

Intellectual property and public health: copying of HIV/Aids drugs by Brazilian public and private pharmaceutical laboratories

DOI: 10.3395/reciis.v1i1.38en



Maurice Cassier

Centre National de la
Recherche Scientifique,
Paris, France
cassier@pop.vjf.cnrs.fr



Marilena Correa

Universidade Estadual do
Rio de Janeiro - Uerj,
Rio de Janeiro, Brazil
mcorrea@ism.com.br

Abstract

Brazilian public and private laboratories' experience in copying ARVs since 1993 has been a technological learning process that in some cases has produced innovations. Reproducing drugs and synthesizing their active principles involves the combination of information available in patent documents and the partial rediscovery of certain know-how through laboratory manipulations. Chemists have to reconstruct the numerous "cat leaps" in patent documents, and in so doing often improve on the published processes or formulae. Generics laboratories are also able to use this knowledge base to invent new formulae, combinations of existing molecules, or to discover new molecules. Since 2000 the five laboratories studied have filed about ten patents on ARVs. We pieced together this technological learning process by interviewing chemists at generics laboratories, using the methods of the sociology of science.

Keywords

Patent, technological learning, pharmaceutical innovations, reverse engineering

Introduction

On 2 June 2005 the Constitutional, Judicial and Citizenship Commission of the Brazilian House of Representatives unanimously passed a bill to place HIV/Aids drugs beyond the scope of patentable objects¹. Member of Parliament Roberto Gouveia justified this reform of the 1996 Brazilian intellectual property law in the following terms: *'Patents have to be suspended if they run counter to the interests of public health'*. Three weeks later,

on 23 June, the Health Minister announced a compulsory licence authorizing the federal government laboratory Far Manguinhos, of the Oswaldo Cruz Foundation in Rio de Janeiro, to undertake the production of a combination of two antiretroviral molecules without authorization from the patent holder. These measures of exclusion of patentability or suspension of patents specifically concerning Aids drugs were a consequence of the failure of the Health Ministry's negotiations with

three international pharmaceutical laboratories (Abbott, Merck, Gilead). The Ministry had hoped to obtain price reductions on four patented antiretrovirals that accounted for four fifths of Brazil's Aids programme expenditures. The international laboratories had also refused to grant voluntary licences to those Brazilian laboratories which had requested them, especially the Far Manguinhos federal laboratory. The granting of a compulsory licence and consequent local production of these drugs by Brazilian laboratories was seen to have a twofold public health and industrial advantage for Brazil. In respect of public health, generic versions were expected to cost half of what patented proprietary drugs did. In respect of industry, Brazilian public- and private-sector laboratories would thus be able to use their production and research capacities developed since the mid-1990s in the field of ARVs to fight Aids. However, a few weeks later the Brazilian Health Ministry backed down on its decision to use the compulsory licence and announced that it had reached a satisfactory compromise with Abbott on the price of the drug in question, Kaletra. Leaders of the Aids programme and NGOs deplored this decision which they believed would compromise the continuity of local production of generic drugs and the viability of the programme for the free distribution of tritherapies in Brazil². These conflicts over intellectual property on antiretrovirals have been recurrent in Brazil since 1996 when the country embarked on a programme of universal distribution of HIV/Aids drugs and local production of generic drugs³.

In this paper we consider the conditions of emergence of this generic industry at the intersection of public health policy, intellectual property rights, and industrial policy in the chemical and pharmaceutical fields. The first section shows how local production of generics corresponds to the policy of universal access to HIV/Aids drugs implemented by the Health Ministry since 1996. The second section presents the very particular situation that prevailed as regards intellectual property in Brazil prior to 1996, that is, the unpatentable status of drugs, which allowed licit copying of ARVs. In the third section we examine the practice of copying drugs in Brazilian pharmaceutical laboratories and the technological learning accompanying it. The fourth section studies the innovation processes likely to be triggered by copying: either the further development of pharmaceutical manufacturing processes or copied drug formulae, or the launching of new research projects on new families of ARVs, which benefit from the knowledge base acquired during the copying phase. The fifth section considers the situation created by the 1996 new patent law which, on the one hand, banned the copying of new generations of antiretrovirals and, on the other, enabled Brazilian laboratories to protect their discoveries of new molecules and new drug formulations. Finally, the conclusion reverts to the exceptional situation in Brazil regarding HIV/Aids drugs which originally could be copied freely and then were patentable from 1997. Today these drugs are a subject of controversy on the granting of compulsory licences and on their possible new

exclusion from patent law⁴. We also show that patents play a dual role in this history, as instruments of reservation of inventions and vehicles of technology transfer. This experience furthermore provides interesting material for reflection on the role of intellectual property asymmetries that are justified by both public health policies and industrial development⁵.

