procuring the raw material for Efavirenz in India. Farmanguinhos replied that Brazilian patent law authorized it to carry out research on the imported medicine provided it was not for commercial ends. In 2004, the confrontation intensified when ANVISA registered three formulations of a “similar” medicine developed by national laboratories, and when the federal laboratory put out a call for tenders to purchase 200kg of raw material for efavirenz. Two rationales clashed directly. On the one hand, the Brazilian federal laboratory defended the possibility of starting R&D work on a patented medicine to register the generic medicine with ANVISA without having to wait for Merck’s patent to expire (this is what is called the “Bolar exemption”, after the 1985 US jurisprudence incorporated into Brazilian law). Farmanguinhos explained that the purchase of 200kg of raw material from an Indian generics manufacturer was for research purposes, namely for to produce samples on a pilot scale. A letter from Farmanguinhos to Merck explained that the federal laboratory sought to “master a new know-how to transform it into a new line of production that could be operational once the patent expires in 2012”<sup>7</sup>. The reverse engineering operations were justified in the name of public health and by acquiring industrial know-how. Moreover, Farmanguinhos defended its call for tenders by pointing at Merck’s inertia in the negotiations for a voluntary licence. On the other hand, Merck sought to protect its monopoly of the production and trade of efavirenz and made every attempt to stop the Brazilian chemists’ reverse engineering work. Merck argued that the call for tenders relating to a patented molecule was illegal, since it was the only authorized supplier given that it held the patent. The call for tenders was seen as “an illegal and inconceivable compulsory licence on the patented product”<sup>8</sup>. Very shortly afterwards, in October 2004, the call for tenders was

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<sup>6</sup> Document of the Ministry of Health, dated 21 July 2003: "Announcement on measures to reduce the cost of Aids medicines" and interview with the Director of FM, Nubia Boechat, in March 2004.

<sup>7</sup> Letter by the Director of FM, Nubia Boechat, dated 15 October 2004.

<sup>8</sup> Merck's appeal against the call for tenders, dated 18 february 2005.

suspended and the negotiations for a compulsory licence resumed. A Merck team visited the federal laboratory's plants, but these negotiations failed due to persisting disagreement over the price Merck was offering Farmanguinhos for the raw material, and Merck's failure to supply the requested quantity "given the increase in the number of patients and the ensuing growth in global demand for Stocrin"<sup>9</sup> (letter from 17 February 2005). Against this backdrop, Farmanguinhos reopened its call for tenders to supply itself with generic efavirenz, and Merck took the matter to court to have the public purchase procedure cancelled.

The outcome of this trial was decisive, as the federal judges, although initially supporting Merck's argument, ruled in favour of the federal laboratory in August 2005 as well as on appeal in December 2006. The judges emphasized the public health interest and the urgent need to acquire the technology for the medicine, to avoid any delays in providing the generics to patients: "delays in developing the abovementioned research will cause delays in the acquisition of the technology and in the manufacturing of the generic medicines ... delaying or prohibiting production would be detrimental to public health due to the lack of generic medicines on the market"<sup>10</sup>. The production of generic medicines and public health took precedence over the interests of the patentee: "Given that there is a clash of interests in this affair, the emphasis must be on the fact that the economic interest of Merck, who owns the patent on the efavirenz medicine, does not stand up to the joint interest of protecting the economic order and public health" (Federal Court, 6 October 2005). Apart from enshrining the Bolar exemption into Brazilian case law, this decision paved the way to a compulsory licence. In December 2006, when the Regional Federal Court confirmed its ruling, the head of Farmanguinhos encouraged the government to issue a compulsory licence for efavirenz. Farmanguinhos argued that it could produce efavirenz for half the price offered by Merck. However, the court case opened by Merck in February 2005 had stopped research on efavirenz for two years<sup>11</sup>.

## **2) From a compulsory licence to a system of collective invention : the constitution of the efavirenz consortium (2007-)**

From 2004, as it devised compulsory licence scenarios, the Ministry of Health envisaged developing an industrial organization structured around a partnership between public pharmaceutical laboratories and private laboratories: "a compulsory licence to allow for national production of generic medicines, through public/private partnerships"<sup>12</sup>. Such an organization would bring together an official laboratory and a private active principle producer to develop a "vertical industrial process" that could integrate all the stages of production of the medicine. The Ministry's plan showed the details of the licence contract, which would attribute the part of the patent pertaining to the synthesis of the active principle to a pharmaceutical-chemical producer, and the part pertaining to the formulation, to an official laboratory. The partnership would achieve industrial complementarity between public laboratories, which specialized in the stage of formulation of the medicine, and private laboratories, generally specialized in the chemical synthesis of active pharmaceutical ingredients (APIs). A table showed this complementarity between raw material suppliers, more or less advanced in reverse engineering (Cristalia, Nortec, Labogen), and laboratories with short-term capacity for the production of the medicine (the public laboratories Farmanguinhos, LAFEPE and FURPE, and Cristalia, the only private laboratory that carries

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<sup>9</sup> Stocrin is the Merck's trademark for efavirenz.

<sup>10</sup> Decision of 6 October 2005, Federal Regional Court of the 2<sup>nd</sup> Region.

<sup>11</sup> Interview with the Deputy Director of FarManguinhos, Jorge Costa, in May 2009.

<sup>12</sup> " Issuance of a compulsory licence by the Ministry of Health to guarantee sustainable access to HIV/AIDS treatment", Technical Report, Ministry of Health, 2004.

out both the chemical synthesis of the API and the formulation of the final medicine). An expert report produced on 15 February 2005 by the federal laboratory's former intellectual property manager also recommended forming "win-win" partnerships to ensure the production of patented ARVs, for which a voluntary or compulsory licence could potentially be issued<sup>13</sup>.

