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*Patents, Innovation and Public Health:
Brazilian Public-Sector Laboratories' Experience
in Copying AIDS Drugs*

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KEY WORDS: anti-AIDS drugs; patents;
reverse engineering; technological learning.

Abstract

The Brazilian experience in producing HIV/AIDS drugs is based on the lawful copying of medicines patented abroad, on a health policy of universal access to antiretrovirals (ARV), and on technological learning, especially in public-sector laboratories through reverse engineering. The information contained in patents has proved to be incomplete and the chemical standards of these molecules are not available in the pharmacopoeias. Chemists at the Rio health ministry's laboratory have had to partially rediscover the qualitative and quantitative composition of these drugs. They have thus acquired knowledge on the synthesis processes of the active principles of drugs, which they are now able to transfer to pharmaceutical companies. Apart from copying existing drugs, the laboratory also develops research both in-house and in partnership with universities, to create new molecules. The learning process initiated through copying is thus combined with a research policy.

Résumé

L'expérience brésilienne de production des médicaments anti-VIH/sida repose sur la copie licite des médicaments brevetés à l'étranger, sur une politique de santé publique visant l'accès universel aux ARV, sur un processus

d'apprentissage technologique, notamment au sein des laboratoires publics, grâce à des méthodologies d'ingénierie inverse. L'information contenue dans les brevets s'est révélée incomplète et les standards chimiques de ces molécules ne sont pas disponibles dans les pharmacopées. Les chimistes du laboratoire pharmaceutique du ministère de la Santé à Rio ont dû redécouvrir partiellement la composition qualitative et quantitative de ces médicaments. Ils ont acquis des connaissances sur les procédés de synthèse des principes actifs qu'ils sont aujourd'hui en mesure de transférer à des firmes de chimie pharmaceutique. Au-delà de la copie de médicaments existants, le laboratoire public développe des recherches internes et externes, en coopération avec les universités, pour créer de nouvelles molécules. L'apprentissage initié par la copie se double d'une politique de recherche.

Introduction

In 1997 the Far Manguinhos state-owned pharmaceutical laboratory was mobilized by the Brazilian health ministry to launch production of copies of medicinal drugs used to treat HIV/AIDS. The main objective was to obtain price reductions so that the Health Ministry's AIDS programme could be supplied with these drugs at a lower cost. Between 1997 and 2002 the volume of Far Manguinhos' drug production increased sevenfold, notably through development of antiretroviral (ARV) production¹. The laboratory premises were totally rearranged. The surface area devoted to drug manufacturing was tripled, separate production lines were created for ARV in order to comply with ANVISA² health safety standards, and construction of a large building is currently underway, to house the chemical analysis and Research and Development (R&D) departments.

This original experience, in which industrial economics and public health policy are closely combined, can be explained in terms of three main factors:

- first, the particular configuration of industrial property rights in Brazil where, until 1996, pharmaceutical inventions were public goods that could lawfully be copied;
- second, the impetus of the Health Ministry which, in a context of health emergency and demands of civil society for care, embarked on a policy of

1. During the same period Far Manguinhos' financial resources were multiplied by twenty.

2. Agencia de Vigilancia Sanitaria. In September 2002 Far Manguinhos received the ANVISA Certificate of approval for Good Manufacturing Practices. This was one of the conditions on which authorization was granted to produce generic drugs.

universal access to medicinal drugs (promulgation of the law on universal access to AIDS drugs in November 1996). Far Manguinhos, a pharmaceutical laboratory belonging to the Health Ministry, plays a key part in the implementation of this policy, alongside other state-owned laboratories and Brazilian private-sector laboratories;

– third, this experience is based on a process of acquisition of knowledge on copied drugs, primarily through reverse engineering.

The Health Ministry's pharmaceutical laboratory plays an essential part not only in Brazil's ARV production (accounting for 40% of Brazilian production of ARV, the remaining 60% being shared between other state-owned laboratories and private-sector industry). In our opinion, it also has a key role in the acquisition of knowledge on these drugs, which it can then transfer either to Brazilian public-sector laboratories or to private-sector pharmaceutical laboratories in Brazil and, in the future, in other countries of the South. It is this gradual acquisition of knowledge that we wish to consider here.

Theories on the economics of knowledge often compare two strategies: one based on the imitation of knowledge created elsewhere, and the other on the local production of research and development that generates new knowledge in situ [1]. The Brazilian experience of AIDS drug production has shown that reverse engineering is a source of acquisition of knowledge for a laboratory. In so far as imitators do not have the complete recipe for the drugs they wish to reproduce, nor the relevant know-how and synthesis processes, they are forced to rediscover basic knowledge on the drug. This reverse identification of the components and formulae of drugs, synthesis processes, and standards concerning active principles. Moreover, during this reverse engineering, chemists identify variants of molecules and diverse synthesis processes, and sometimes even propose improvements. Reverse engineering is therefore basically a process of technological learning, that is, of local knowledge production. The Far Manguinhos laboratory uses accumulated knowledge to develop systematic applied research on these molecules, and especially on processes for synthesizing active principles – which can be transferred to the Brazilian pharmaceutical industry – on combinations of molecules, and on polymorphic variants of those same molecules, likely to produce new technical effects. The laboratory is also working on the identification of new ARV in partnership with university researchers. The challenge is therefore not only to rediscover basic knowledge on molecules created elsewhere, but also to create new knowledge on new pharmaceutical products.