Public health policy and local production of generic drugs

In Brazil's experience in combating Aids, with its approach based on universal access to treatment and on the copying of antiretrovirals by Brazilian pharmaceutical laboratories, the most singular feature is the entanglement of public health policies and industrial drug policies. This mixture distinguishes Brazil from India where the generic drug industry has developed in the strict framework of market incentives⁶. In November 1996 the Brazilian State President passed a law instituting 'the free distribution of drugs for HIV/Aids carriers'⁷. This presidential decree, which granted an exceptional status to the Aids epidemic, put Aids drugs beyond the scope of the market since they were to be bought and distributed freely by the Health Ministry via the public health system. The decree also provided for the creation of a commission to define the list of drugs that could be classified as tritherapies. This list was to be revised annually 'to take into account the advancement of scientific knowledge and new commercialized drugs'. The most original fact is that the Brazilian State did not stop at this role of distributing goods considered to be essential. It also became a 'health entrepreneur' via the work of government pharmaceutical laboratories which embarked on the local production of antiretrovirals. These public laboratories are a highly original institution in Brazil. They are either the property of the Health Ministry, as in the case of the Technological Drug Institute of the Oswaldo Cruz Foundation in Rio de Janeiro, known as Far Manguinhos, or the property of local States⁸. In 1996 the heads of government laboratories and the Health Ministry agreed to launch a programme for the copying of ARVs, aimed at sharply reducing the price of these drugs that absorbed a huge proportion of the Ministry's budget. The development of production of generic or similar drugs in Brazil was intended to reduce the amounts of patented molecules bought from leading international laboratories and to force prices down⁹. The Aids programme had the effect of reviving public pharmaceutical laboratories' production. The federal laboratory Far Manguinhos, largely inactive in the early 1990s, multiplied its production by seven and its income by 20 in the period from 1995 to 2002. It acquired a special production line for ARVs, certified by the Brazilian drug agency ANVISA in September 2002. Far Manguinhos reinvested its profits in research, recruited chemists from industry and academia, and acquired research equipment and facilities. Today this

laboratory is a technical platform that serves as a reference for the Brazilian pharmaceutical industry.

From 1993 several laboratories in the private sector also undertook the copying and production of ARVs for fighting HIV/Aids. In that year a small pharmaceutical chemistry laboratory, a start-up founded by chemists from the Federal University of Rio de Janeiro, started to copy AZT. Two other laboratories, located close to the University of Campinas and the University of Sao Paulo, initiated their programme for copying AZT and proteases inhibitors in 1994 and 1996. The last privately-owned laboratory to launch into the ARV field did so in 2000 at the request of Far Manguinhos which needed raw material for its production of ARVs. This manufacturer of generic drugs located near Rio de Janeiro, created in the 1980s by chemists from the federal laboratory, works in close cooperation with Far Manguinhos. The two organizations, one public and the other private, are bound by a technology cooperation contract. For private-sector laboratories working in this field, the Health Ministry's purchases were a promise of markets, at least before the government procurement system turned towards Indian and Chinese laboratories, at the expense of local producers. Private laboratories are sometimes requested directly by the Health Ministry to develop ARV synthesis technologies, especially when the Brazilian government wants to pressurize international laboratories into reducing their prices. The government is still able to rely on private generics producers to replace the products of an international laboratory that withdraws from Brazil: *"For Ganciclovir, when Roche stopped supplying the Brazilian government, the government asked us whether we would be able to develop this drug in Brazil. We answered: we'll develop the synthesis, and we helped the government to develop the lyophilization methodology"*. (laboratory director)

Government pharmaceutical laboratories have a limited industrial capacity in pharmaceutical production. They are able to carry out only the final manufacturing phase, that is, formulation and production of the drug, not the synthesis of its active principles. These they buy from Brazilian, Indian or Chinese laboratories in the private sector. There is thus a complementarity between public-sector laboratories, specialized in formulation, and commercial laboratories, which supply the raw material. In the case of certain antiretroviral molecules, public- and private-sector laboratories cooperate and exchange knowledge and technology transfer¹⁰. In some cases laboratories in the two sectors compete when they formulate the same drugs.