The intellectual property implications, the compulsory licence, the aspects of industrial organization and the formation of a consortium all developed simultaneously. On 3 April 2007, the federal laboratory published a call for tenders for the pre-selection of laboratories to produce the active principle of efavirenz. A director of Farmanguinhos visited the Brazilian laboratories to assess their production capacities and wrote a technical report that was to be a building block for the formation of the consortium: "he wrote a report which selected six Brazilian companies capable of meeting the requirements of production" (interview with the assistant director of FM, May 2010). In the meantime, on 24 April 2007, the Ministry of Health issued a decree that declared "the public interest" of the patent on efavirenz with a view to granting a compulsory licence for public and non commercial use. The compulsory licence decree was then taken on 4 May 2007 for a renewable period of 5 years<sup>14</sup>. Insofar as the compulsory licence is by definition non-exclusive, it could be distributed to all interested laboratories in the country. In Brazil, it was used by a collective of public and private laboratories bound by a consortium contract.

Since it was dedicated to "public and non-commercial use within the framework of the Brazilian AIDS programme" (Article 1 of the compulsory licence decree), it was placed under the authority of the Ministry of Health. Thus the Farmanguinhos federal laboratory was entrusted with organizing a jury to audit the nine pre-selected national companies and selecting the three firms that would be members of the efavirenz consortium<sup>15</sup>. The jury was composed of chemists from the federal laboratory, the Director of the official laboratory of the State of Pernambuco, an external consultant, a legal practitioner, and a member of the pharmaceutical industry trade union, ABIFINA. Each of the nine companies was assessed based on "its technology, the estimated time needed to develop production, its production capacity, its estimated costs, its R&D capacity, etc." (Jorge Costa, May 2009). On 24 July 2007, the outcome of the call for tenders was published in the Official Gazette. The consortium agreement binding the three private laboratories to the Oswaldo Cruz Foundation was signed in December 2007, and renewed in 2009<sup>16</sup>. Industry-related decisions and those pertaining to intellectual property were completely intertwined, under the supervision of the Ministry of Health. The federal laboratory of the Oswaldo Cruz Foundation was the obligatory point of passage in the process of nationalizing efavirenz, from the first steps of reverse engineering, the lengthy trial with Merck, and the public interest and compulsory licence decrees, through to the creation of the efavirenz consortium. This consortium is the product of the compulsory licence, its industrial arm.

Let us look at the justifications and rationales underpinning the collective organization put in place to produce this public interest medicine. Sharing the development of the technology and production of the medicine under compulsory licence was initially motivated by a short-term rationale, concerned with supplying the Brazilian AIDS programme with a

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<sup>13</sup> "Analysis of medicine patents on ARVs, for which applications for licences have been filed with the Ministry of Health", 15 February 2005. This expert report was dated three days before Merck filed its complaint against FarManguinhos. Communicated by the author.

<sup>14</sup> In the autumn of 2011, the federal laboratory consulted firms in the consortium on the renewal of the compulsory licence in 2012.

<sup>15</sup> Interview with J Costa, May 2009.

<sup>16</sup> The consortium agreement was provided to us by Jorge Mendonça who currently supervises in FarManguinhos the running of the consortium.

generic medicine certified by ANVISA. The industrial collective created made it possible to organize complementarity and a vertical division of labour between the private laboratories, in charge of producing the active principle, and the official laboratories – initially Farmanguinhos in Rio and LAFEPE in Recife – that were to take care of the formulation. Insofar as three private laboratories were involved in producing the raw material on a rotating basis, and two public laboratories had been identified to jointly ensure the production of the final medicine and its delivery to the AIDS programme, the consortium ensured secure supplies. It was thus able to compensate for any problems the participants may encounter, of any failure on their part. For the designers of the consortium, the idea was also to encourage technological improvement within the different laboratories by providing an incentive with a fixed price: “the aim is to avoid being dependent on a single supplier, but to have a single price, thereby encouraging the optimization of the processes involved” (Jorge Costa, Farmanguinhos, May 2009). The consortium introduced complementarity between the public and private participants, and guaranteed a secure supply, which the government considered to be strategic (any failure on the part of the Brazilian laboratories would undoubtedly ruin any chances of compulsory licences being used in the future for medicine in Brazil).

It also allowed for the mobilization of the R&D capacities of the different laboratories, which are medium-sized laboratories (the largest one, Cristalia, has 2,200 employees). All the laboratories, both public and private, had access to the technological expertise of the Farmanguinhos federal laboratory’s Analytical Center, dedicated to knowledge sharing. For the development of certain technologies, the consortium allowed for the pooling of R&D investments, part of which was covered by the State. It is worth pointing out a peculiarity of this technological development programme: the acquisition of technology through reverse engineering was part of a production programme shared amongst the participants and guaranteed by the Ministry of Health’s public purchases. The “service contracts” the Ministry of Health entered into with the private laboratories to acquire APIs secured their investment expenses. Also significant is the fact that the process of acquiring the technology for efavirenz partly took place during production, to overcome difficulties, to perfect and improve processes that were not patented by the participants which, on the contrary, they were likely to share.

The creation of the efavirenz consortium simultaneously followed a short-term and long-term rationale. The duplication of a medicine as sophisticated as efavirenz involved a learning process for all the different participants. All the members of the consortium had to improve their technology to meet the production standards set by the federal laboratory and to increase their margin on the price fixed in the contract. By participating in the consortium, the laboratories were able to stay at the forefront of technological development. By sharing the volume of efavirenz production across three laboratories, the government also clearly demonstrated its interest in strengthening a group or cluster of national laboratories capable of producing pharmaceutical raw material for which the Brazilian industry was highly reliant on Indian or Chinese suppliers: “in Brazil you have a small number of companies in this sector; it is too small; Nortec, Cristalia, Globe, Cyg Biotech, etc.” (Jorge Costa, Director of Innovation at the Oswaldo Cruz Foundation, October 2011). The consortium helped to consolidate this industrial core, which the federal laboratory’s management and the Ministry of Health felt was still too limited. The selected firms benefited from economic advantages – increased production and sale of sophisticated raw material – as well as technological advantages – as a result of learning about the duplication of a complex molecule. While this cluster of national laboratories was strengthened by the consortium, it was also the fruit of pre-existing cooperation between the participating firms. The three private laboratories selected through the call for tenders to constitute the efavirenz consortium, namely Cristalia, Nortec and Globe, had been cooperating with public laboratories for several years, especially with

Farmanguinhos in Rio, as well as the Lafepe laboratory in Recife, with regard to the copying of ARVs. Two of these private firms, Cristalia and Nortec, had directly worked together in 2006 to share the reverse engineering of the synthesis of another ARV, tenofovir. Nortec also had specific historical ties with the federal laboratory, seeing as this pharmaceutical raw material producing firm was a spin-off of the federal laboratory, to which it had remained bound by research contracts renewed periodically. Nortec entered the field of ARV copying in the early 2000s, at the federal laboratory's request (1/5 of its capital was held by a public bank).