The unpatentable status of drugs in Brazil from 1945 to 1996: a licit copying regime

Brazilian public- and private-sector laboratories' engagement in the copying of HIV/Aids drugs was possible owing to the particular status of drugs as 'public goods' in Brazil from 1945 to 1997. In 1945 President Getulio Vargas decreed the non-patentability

of pharmaceutical products, with the twofold public health and industrial development objective. The idea was to stimulate the production of drugs for the most serious diseases in the country, and to encourage the creation of a local pharmaceutical industry to produce substitutes for foreign imports. This exclusion was reinforced under the military government in 1971. The new industrial property law excluded both manufacturing processes and pharmaceutical products from patenting, with the aim of promoting technology transfer and strengthening a sector that was essential for the local population¹¹. The copying of drugs patented abroad was therefore perfectly legal.

The policy of copying ARVs for HIV/Aids was a continuation of experiments in reverse engineering in the seventies and eighties. During the 1980s the Health Ministry set up a system of tax incentives and financial advantages to encourage the copying of drugs and the production of pharmaceutical raw materials by the pharmaceutical and chemical industry. The laboratories currently working in the Aids field benefited from this aid. The technical director of a laboratory producing generics, founded in 1989, explained: *'our company's first projects were financed by the Health Ministry's projects'*.

This legal situation favourable to the copying of foreign inventions and the creation of a pharmaceutical industry to replace drug imports lasted until 1996. Paradoxically, Brazil amended the legal status of drugs in February 1996, just a few months before the law on universal free access to HIV/Aids drugs was passed. Consequently, local production of antiretrovirals can concern only the first generation of drugs, patented before 1996. The second generation of ARVs, protected by patents, can be copied only under compulsory licence.

Copying and technological learning

Brazilian and Indian generics laboratories' practice of copying drugs¹² has been a subject of intense international controversy. Brazil has been accused of 'piracy', even when copying was legal in that country, since it reproduces drugs without paying the R&D costs involved in inventing them. Reverse engineering has also been criticized as a redundant and futile activity because it reproduces what has already been invented elsewhere. In November 2002 GlaxoSmithKline summed up copying as a wastage of resources: *"The remaining engineers in the pharmaceutical industry in India have, at least until recently, spent their time on reverse engineering to circumvent existing 'process' patents (i.e. reinventing the wheel) rather than on innovation ... India's history demonstrates how a weak IP system can at best lead to waste of R&D effort on re-engineering"*¹³

Our survey on chemists directly involved in the ARV copying projects of Brazilian public- and private-sector laboratories and on people in charge of intellectual property and technology transfers¹⁴ shows, on the contrary, a process of technological learning or the phenomenon of learning-by-doing that results from copying. The practice of copying ARVs involves the creation and acquisition of knowledge by Brazilian

chemists and results in the development or enhancement of these laboratories' R&D capacities. In certain cases this new knowledge base is used to open research projects on new families of ARVs. This invaluable result for pharmaceutical industrial policies has been obtained via the methodology of the sociology of science and innovation which reconstructs the practices of production and circulation of knowledge in laboratories¹⁵.

Consider the work of chemists who embark on the copying of an ARV. The process starts with bibliographic research, first on international patents and then on scientific articles or articles published in professional journals. Here the researchers exploit the documentary use value of patents, which varies, depending on the molecule. The Far Manguinhos federal laboratory's engagement in ARV production, for instance, started with a detailed analysis of the patents concerned. This research, carried out by an experienced chemist, revealed problems in highly specific syntheses as well as bottlenecks in the procurement of certain reagents. In a privately-owned laboratory a chemical engineer was entirely devoted to reading and synthesizing patents, and to identifying the steps that would be difficult to reproduce. Reading patents involves a process of interpretation and transposition. It is therefore necessary to adjust the processes described in the patent to local conditions of production which are not strictly equivalent to those described in the invention. The knowledge contained in the patent is fundamentally incomplete, due to the owner's restrictions and, more generally, to the absence of know-how required to apply the described technology. Chemists in generics laboratories, who lack the patent owner's know-how, therefore have to undertake the patient reconstruction of the technology. For that purpose they draw on information found in publications, knowledge obtained from other generics producers (Far Manguinhos chemists have visited their suppliers' factories in India several times), and the expertise of university chemists who advise them. Basically, they have to complete the patent by laboratory research to reconstruct certain processes or analyse the drugs or raw material obtained commercially. Step-by-step, products have to be characterized and synthetic processes reproduced. The difficulty of this reconstruction, between patent documents, scientific articles and reverse engineering itself varies, depending on the complexity of the molecules and the documentary use value of the patents. It took a generics manufacturer in the private sector two years to reproduce the synthesis of Ritonavir, a protease inhibitor. One year was spent on reaching the laboratory scale and another year on the scale-up. In the process the laboratory did of course learn a great deal on the same families of molecules. The R&D manager explained:

"For Ritonavir, developing the synthesis took us two years; for Lopinavir, six months, because Lopinavir and Ritonavir have partly similar structures; similar types of chemistry and expertise; it's much easier today to develop new syntheses".

Generics producers also had to reconstruct the references or standards of the molecules that they copied. Since these were patented molecules, their chemical references were not divulged in the international pharmacopoeias. For example, the Far Manguinhos laboratory produced references of these molecules for its own use – quality control in the factory – and for the Brazilian pharmacopoeia. The quality service of a private-sector generic drug producer devised its own analytical methods to control its production and obtain approval from ANVISA, the national drug agency. Copying thus produces reports, data files, test methods and abundant documentation for internal or public use.

The production of generic Aids drugs triggered the creation or improvement of the R&D capacities of both public- and private-sector laboratories. Consider the example of the Far Manguinhos federal laboratory. It recruited chemists from industry and universities and acquired a large amount of research equipment, financed by the profits from ARV sales. The result is a technical platform that serves as a reference for the Brazilian pharmaceutical industry. Since this laboratory had to buy raw materials for its drugs from commercial Indian, Chinese or Brazilian laboratories, it first had to equip itself with a large analytical department for performing characterization tests on the molecules. These tests were then routinely used to control the quality of the raw material purchased. Although it was not equipped to carry out chemical syntheses on an industrial scale, Far Manguinhos then created a synthesis laboratory in which it reproduced steps in synthesizing processes for the purpose of characterizing molecules or developing synthesis procedures to be transferred to industry. Finally, the public laboratory formed a team to formulate drugs, for transfer to other Brazilian public-sector laboratories. Within a few years, between 1996 and 2002, Far Manguinhos had created an R&D laboratory for analyses, syntheses and formulations, which accounted for close to 30% of the laboratory's staff (215 researchers out of a total of 739 employees).

The ARV copying programme has also been accompanied by knowledge trading and even technology transfer contracts between laboratories in the public and private sectors. Consider the following two examples. In the first case, the government laboratory carried out a bibliographic study and developed the complete synthesis of a molecule that was then transferred to an industrial laboratory which took care of the scale up and production. In the second case, the federal laboratory and the industrial laboratory negotiated an agreement on several operations: the federal laboratory would buy raw material from the industrial laboratory which would transfer to it the drug formulation technology in its possession. The two partners also agreed to cooperate on an R&D project on a new family of anti-proteases identified by the Federal University of Rio de Janeiro.

Copying thus leads to local production of knowledge generated by the study of patents and laboratory manipulations. Patents constitute an important vehicle of technology transfer, although they are fundamentally incomplete. Knowledge is traded between generics producers who specialize in the different phases of drug production or enter into partnerships. This knowledge created by copying is likely to be transferred to other laboratories. The Far Manguinhos federal laboratory transfers its technologies to other Brazilian laboratories and the director has offered the technology acquired by Brazilian chemists to laboratories in eastern and southern Africa.