The consortium was thus constituted within a community of public and private laboratories that were regularly sharing technological information with one another and were linked through commercial transactions and research and development contracts. The consortium benefited from this tradition of "know-how trading" (Von Hippel, 1987), as much as from the circulation of chemists from one laboratory to another, from Farmanguinhos to Nortec (the current Director of Nortec is a former researcher from FM) and from Nortec to Farmanguinhos (the federal laboratory's Assistant Director, who initiated the consortium, was a former researcher at Nortec). Such cooperation is currently encouraging the proliferation of new partnerships: the members of the Efavirenz consortium are involved in a large number of PDPs (Product Development Partnerships) supported by the new public incentives of the December 2010 law (preferential margin for national laboratories committed to developing new technology and products). Taking Cristalia alone, as of autumn 2011 the firm was involved in a dozen PDPs, which led to the strong growth of its API R&D and production units<sup>17</sup>. Participation in the Efavirenz consortium has constituted a stepping stone to enter into recent PDPs.

### **3) Contractual obligations and the consortium's collective invention practices**

The most remarkable aspect of the consortium agreement reached between the Oswaldo Cruz Foundation and the three private laboratories (Cristalia, Nortec and Globe) is that it advocated industrial cooperation to support the goal of "supplying the Ministry of Health's AIDS Programme" (title of the contract). The industrial organization is based on a public interest mission, as the consortium is part and parcel of Brazil's health policy. This explains the crucial role of the Farmanguinhos federal laboratory in the constitution and day-to-day running of the consortium. We have seen how the private laboratories were integrated into the government's policy of universal access to ARVs: they had been supplying the AIDS programme for several years and knew that their local production offered the government precious leverage against international laboratories: "Cristalia was already involved in antiretroviral drugs before, so, we have a partnership; we didn't always win the tenders, but just the Ministry of Health knowing there was a local supplier meant it could put more pressure on the other multinational companies" (Cristalia, September 2011). Their industrial interest in antiretrovirals was closely linked to the Brazilian government's health policy: "we are Brazilians, and we don't have too many API producers in Brazil to trust; it was the time to show we can do these kinds of things" (Cristalia, op. cit.).

The consortium brought the three private laboratories together to form a collective organization, the CNG (Cristalia-Nortec-Globe) consortium, which entered into a contract with the Oswaldo Cruz Foundation to supply it with active principle according to the technical specifications set by the federal laboratory. This collective has a hierarchy, with one laboratory, Cristalia, identified as "the leader laboratory": it is bigger than the others, has

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<sup>17</sup> Interview with the head of the API Division at Cristalia, and visit to the industrial site undergoing extension, at Itapira, State of Sao Paulo, September 2011.

greater R&D capacities and can produce both the API and the final medicine in the event of having to take over production from the federal laboratory. The first obligation faced by the companies in the consortium was to possess a factory on national soil within which the API would be produced. The domestic production constraint was motivated both by the compulsory licence legislation, which was only valid on Brazilian soil, and by the government policy of developing the national production of pharmaceutical active principles. All the API production, circulation and stocking operations were codified and programmed by the contract – from the arrival of the raw material purchased by the companies to produce the API, the industrial transformation processes they use, the manufacturing best practices they must observe, to the conditions in which the final products are stocked, manipulated and transported to guarantee their quality. The contract provides the structure and framework for managing the contracting firms' production, by providing detailed regulation on the circulation of the products and technical information. Thus, API producers have to share all their technical material with the federal laboratory. All production incidents must immediately be reported to all the members of the consortium, and the latter must honour the federal laboratory's information requests: "the firms that belong to the consortium must provide all the information pertaining to difficulties encountered that is requested by the contracting party – the Oswaldo Cruz Foundation" (Article 7.10). Meanwhile, the federal laboratory must keep a record of production incidents and share it with the firms (Article 6). The federal laboratory centralizes all this technical information and oversees and steers production, through its technical specifications to which the firms must conform and through direct supervision exercised by its technical services (Article 10). In the event that difficulties are encountered, if the participating firms propose solutions, the federal laboratory must agree before production can resume. The flow of technical information, both during routine production and when production problems arise, has strengthened the integration of the industrial collective, under the authority of the public laboratory. This vertical flow is complemented with horizontal flows between the private firms that must share information on production incidents. They are also authorized to agree amongst themselves how to divide up the production if one of them were to leave the consortium (Article 7.11).

What can we make of the concrete exchange economy within the consortium, in light of the narratives collected from the federal laboratory and the private firms? To what extent is knowledge pooled within a consortium that brings together both competing firms (the three API producers) and complementary firms (the laboratories that produce the APIs on the one hand and those that produce the final medicine on the other)? And to what extent has this collective managed to overcome the production problems or even crises that were an inherent part of the process of implementing the compulsory licence? What did the participants gain in terms of pharmaceutical knowledge?

Let us first look at the creation of technology for both production and the analysis of the active principle and the medicine. It occurred in a situation of emergency, even though the Brazilian laboratories had already carried out work on efavirenz before the compulsory licence decision was reached: "the involvement of Cristalia with efavirenz started before the compulsory licence ... we didn't know about the compulsory licence ... we were not expecting that ... we just wanted to have some new development ... we wanted to develop the technology to be able to make efavirenz" (Director of the API unit). We have already discussed the fact that the federal laboratory had been carrying out reverse engineering work on the medicine since 2001, and that several laboratories had registered a medicine similar to efavirenz with