Copying and pharmaceutical innovations

We have observed some degree of continuity between pharmaceutical copying and innovation. In the laboratories studied, copying leads to innovation in various ways. The first is incremental innovation, which derives directly from the copied activity: generics producers improve the synthesis routes or formulations of the drugs that they copy. These adjustments can lead to patents relating to improvements (formulations) or are kept secret (new synthesis routes). The second way is more radical innovation that can lead to the development of new drugs, for instance by combining several existing molecules, by discovering new properties in the polymorphous molecules of the copied molecule, or by identifying new families of antiretroviral drugs. For example, the Far Manguinhos laboratory analyses the polymorphs of existing antiretroviral drugs to discover new therapeutic properties. It is also involved in research projects on new families of antiretroviral drugs derived from research initiated in-house or in academic laboratories. In the latter case, a patent has been filed jointly with the Federal University of Rio de Janeiro on a new protease inhibitor. These research projects on new molecules, which no longer rely on the copying of foreign inventions, benefit from these laboratories' technological learning during the imitation phase. The reproduction of existing molecules has been accompanied by the creation of R&D teams and by the acquisition of competencies on antiretroviral molecules, that can be applied to new research projects. We witnessed this dynamic in one of the industrial generic drugs laboratories that we studied, which started by copying ARVs before developing its own molecules, in partnership with São Paulo University.

These new molecules discovered by university laboratories or the new formulations invented by generic drug producers are patented. For example, a new family of protease inhibitors, discovered by a university chemist and developed by the Far Manguinhos laboratory, was patented by the Federal University of Rio and the Health Ministry's laboratory. The patent covers Europe, the United States, Japan, Chile, India and South Africa. This patent should enable the university and the government

laboratory to control the diffusion and industrialization of the invention. Generic private laboratories have registered patents on new formulations, on their preparation processes – e.g. for protease inhibitors – and on the new molecules that they have identified. New synthesis routes based on chemical engineers' very specific know-how, and which represent a source of productivity gains for generics producers, are generally kept secret.

Technological improvements or new molecules discovered by Brazilian generic drug producers benefit from the new law on intellectual property in terms of which pharmaceutical products and processes can be patented. The Far Manguinhos federal laboratory intends to use its patents to control and regulate the drug market. In most cases it will leave other laboratories or firms to industrialize new drugs and to produce raw materials, and will use its patents to transfer its technologies towards Brazilian laboratories. More generally, with or without patents, Far Manguinhos has a systematic policy of technology transfer towards private industry. Processes developed on a laboratory scale – a scale of one kilogram – are simultaneously sent to the firms concerned. A chemist at the federal laboratory commented:

“We had three molecules for which reactions were developed on a laboratory scale; afterwards they were transferred to customer firms that wanted the technology”.

Brazilian universities also have intellectual property policies and in some cases a particular person is responsible for monitoring patent applications and technology transfers¹⁶. For example, a Federal University of Rio team of chemists patented several new molecules as part of a strategy to valorize academic research and to transfer and control technology. A Brazilian university network exists to promote intellectual property and diffuse transfer tools. In the course of their activity of copying generics, Brazilian generic drug producers apply for patents relating to improvements, or patents on new molecules, when they wish to develop pharmaceutical research aimed at inventing new products, generally in cooperation with university laboratories. These innovation projects on new molecules are nevertheless still at a very early stage.

Conflict between the Brazilian Health Ministry and international laboratories: negotiations on prices and compulsory licences

Although the 1996 patent law serves to protect new molecule inventions, it also excludes the possibility of copying new generations of antiretrovirals. The production of Brazilian generic Aids drugs is expected to decline as soon as the drug 'cocktails' adopted by the Health Ministry for its tritherapies have included the new patented molecules. As more of these new patented molecules are included in the treatments opted for by the Ministry, the market for copied drugs will gradually shrink.

On three occasions, in August 2001, September 2003 and June 2005, the Brazilian government brandished the threat of a compulsory licence on patented ARVs during price negotiations with international laboratories. The four second-generation ARVs bought by the Health Ministry accounted for 80% of the Aids programme's budget and patent holders refused to grant the price reductions requested. In June 2005, for example, the Health Ministry threatened to have the generic equivalent of Abbott's Kaletra manufactured by the Far Manguinhos federal laboratory for almost half the price of the proprietary drug¹⁷. The threat was credible in so far as the government laboratory had extensive experience in the antiretroviral field and had prepared reverse engineering of the drug at the Health Ministry's request. Since the preparation of a compulsory licence requires reverse engineering on the licensed molecule, the Health Ministry directly requests public- and private-sector laboratories to prepare the synthesis of specific molecules. This preparatory work of knowledge acquisition is crucial to the Brazilian government, for it can decide on a compulsory licence only if the country's chemists are able to manufacture the generic molecule at a satisfactory price. Finally, in July 2005 the Health Ministry announced a compromise on the prices of Kaletra and gave up the option of a compulsory licence and the production of generic versions. One of the leaders of the Ministry's Aids Programme criticized this decision that reduced the scope of local generics production: *'ARVs copied here are used less and less with the appearance of new treatments'*. In fact, despite several threats, Brazil has never implemented this type of compulsory licence.

Parallel to this battle over compulsory licences, members of parliament supported by NGOs proposed another, more radical solution: the amendment of the 1996 law on intellectual property, so that ARVs would be excluded from patents. On 2 June 2005 the Constitutional, Judicial and Citizenship Commission of the Brazilian House of Representatives unanimously passed a bill placing HIV/Aids drugs outside the scope of patentable objects¹⁸. This article, that ratifies the exceptional status of Aids, is explicitly designed to guarantee the viability of the Health Ministry's Aids programme. The aim is not only to reduce the prices of ARVs, but also to ensure that their local production can continue. This exclusion of ARVs from patents could, however, prevent the patenting of new molecules discovered by researchers in the public and private sectors.

Conclusions

The Brazilian experience in copying HIV/Aids drugs illustrates a number of points. First, it highlights the exceptional status of drugs as regards intellectual property. Considered as public goods, drugs could be copied freely in Brazil until 1996. Although they again fell under patent law in that year, they remained 'essential goods' in respect of the norms of public health policy. In

1996, a few months after the new intellectual property law had been passed, a presidential decree proclaimed universal free access to drugs for HIV/Aids carriers. To implement this policy the government mobilized public-sector pharmaceutical laboratories to produce generic drugs. These public health objectives entered into conflict with the patentable status of new generations of antiretroviral drugs as soon as the prices of the new molecules weighed too heavily on the Health Ministry's budget. Hence, the numerous conflicts with the proprietary laboratories and controversies over compulsory licences since 2001. This limit on patent rights is inscribed in the new patent law and can apply if the patented product is not produced locally within three years. In 1999 a presidential decree strengthened the possibilities of compulsory licences 'for the public interest' and especially for public health. In September 2003 a new presidential decree specified the conditions for the application of a compulsory licence for national emergency reasons, in the public interest. Intellectual property of ARVs had to compromise with public health norms. Finally, the Health Ministry's public incentives concerning Aids were decisive in reviving the production of generic drugs in Brazil.

Second, this experience also reveals the possibilities opened by an asymmetry in the intellectual property rights of different countries, for public health objectives and technological transfer and learning¹⁹. In this respect, compulsory licences can be considered from the angle not only of public health policies but also of technology transfer. The 30 August 2003 WTO agreement on the application of the Doha Declaration contains an article which 'recognizes' and encourages 'technology transfer' between generic drug importing and exporting countries²⁰. The Brazilian President's September 2003 decree concerning compulsory licences was designed to compel patent holders to transfer the know-how in their possession. Preparation of compulsory licences is itself a phase in the acquisition of knowledge and technological learning, via the analysis of patent documents, reverse engineering in laboratories, exchanges between public- and private-sector laboratories, and Brazilian chemists' visits to Indian and Chinese generic drug producers²¹.

Third, the complexity of patents is revealed. Patents are tools to protect inventions and ban copying, to the detriment of generics producers. They are also vehicles for technology transfer when copying is declared legal either because the drug is excluded from patentability or because the patents in question are subject to a compulsory licence. Lastly, patents are double-edged instruments for pharmaceutical firms in Brazil. On the one hand, if ratified, the reform to intellectual property law, passed by the House of Representatives in June 2005, will exclude ARVs from patents and promote the extension of the market to copying. On the other hand, it will prevent laboratories in the public and private sectors from patenting improvements or new molecules. A generics producer that manufactures the active principles of existing ARVs and that discovers new ARVs could face this dilemma.