ANVISA in March 2004. This work, however, had been carried out on a laboratory scale<sup>18</sup>, rarely on an industrial scale. The federal laboratory's research was brought to a halt from February 2005, in the wake of the legal proceeding instituted by Merck. The federal court authorized reverse engineering work to resume in December 2006 only. In April 2007 the Ministry of Health issued a public interest decree for efavirenz that seemed to announce a new showdown. The Cristalia laboratories were attentive to the government's decisions and pursued their development work: "here we were at the beginning of 2007, developing the synthesis of efavirenz; and all of a sudden, came this first publication from the Ministry of Health". In spite of the initial work they had carried out, they had to change the technology to increase the safety and productivity of the synthesis process: "we had to change that technology after those first batches because the chemical yield was low, so the cost would be very high; so we changed it" (op. cit.). For technical as well as economic reasons, this change of technology involved further investments and was carried out in a rush, to meet the demand from the Ministry of Health and to take part in the pre-qualification evaluations for the future consortium: "so it was a great effort, a lot of rush in those days, to buy materials, and try, and improve the synthesis". Cristalia later found out that the other firms were also changing their synthesis process: "we learned later that the other two companies also changed it in the same ways". Why later? Because that was still the competition phase, before the private laboratories were selected for the consortium. Each API producer developed its own synthesis process separately. Cristalia discovered the other laboratories' respective technology only after the consortium had been set up, once production was launched (the consortium agreement was signed in December 2007). It is interesting to see how the different private laboratories converged towards the same synthesis process, with but a few differences: "so all the companies have the same chemical route ; we may use different solvents, but, we use the same materials for production" (Cristalia). Yet to develop this synthesis process, the Brazilian laboratories could rely neither on the patent, which turned out to be very incomplete, nor on a transfer of technology from Merck, in spite of an article of the compulsory licence obliging the patentee to share the information it held (Article 5). They did however draw on the scientific literature and reviews on the evolution of the synthesis of efavirenz. Furthermore, one of the articles published in 2008 in the international literature on the synthesis of efavirenz was the work of two Brazilian chemists, respectively the former Director of the federal laboratory, Eloan Pinheiro, who was then a consultant for the Ministry of Health, Octavio Antunes, a professor at the Federal University of Rio de Janeiro who was a scientific adviser to Nortec, one of the members of the consortium, and a third author, Joseph Fortunak, a Harvard chemist who served as an adviser to the Brazilian laboratories (Pinheiro, Antunes, Fortunak, 2008). The Brazilian laboratories were perfectly up to date with international knowledge on the synthesis of the different antiretrovirals. The synthesis method they eventually chose was not the one indicated by Merck in its patent. We therefore cannot speak of a copy or duplication of the patented technology, but of the acquisition of a technology disseminated through the channel of open science and sharing between industrial laboratories and university laboratories: "it's a classic path, the three industrial laboratories are following the same path" (Director of Innovation, Fiocruz)<sup>19</sup>. The federal laboratory researchers contributed to certain tasks: "I know that Marcus from Nortec has helped with some part of the synthesis, of the process: doing some purifications, the samples of companies of the

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<sup>18</sup> The Synthesis Department at FarManguinhos had developed a synthesis process for Efavirenz on a laboratory scale in 2003 (interviews with the laboratory's chemists, april 2003).

<sup>19</sup> A chemist who was a member of the efavirenz consortium's selection committee informed us that one of the laboratories whose tender had not been accepted, Microbiologica, had proposed another and very original synthesis route. This proposal by a pharmaceutical laboratory that was highly efficient in terms of R&D attests to the technological resources of Brazilian laboratories.

consortium like Cristalia; people in my group went to Cristalia to see the process; but just to help” (R&D Director, FM, May 2010).

As for the method of analysis of Efavirenz, it was developed by the federal laboratory that distributed it to the three private laboratories of the consortium. It took 18 months of work involving four chemists from the Farmanguinhos Analytical Center to develop the method. Here too, relying on Merck’s patent was not an option: “the method of analysis described in Merck’s patent does not correspond to the product” (May 2009 meeting at the federal laboratory). The chemists drew on the work they had carried out in 2002 for the Health Surveillance Agency to develop the standard for the molecule. The specifications and the method of analysis of the molecule produced by Farmanguinhos were shared among all the members of the consortium and constituted a means of controlling production. Two laboratories sent personnel to Farmanguinhos to learn the method and Farmanguinhos also dispatched its chemists to the companies. The federal laboratory carried out the testing of the three industrial laboratories’ product samples. The test results were given to the laboratories in consortium meetings, or separately with each one of them for more sensitive information. The public laboratory provided both a collective space in which to share data, and reserved spaces. Apart from test results, FM sometimes suggested possible improvements to the synthesis processes used by the API producers. It furthermore developed the technology needed for the formulation of the final medicine, in a spirit of urgency and on the basis of a deficient patent. Real progress was made when FM managed to obtain a quality active principle. The chemists responsible for the formulation told us that this technology did not require any particular inventive work (it was decided that the same excipients as Merck’s would be used, even though it was difficult to get hold of them in Brazil).

Two modes of development of Efavirenz technology stand out. On the one hand, the synthesis technologies were developed separately by private laboratories in the context of the selection of the future consortium members. Information on the synthesis processes was only shared later, during production. On the other hand, the federal laboratory opted for deliberately sharing the method of analysis of the molecule, which was taught to all the members of the consortium. It assertively played its part as a technological platform available to all Brazilian laboratories, both public and private.

Faithful to the letter and spirit of the consortium agreement, Farmanguinhos oversaw the private laboratories’ production and centralized all the technical information. In early 2007, FM began to collect information on the firms’ technological capacities and the synthesis processes they intended to use during visits to the industrial sites for the phase of pre-selection of the private laboratories. Once the consortium was set up, FM created a commission to monitor the production of API, composed of two branches: a logistic branch to monitor and raise any supply issues the private laboratories may encounter; and a technical branch to resolve any problems that could arise in the production of APIs. This technical commission was comprised of four individuals from the Farmanguinhos production, development and quality departments<sup>20</sup>. It was very active in the starting phase of production and in times of production crises; afterwards the meetings became less frequent. The industrial laboratories described to us the federal laboratory’s close supervision from the moment a “service contract”<sup>21</sup> was agreed between the two parties to supply Farmanguinhos:

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<sup>20</sup> Interview with Jorge Mendonça, FM, September 2011.

<sup>21</sup> Service contracts were introduced by a law in 2008, which authorized the Ministry of Health to acquire pharmaceutical raw material without going through the standard procedure of public markets. This procedure is governed by the rule of the lowest bidder wins, which would be to the detriment of the quality of APIs. Service contracts were signed for five years with a laboratory established in Brazil, to acquire high-quality API.