Finally, the Brazilian experience offers an original solution to the alternative proposed by Paul Romer in an essay on the knowledge and development economy: using ideas invented elsewhere or producing one's own ideas²². In an article Romer compares two contrasting models: that of Mauritius which uses ideas from elsewhere by encouraging foreign investments; and that of Taiwan which encourages the domestic production of knowledge by increasing its investments in R&D. Brazilian generics laboratories represent another model consisting of the use of foreign inventions through reverse engineering and the local production of innovations derived directly or indirectly from copying: directly when the copying of drugs is accompanied by additions and improvements that are likely to be patented, and indirectly when the generic laboratories reuse knowledge acquired during the copying phase to launch new research projects. Two pharmaceutical laboratories out of the five that we studied developed this trajectory, from copying to research on new drugs. Apart from the knowledge production implicit in copying, it also leads to the creation or extension of R&D laboratories. These are mainly analytical laboratories – to characterize and control raw material – and synthesis and formulation laboratories. The production of generic drugs for the Aids programme furthermore revived reflection and initiatives towards the reconstruction of a pharmaco-chemical industry in Brazil by the State, private industry and universities^{23,24}. In 2003 several seminars were held in Brazil on the topics 'Health-related Innovation

Projects' (Oswaldo Cruz Foundation, 9-10 June 2003) and 'The Industrial Complex in Health' (BNDES, Ministry of Development, Industry and Foreign Trade, 5-7 May 2003). In 2005 and 2006, the Academy of Science organized a cycle of conferences on the theme of pharmaceutical policy and innovation. See also the report "Arvs production in Brazil " by Antunes and Fortunak, 2006.

Notes

1. This law amends Article 18 of the Brazilian patent law on exclusions from patentability: 'The following are not patentable: [...] drugs as well as the processes for obtaining them, specifically for the prevention and treatment of Aids', Law N° 22/03, June 2005.
2. Interview with C. Gossas, Brazilian Aids Programm, september 2005.
3. There have been three crises concerning compulsory licences for ARVs: August 2001, September 2003 and June 2005. On all three occasions the Health Ministry brandished the threat of a compulsory licence but finally backed down when agreement was reached on the prices of ARVs bought from the leading international laboratories.
- 4 This exclusion is discussed in the bill passed by the House of Representatives in June 2005.
5. On this question the reader is referred to the work of the British Commission on Intellectual Property Rights, 'Integrating Intellectual Property Rights and Development Policy', London, September 2002.

6 Cf. The work of Jane Lajouwe on the Indian pharmaceutical industry: 'The introduction of pharmaceutical patents in India: Heartless Exploitation of the Poor and Suffering?', NBER Working Paper N° 6366, January 1998.

7. Decree 9.313 of 13 November 1996. Note that universal access to health services is a constitutional right in Brazil (Article 196 of the 1988 Constitution).

8. Brazil has 18 government laboratories. Six are involved in the production of ARVs for the Aids programme.

9. Between 1996 and 2001, public-sector laboratories' production resulted in a 71% drop in prices, on average, compared to the prices of molecules purchased from international labs.

10. This type of technology exchange and cooperation in the field of ARVs concretizes a recommendation in a World Bank report on the pharmaceutical sector in Brazil: 'Public Policies in the Pharmaceutical Sector: A Case Study of Brazil', Jillian Clare Cohen, January 2000, 25 pages.

11. However, the investments of Brazilian privately-owned laboratories were inadequate to meet this objective. In 1988 foreign laboratories controlled two-thirds of the market.

12. The two are linked by trade, as Indian laboratories supply Brazilian ones with raw materials.

13. Commission on Intellectual Property Rights' Report on Integrating Intellectual Property Rights and Development Policy – Comments from GlaxoSmithKline, November 2002, 15 pages.

14. We collected 45 interviews in 2002, 2003 and 2004. We also visited the R&D laboratories and industrial sites of these different pharmaceutical laboratories. This survey was financed by the ANRS (*Agence française de recherche sur le sida*) the French national agency for Aids research.

15. Cassier, M. and 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*, Ed. ANRS, 89-107; Cassier, M. and Correa, M., 2004, 'Patenting Drugs? An anthropological vision of property', 4S and EASST Conference, Public Proofs, Science, Technology and Democracy, August 2004, Ecole des Mines, Paris; Cassier, M. and Correa, M., 2005, 'La copie des antiretroviraux dans les laboratoires publics et privés brésiliens', Montréal, International Congress on Drugs, 30 August to 2 September.

16. The number of patents filed by Brazilian universities has grown substantially since 1997.

17. The government laboratory would have produced a generic version of Kaletra for 68 cents, instead of Abbott's Kaletra at \$1.17.

18. The law amends Article 18 of the Brazilian Patent Act that covers exclusions from patentability. In terms of this law the following are not patentable: '... drugs and the processes required to obtain them, specifically for the prevention and treatment of Aids', Law n° 22/03, June 2005. This law subsequently still has to be passed by the Senate and ratified by the State President.