“we have to buy the raw material, the intermediate, and they contract production, and they monitor the production. They come to see the analysis of the raw material, they come to see the production, they come to see the analysis of the final API; they really follow up” (Director of Nortec, May 2010). Technical discussions were particularly frequent between Nortec and the federal laboratory, since the two partners were in close proximity to one another and shared historical ties through technological cooperation.

Farmanguinhos held knowledge about all the consortium partners’ production processes, whereas their knowledge was fragmented: “each company has the freedom to choose the small variations of the process, provided that the final quality against specifications is the same; and then FM goes to Cristalia, goes to Globe, and comes here, they have the whole view of the three processes; but I do not have the complete view of the others companies’ processes” (CEO, Nortec, op. cit.). FM governed a common space for technological sharing while also providing private space for each firm: “we have meetings among the consortium members; but the information exchanges are done one by one; we have some common rounds for the discussion: everybody uses the same intermediate, yes; everybody uses the same material triphosgene, yes; ok; one uses two or three; Cristalia uses two of the same as mine, the third is different, and Globe, I don’t know what salt they use; we define some broad variables that are the same” (Nortec, op. cit.)<sup>22</sup>.

The exchanges within this consortium went beyond this half-individual half-collective framework during the times of difficulty or crisis that characterized the first few years of production, between 2008 and 2010. Crises and their resolution accelerated the development of ties and collective learning between the firms: “we also learn how to work together, it’s another level of learning” (Cristalia, September 2011). The first issues arose in 2008 during the bioequivalence trials for the registration of the federal laboratory’s Efavirenz as a generic medicine. The first trial on 60 healthy volunteers did not yield the results anticipated and the researchers at Farmanguinhos had to go backwards to modify the formulation as well as the method of analysis of the molecule (the Brazilian chemists had initially used the method indicated by Merck in its patent, which turned out to be insufficiently reliable to evaluate the products<sup>23</sup>). The second trial was satisfactory and the Brazilian efavirenz was certified as a generic medicine by the Brazilian Health Surveillance Agency, ANVISA. In 2010, Farmanguinhos encountered serious production issues, to the extent that manufacturing had to be put on hold for several months. In the meantime, the laboratory lost batches of product.

The problems were mainly to do with the delivery of APIs from one of the three suppliers (the consortium had planned for the suppliers to alternate over time: there were no issues with the first supplier; with the second, there were problems with a few batches; with the third, production had to stop). The chemists made several hypotheses: was it do to with polymorphous molecules or was it because of the stocking and transportation conditions? The technical commission went to visit the factories and the industrial laboratories came to Farmanguinhos to identify the problem. The federal laboratory put pressure on the private laboratories to harmonize their synthesis processes, which turned out to be very similar to one another: “it seems that FM had some difficulties with different materials; the chemical roads were the same; and they worked with Cristalia’s efavirenz, Globe’s efavirenz, Nortec’s efavirenz; and at some points the results were a little different; the dissolutions, a key issue for pharmaceutical production, were not homogeneous; and they put a lot of pressure on us,

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<sup>22</sup> This management of private and collective spaces within the consortium is similar to that found in biotechnology research consortiums, described in Cassier, 1998: "Le partage des connaissances dans les réseaux scientifiques", *Revue Française de Sociologie*. (The sharing of knowledge in scientific networks).

<sup>23</sup> Interview with the head of bio-equivalence tests for Efavirenz, Fiocruz, Rio, May 2010.

you have to do the same chemical roads” (Cristalia). Two of the three laboratories decided to use the same Indian supplier for a key intermediary product in the synthesis of efavirenz, in order to minimize sources of variation in the APIs. Nortec decided on an Indian generics manufacturer who had a formulation of efavirenz. At one point, the laboratories considered sharing information with Indian chemists, and inviting them to Farmanguinhos to resolve the problem (interview with the Assistant Director of FM, May 2010). Farmanguinhos eventually posited that the size of the crystals was to blame: “we learn, everybody was learning about this; that the API should be as we say ‘micronized’, the size of the crystal had to be very small; and FM says ‘Oh, this is the problem’; and they included this in the specification; the size of the crystal is key; but at first no one knew that!” (Cristalia). The federal laboratory modified its specifications and the private laboratories adjusted their process to meet the new specifications. During this crisis, the private laboratories discussed amongst themselves the question of the size of the crystals: “we discussed this with other companies that used to make efavirenz; we asked: “have you had any problems when you micronize; yes! I have to micronize but it depends: every client asks for different crystal sizes; so it depends on the client; we knew, all three producers, we knew the problem was not the API” (Cristalia). They formulated another hypothesis, that the production issues surely had less to do with the size of the API than with FM’s steering of the production process: “we knew, all three producers, we knew the problem was not the API; it was not the formulation, I don’t think it was the formulation, but it was the way they were producing, more time here, less time there, drier, the size of the powder after the granulation” (Cristalia, op. cit.). Formulating such a diagnosis implies the pooling of knowledge within the consortium, both between the private laboratories, and between them and the federal laboratory.

The pooling of knowledge further increased during the few months when the federal laboratory put its production on hold and when it was replaced by Cristalia for the production of the final medicine (as Cristalia did both the production of APIs and the formulation of the medicine, it could take over from the public laboratory). For this, Cristalia received a special service contract: “last year we took over part of FM’s production” (Cristalia, 2011). This substitution of laboratories within the consortium changed the way the products and technical information circulated: Cristalia was now receiving all the APIs from the other laboratories, as well as the relevant technical information. The rotation of roles within the industrial collective entailed a de facto pooling of technical knowledge. By using all the producers’ APIs, Cristalia was able to show that the production problems encountered by the federal laboratory were due not to the APIs’ characteristics but to the production process used: “they all ship their APIs to Cristalia; Cristalia didn’t work only with the API we make; we work with the others too; and they worked; and they worked !” (Cristalia, 2011).

To what extent can this be seen as collective learning, if not “collective invention”<sup>24</sup>, within the efavirenz consortium? Whereas the development of the synthesis technology was carried out separately by the Brazilian laboratories in the context of the selection of firms competing for the call for tenders, to become part of the Efavirenz consortium, the implementation of the consortium agreement and the subsequent launch of production led to direct knowledge trading between the private firms and between these firms and the federal laboratory. Resolving production problems required mutual adjustments, as well as the adoption of new product specifications, which accelerated the sharing of technical information, including between rival private firms. The rotation of roles within the

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<sup>24</sup> The notion of collective invention was coined by R. Allen in 1983 to characterize the improvements to iron and steel technologies in a 19<sup>th</sup> century English industrial district, through a process of disclosure and circulation of information between local firms. He also described a dynamic of collective invention in the network of owners of the Bessemer patent in the USA ; R. Allen, 1983, “Collective Invention”, *Journal of Economic Behavior and Organization*, 4, p 1-24 .

consortium, when the Cristalia laboratory replaced the federal laboratory to produce the final medicine for a few months of 2010, further reinforced the pooling of information. All these adjustments to produce a medicine specified and certified by ANVISA were thus shared by a collective of Brazilian firms, whose technological capacities had been reinforced: “we all learnt a lot on the technology, there was a lot of learning; we learnt, but Farmanguinhos learnt a lot; so did Globe Chemical and Nortec; we also learnt how to work together, it’s another level of learning; one thing, Cristalia knows how to make efavirenz, Nortec too, and Globe Chemical too; so to do it together is different” (Director of APIs, Cristalia). The strength of the collective was demonstrated on several occasions, namely when it was necessary to compensate for the production deficiencies of the Pernambuco public laboratory, the LAFEPE, that had not managed by that stage to obtain ANVISA's certification for its generic efavirenz, to the extent that Farmanguinhos ended up ensuring full national production, which was initially meant to be shared between the two public laboratories, and when the federal laboratory’s own production was put on hold for several months in 2010.

At the same time, exchange between the participants was not perfectly reciprocal; closer ties and sharing initially developed between two of the three laboratories: “we have meetings among the consortium; but the information exchange is one by one; we have some common rounds for the discussions: everybody uses the same intermediate. Yes; everybody uses the same triphosgene material; Cristalia uses two that are the same as mine, the third is different, and Globe, I don’t know what salt they use” (Director of Nortec). The federal laboratory then adopted a policy of deliberately sharing the technology it had developed, namely the methods of analysis of the product, whereas the private laboratories shared knowledge mainly to overcome production crises. From the start, the public laboratory’s technology and specifications were common goods within the consortium. A crisis between Farmanguinhos and one of the private laboratories came to a head in 2010, due to production problems with some of the API batches and the supplier's reluctance to cooperate with the federal laboratory’s chemists.

If there was genuinely collective learning, can we speak of “invention” even though it pertains to the reproduction of a known molecule? First, whether it be the synthesis technology or the methods of analysis or formulation, they were never the fruit of simple duplication of the information contained in Merck’s patents, which proved very limited on these different points. Merely copying the indications contained in the patent resulted in a method of analysis which was insufficiently discriminating. The reproduction of patented technology involves re-invention work by the generic manufacturers’ chemists. Secondly, the synthesis processes actually implemented by the Brazilian laboratories were not the ones indicated by Merck in its patent, simply because many improvements had been suggested since: “what I know it is 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 their synthesis; now there are more practical syntheses, more straightforward, safer, less expensive; a lot of improvements; after that patent different processes were developed; much more efficient; and safer ... our synthesis is different from Merck’s” (Cristalia). The Brazilian chemists drew on the scientific literature on the topic, as well as direct interaction with academics. Thirdly, we pointed out that the Brazilian laboratories modified their specifications, processes and raw material in the course of production. These process improvements occurred through “learning by doing” (Arrow, 1962) and were shared within the consortium. This is similar to the gradual technical improvements made by English steelworkers in the nineteenth century, drawing both on the technical literature and on their neighbours’ techniques to improve the efficiency effectiveness of their blast furnaces (Allen, 1983).

#### **4) The limits of vertical integration in the Brazilian efavirenz industry and collective R&D**

While efavirenz is now routinely produced by the Brazilian laboratories, to the extent that consortium meetings to resolve technical issues are no longer frequent, the process of nationalizing the medicine under compulsory licence nevertheless remains limited to the last stages of production. The Brazilian laboratories carry out only the last two stages of the API's chemical synthesis and purchase the key intermediary products in India or China: "so, today we don't have the process totally integrated; I am not happy with this situation, because, Brazil is strongly dependent; we produce the tablets, but we are strongly dependent on the Chinese and Indian producers; because Cristalia, Nortec and Globe make in Brazil the last step or the last two steps; in my opinion it's not good" (Director of Innovation at the Oswaldo Cruz Foundation, October 2011).

Although the federal laboratory had drawn up a R&D programme to develop the technology needed to produce the strategic intermediary products, the private laboratories producing the API did not follow. Admittedly, the consortium agreement was exclusively dedicated to the organization of the production of the medicine for the short-term supply of the Brazilian AIDS Programme and did not include any clauses pertaining to R&D tasks. The industrial collective therefore served to produce the medicine in a situation of emergency, but not to encourage, let alone pool, the firms' R&D efforts. In 2007, the Farmanguinhos management had envisaged an ambitious research strategy based on cooperation agreements between the industrial firms and universities: four academic research groups had been identified. The idea was that the firms interested would have two parallel contracts with the universities to put them in competition (interview with Farmanguinhos, May 2009). Only one firm had shown interest. In 2010, the Director of the federal laboratory bitterly remarked that this strategic R&D work to further integrate the Brazilian pharmaceutical industry had made no progress. He thought it was necessary to organize the co-development of technology, but saw this as "utopian" in light of the non-cooperative strategy of the firms in question when it came to R&D. This says a lot about the gap, in this area, between the policies of the federal laboratory and those of the private firms.