19. This situation has a long history in the pharmaceutical field. For instance, at the beginning of

the century researchers at the Poulenc laboratory in France took advantage of the non-patentable status of drugs in France to systematically copy German pharmaceutical patents. Cf. Cassier, 2004, 'Pharmaceutical patents and public health in France: opposition and specific drug appropriation devices, 1791-2004', *Entreprises et Histoire* n° 36. See also the example of chemistry and pharmaceuticals in Switzerland in the nineteenth century and early twentieth century, 'The patent controversy in the 19th century', C. Macleod, conference on 'History and Economics of Intellectual Property Rights', 3-4 June 2005, Paris.

20. 'Implementation of the Doha Declaration on TRIPS and public health', 28 August 2003, World Trade Organization.

21. Conflict over compulsory licences for Efavirenz and Nelfinavir in September 2003 was preceded by a mission by Brazilian chemists to India and China.

22. 'Two strategies for economic development: using ideas and producing ideas', P. Romer, Proceedings of the World Bank Annual Conference on Development Economics, 1992.

23. In 2003 several seminars were held in Brazil on the topics 'Health-related Innovation Projects' (Oswaldo Cruz Foundation, 9-10 June 2003) and 'The Industrial Complex in Health' (BNDES, Ministry of Development, Industry and Foreign Trade, 5-7 May 2003). In 2005 and 2006, the Academy of Science organized a cycle of conferences on the theme of pharmaceutical policy and innovation. See also the report "Arvs production in Brazil" by Antunes and Fortunak, 2006.

Bibliographic references

ANTUNES, O.; FORTUNAK, J.M. **Arvs Production in Brazil: an Evaluation**, report for the Brazilian Interdisciplinary Aids Association (ABIA) and MSF Brazil, 2006, 8p.

CASSIER, M.; CORREA, M. '**Patents, innovation and Public Health: Brazilian Public-Sector Laboratories' Experience in Copying AIDS Drugs**' in *Economics of Aids Aid and Access in Developing Countries*, Ed. ANRS, 2003, p.89-107.

CASSIER, M. **Brevets pharmaceutiques et santé publique en France entre 1791 et 2004: opposition et dispositions spécifiques d'appropriation des médicaments**, revue *Entreprises et Histoire*, 2004, p.29-47.


COHEN, J.C. **Public policies in the pharmaceutical sector: a case study of Brazil**, January, World Bank, 2000, 25p.

COMMISSION ON INTELLECTUAL PROPERTY RIGHTS (CIPR). **Integrating property rights and development policy**, s.d. 178p.

GLAXOWELLCOME, **Commission on intellectual property rights report on integrating intellectual property rights & development policy: comments from GlaxoSmithKline**, November, 2002, 15p.

LANJOUWE, J. **The introduction of pharmaceutical products patents in India: heartless exploitation of the poor and suffering?** s.l. Economic Growth Center, Yale University, 1997, 54 p.

MACLEOD. **The patent controversy in the 19th century**. Conference on 'History and Economics of Intellectual Property Rights', 3-4 June 2005, Paris.

ROMER, P. Two strategies for economic development: using ideas and producing ideas, of World Bank Annual Conference on Development Economics, **Proceedings...** The World Bank, p.63-91. 

About the authors

Maurice Cassier

Maurice Cassier is a sociologist and research director at the CNRS (French national scientific research institute). The main focus of his work is property rights on knowledge, techniques and products in the fields of science, life forms and health, in the 19th and 20th centuries. His most recent publications concern the appropriation of Louis Pasteur's vaccines, opposition to patents on breast cancer genes in Europe, and reverse engineering in Brazilian generics laboratories.

Marilena Correa

Marilena Correa is a psychiatrist specialized in public health. She has a Master's degree in Social Medicine and a PhD in Social Science and Health. She is presently a guest researcher at the Cermes-CNRS, EHESS, and at the Ensp-Fiocruz, and Professor at IMS-Uerj. Her current research field is biomedical innovation. She has published a book, chapters in collective volumes and articles on human reproduction and medically-assisted procreation, biotechnology, bioethics and ethics in biomedical research. She was a member of the Research Ethics Committee of the Fundação Oswaldo Cruz from 1999 to 2006 and is vice-chairman of the Research Ethics Committee at the Uerj.