The interviews we held with the management of the private laboratories confirmed this lack of integration of production: they continued to depend on Indian and Chinese suppliers for intermediary products and were sceptical about the prospect of producing them in Brazil in the short term: "regarding efavirenz for instance, two or three years ago, people said "we will integrate, yes, the government is interested in integration"; but there is no formal initiative for integration ... The idea is there; it is just a matter of making it operational; but I would not expect it to happen soon" (Director of Nortec, May 2010). At the same time, discussions between the private firms and the Ministry have continued and have facilitated the identification of bottlenecks that do not just result from non-cooperative behaviour. Indeed, on their own, medium-sized companies like Nortec are not able to integrate a production unit for the key intermediary of efavirenz. The industrial investment required is beyond the reach of this kind of company: "we Nortec, are not interested in manufacturing the intermediate ourselves. Why? Because our plant is following GMP (Good Manufacturing Practices); so to run some of the reactions involved in the synthesis of efavirenz in a GMP plant is too expensive" (Director, *op. cit.*). Hence the idea of creating a national production unit that could supply the different API producers. This prospect could encourage inter-firm cooperation: "So if, I don't know how, this production process is developed, we are interested in cooperating to develop it; but we have to find a place to run those reactions" (Nortec, *op.cit.*). Whereas Nortec, a medium-sized chemical company, is reluctant to get involved insofar as it does not

envisage producing this intermediary in situ, Cristalia, a company with greater industrial and scientific capabilities, has in fact initiated an internal R&D project to develop this technology, though it has not been successful. The issue here is getting hold of a product to carry out the synthesis reaction: “so we have to use some chiral material to make this intermediate: part of this material that gives this special property to the intermediate is a derivative of ephedrine; so I wanted to buy 3kg of this derivative to do the tests. What's the problem? The problem is that ephedrine or pseudo ephedrine, is a banned drug in Brazil”. Cristalia’s multiple requests to the Brazilian Health Surveillance Agency to import this product have been unsuccessful: “I wrote to persons in charge of ANVISA: it’s for our production of efavirenz which is critical for Brazil; I want to make this intermediate that we import a lot; well, you do this, you write this, send me a letter explaining and then we evaluate ...” (Cristalia, September 2011). The Director of APIs at Cristalia also pointed out that it was easier to import the intermediary, given that the product purchased in India was of good quality and its supply was unrestricted: “I think it’s because we have reliable suppliers; they have the product; they have the product in good quality; at any time we need it; so, I think it put us in a sort of comfort zone”. The industrial actors interviewed concluded that there was a lack of initiative to develop this technology and organize industrial production in Brazil, despite the government’s policy to reinforce the Brazilian production of pharmaceutical raw material: “in Brazil, I would only say the technology is there, but we have to collect it; someone knows; but there is no structure for that” (Director of Nortec); “but there are now some companies in Brazil interested in making that intermediate; waiting to see if it works, it could to be good for us” (Cristalia).

Either the private firms do not have the industrial capacity to integrate the production of sophisticated pharmaceutical raw material (Nortec), or they are carrying out development work separately to try to capture the market (Cristalia). Either way, they are content with importing raw material that meets the production norms and specifications of the public laboratory. Nevertheless, in 2011 there was no lack of collective initiatives, several of which involved the Ministry of Health and the federal laboratory. We have noted a first partnership being discussed between the synthesis department at Farmanguinhos and a pharmaceutical chemistry company that is a spin-off of one of the consortium member firms, Globe. A work programme is in place between the two parties to develop a project for the verticalization of efavirenz production. The federal laboratory has put forward a second proposal to involve the petroleum industry public group, Petrobras, to develop a production capacity for pharmaceutical raw material. API firms like Nortec are also in favour of this idea: “we have proposed [this] to Petrobras because they are interested in an intermediate plant close to their petroleum complex. We proposed some ideas” (Nortec, 2010). This kind of production unit would allow the Brazilian pharmaceutical firms to overcome the problems of scale they currently face. This new factory would provide raw material for both agrochemistry and pharmaceutical chemistry. The Director of Innovation at the Oswaldo Cruz Foundation is also turning towards several pharmaceutical firms to introduce them into the field of pharmaceutical raw material (Director of Innovation, October 2011). A first project is already at a very advanced stage, concerning Glivec, an anti-cancerous molecule whose patent will soon be falling into the public domain. Others concern ARVs. Finally, one of the firms from the efavirenz consortium is currently involved in several partnerships to increase the Brazilian production of intermediaries: “we have found one company that could produce AZT that can make all the intermediates, for Lamivudine, maybe, for efavirenz, not yet, for tenofovir, could be; so it’s a matter of, we are trying to improve this model” (Nortec, op.cit.). This proliferation of initiatives to build broader industrial foundations for the pharmaceutical industry bears witness to the development of a highly active industrial environment, between a core of private firms and the public pharmaceutical laboratories.

### **5) The role of the State and of the federal laboratory**

The Brazilian State has played a crucial role in authorizing and organizing the nationalization of this medicine. It has done so through legal decisions regarding intellectual property and service contracts with which the federal laboratory could buy the active principles from the national producers, and through the federal laboratory's numerous actions to coordinate the consortium and directly produce technology and the final medicine. The nationalization process required the State to promote it as being in the public interest, so as to play on the flexibility of intellectual property law. The nationalization of efavirenz was thus instituted and managed through a series of State decrees and acts, namely the efavirenz public interest decree of April 2007, the President of the Republic's compulsory licence decree of May 2007, and the April 2007 call for tenders for the pre-selection of the API producer laboratories, the results of which were published in the Official Gazette in July 2007.

The Oswaldo Cruz Foundation and the federal laboratory, which is the foundation's industrial arm for medicine production, played a crucial role throughout this process. Both belong to the Brazilian Ministry of Health and also form one of its strategic arms. The federal laboratory and the Oswaldo Cruz Foundation were the first to start reverse engineering work that would be able to serve as a credible threat when the Ministry of Health's civil servants negotiated the price of efavirenz with Merck. The Oswaldo Cruz Foundation also provided the support needed throughout the court case opened by Merck in 2005 to stop reverse engineering operations. When the judges at the federal court in Rio dismissed Merck by defending the public interest, it was the federal laboratory that called for a compulsory licence decision to produce a generic efavirenz that would be 50% cheaper than the proprietary medicine. From this point onwards, the federal laboratory resumed R&D work to develop the necessary technology. It set out to visit, evaluate and select private laboratories, and even to take part in the production. Farmanguinhos had two priorities: a technical priority to elaborate the methods of analysis and the specifications to be communicated to all the parties involved, and a State or official one, to constitute the jury of the consortium, select the API producers and negotiate the consortium agreement. This agreement entrusted the federal laboratory with overseeing the private laboratories' production operations. It centralized the consortium's technical records (all the documentation that the private laboratories were required to provide) and the hierarchical authority that ultimately decided whether production could resume or not if problems were to arise.

This official authority can still be felt in its management of the technical information it communicates to the private laboratories, either collectively or separately, depending on the nature of the information, thereby protecting the interests of each partner within the consortium. It still plays a special role in the pooling of technology, by sharing its work with all the parties. The federal laboratory has also been responsible for the tasks surrounding the registration of the generic medicine with ANVISA and recently announced its willingness to enter into a procedure to pre-qualify the Brazilian efavirenz with the WHO, which would make it the first Brazilian ARV to be certified by the international organization<sup>25</sup>. Lastly, it has initiated several projects to create a national production of pharmaceutical intermediaries to complete the nationalization of Efavirenz. Thanks to its joint scientific and political authority, it could create a framework for cooperation with the ability to go beyond or to federate the API producing laboratories' scattered initiatives. We could say that the State is not just a blind spot from which all these actions are organized, but equally the fruit of these multiple legal, scientific, industrial and sanitary decisions and actions. The roles of the federal laboratory, the strategic arm of the Ministry of Health, in production, the creation of

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<sup>25</sup> Unfortunately, this procedure was not completed by the Brazilian laboratory so that today all generic efavirenz prequalified by the WHO are produced by Indian, South-African or American laboratories (WHO List of Prequalified Medicinal Products, December 2016).

technology, intellectual property matters, the coordination of partnerships with the private sector, the regulation of the generic medicine's price and the field of certification, have made it an essential actor in the formation of this political economy of medicine.

### **Conclusions**

The process of nationalization of efavirenz sheds light on the particular case of the interlinking between bio-industry and bio-politics in Brazil. The medicine's history shows the politicization of the medicine industry, resulting from its role in the legal showdown engaged in by the Brazilian State to promote the interest of public health over intellectual property requirements. Efavirenz is associated with the President of the Republic and the Ministry of Health that prepared and decided on the compulsory licence, working with what could be called the "civil society" of patient organizations and international NGOs and with the Brazilian generic medicine industry that willed and supported the showdown in the hope of recovering its reverse engineering investments. Key events marked this politicization: the court case, the compulsory licence decree in May 2007, the first batches of Brazilian efavirenz inaugurated by the Ministry of Health in February 2009. In turn, the organization of efavirenz production through the implementation of the industrial consortium provided a social laboratory to experiment with and formalize the government's new industrial policy for pharmaceuticals.

This policy that emerged from 2006-2008 with the implementation of "service contracts", of the "industrial health complex" in 2008 and later of the Product Development Partnerships in 2010, can be said to be neo-developmental. These measures allowed for exceptions to the public market rule, and authorized price surpluses for the purchase of pharmaceutical active principles produced on Brazilian soil. The aim is clearly to encourage the substitution of imported products with national ones. This policy revives the developmental policies of the 1960s and 1970, which sought to acquire greater technological autonomy<sup>26</sup>. In the field of medicine, this policy was particularly active in the 1980s with the medicine central purchasing agency that funded a reverse engineering company, Codetec (Etkovitz & Brisolla, 1999 ; Cassier & Correa, 2008). Codetec went insolvent in the 1990s due to a policy of deregulated opening of pharmaceutical markets. There is now talk of recreating a R&D organization similar to what Codetec once was. This neo-developmentalism is characterized by: 1- close ties between industrial policy and public health policy (PDPs are launched and steered by the public laboratories); 2- technological development obligations (the authorization of a price surplus is justified by the laboratories' acquisition of new knowledge); 3- a policy of partnership between public and private laboratories; and 4- a possible opening to international generic medicine markets once efavirenz has been pre-qualified by the WHO (the Brazilian efavirenz could then supply the global fund or the Clinton Foundation). For the time being, Brazilian efavirenz remains a good for domestic consumption. This neo-developmental policy which associates domestic health needs and the acquisition of advanced technology by Brazilian firms may illustrate the notion of "social profitability" introduced by Celso Furtado in an article published in 2000 in the CEPAL journal. Furtado argues that "social profitability" associates national politics, the domestic market, technological learning and the reduction of inequalities. National efavirenz fits this model of development quite well.

Collective invention, through consortiums, PDPs, or innovation networks, provides a key tool for the new neo-developmental policy. It relies on collective learning processes in a context of "learning by doing", or on technological sharing. In the case of the efavirenz

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<sup>26</sup> Cf. C Furtado, 1981, "Commentaires", in *Technologie appropriée ou technologie sous-développée*, E. Arghiri, PUF, p 127-134 ; several public laboratories were created or revived during this period : Cassier & Correa 2003.

consortium, the pooling of knowledge was rushed and justified by the urgency of implementing a compulsory licence to support the credibility of the Brazilian State on the national and international scene: “there were a lot of risks for all the HIV programme; because, if we didn't make it, Brazil would just switch this production to India; and was still depending on them” (Cristalia, op.cit.). Industrial stakes aside, the application of this licence was crucial for medicine patent law both nationally and internationally: this is one of the first compulsory licences issued by a country from the global South and it was the first compulsory licence of a medicine in Brazil.

Collective invention was more difficult to develop during the constitution of the consortium, when rivalry prevailed between the firms for the selection of the consortium participants, and then later in making medium- to long-term R&D investments to create or recreate a national pharmaceutical raw material industry, as the firms had unequal scientific and industrial capacities and some were tempted to go it alone. Nevertheless, we have seen that the Ministry of Health and the federal laboratory have been actively seeking to build new alliances between the public sector, the private sector and universities; in other words to recreate a collective to produce pharmaceutical intermediaries. The creation of an “industrial health complex” led by the State, and the strategy consisting in reinforcing a cluster of national laboratories to produce APIs have justified collective actions: by setting up the efavirenz consortium, the federal laboratory has strengthened several national laboratories relatively equally.

Ultimately, the evolution of this medicine in Brazil has proved particularly fruitful for law, technology and industrial organization.

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