This technological learning process has important implications in terms of industrial economics and the economics of industrial property rights. First, there

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is a real process of knowledge acquisition based on the imitation of inventions. Second, this example shows the advantages of the right to free use of knowledge – in this case the non-patentability of medicinal drugs that Brazil enjoyed from 1945 to 1996 and which allowed the lawful reproduction of protected pharmaceutical inventions. The adoption of patentability of drugs in Brazil in 1996, ahead of the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement schedule, complicated the task of Brazilian public-sector laboratories as regards the copying of new patented molecules. The different actors involved in this experiment – public laboratories, patients associations and Non Governmental Organizations (NGOs) – therefore now wish to demand the application of compulsory licensing in Brazil in order to be able to produce ARV patented since 1996³.

I
EVOLUTION OF THE ECONOMIC STATUS OF DRUGS IN BRAZIL:
FROM PUBLIC GOODS
TO PRIVATE GOODS PROTECTED BY PATENT

From 1945 to 1996, in Brazil like many other countries, drugs were considered to be public goods that could be copied freely for industrial purposes⁴. The first stage of the exclusion of drugs from patenting was during the presidency of Getulio Vargas in 1945. Already at that time the idea was to encourage the transfer of inventions patented abroad and local production of medicinal drugs. This policy was reaffirmed in the early 70s. The 1971 industrial property act excluded pharmaceutical patents on both processes and products. This political exclusion of pharmaceutical inventions from patenting had two objectives: first, public health – the law highlighted the importance of the pharmaceutical sector for the population – and second, industrial policy – to

3. Our research consisted of a laboratory study based on the principles of the socio-economics of innovation, aimed at revealing the pharmaceutical laboratory's technological learning process. Twenty three in-depth interviews were held with the far Manguinhos laboratory management, the individuals responsible for industrial property rights, and chemists in the different departments of the laboratory. We also recorded a meeting with synthesis chemists responsible for ARV, and interviews were held with the patients associations and NGOs involved.

4. In France, medicinal drugs were excluded from patentability from 1833 to 1959; and in Germany from 1877 to 1969 (only chemical processes were patentable in Germany). They only became patentable in 1976 in Japan, in 1977 in Switzerland, in 1978 in Italy and Sweden, and in 1992 in Spain.

boost technology transfer and local laboratories. In May 1970 a new Drug Production Institute was created by presidential decree within the Oswaldo Cruz Foundation. During the 80s, the Health Ministry ran a chemical synthesis laboratory for copying and transferring formulae to Brazilian industry. In the mid-90s a private-sector laboratory, Microbiologica, took advantage of this opening to undertake the copying of AZT. Finally, since 1997 Far Manguinhos has used the possibility of lawfully copying drugs patented abroad to start producing ARV in Brazil.

The 1996 patent law, which allows patenting of pharmaceutical products and processes, finally put an end to the public goods status of pharmaceutical inventions. It nevertheless contains limits to patent rights in the form of compulsory licensing in cases where the patented product is not produced locally (the aim being to curb the wave of closures of international manufacturing plants) and in cases of national emergency and public interest. These exceptions were stipulated in 1999 in a decree based on the TRIPS agreement which provides for exceptional measures to protect public health. The decree was drafted in a context of controversy with the United States over Brazilian law, in which the US challenged the obligation for pharmaceutical companies to manufacture patented drugs in Brazil within three years [2].

These compulsory licences were the subject of a tug of war with international pharmaceutical laboratories, and the Brazilian Health Ministry used them in negotiations on the purchase price of molecules patented after 1996. In the summer of 2001 it challenged Roche with a threat to produce Nelfinavir in Brazil from 2002, until the company agreed to a substantial price reduction. Another example is Merck, which accepted a 60% cut in its prices in exchange for a commitment by the Health Ministry not to produce patented molecules locally. Chemists in Brazilian public-sector laboratories are demanding application of compulsory licences to be able to continue reproducing new generations of ARV. To date, no compulsory licence measure has been taken. Government laboratory lawyers also complain about very restrictive conditions for application of these licences, and are calling for amendments to Brazilian law⁵.

5. Brazilian law is more restrictive than the TRIPS agreement as regards compensation for patentability in cases of compulsory licensing. Article 31 of the TRIPS agreement stipulates that the patentee will receive adequate remuneration, depending on the case, in view of the economic value of the authorization. Article 71 of the Brazilian law states that a compulsory licence must be granted "without prejudice to the rights of the respective patentee". This condition is judged contradictory to the very notion of a compulsory license which naturally entails loss of a market for the patentee. It increases the possibilities of lawsuits in which the patentee wins.

II
THE PROCESS OF COPYING AND ACQUIRING KNOWLEDGE
ON DRUGS (1997-2002)

Brazilian public-sector laboratories are not in a position to incorporate the entire drug manufacturing process. Their capacities are too limited to produce the active principles of the drugs, which have to be obtained from Indian, Chinese, Korean and, to a lesser extent, Brazilian companies. Consequently, the Far Manguinhos laboratory has specialized in the final production phase: purchasing raw material, formulation, and production and packaging of drugs. It may seem that such narrow specialization would have limited the laboratory's expertise on these drugs. Yet as we are about to see, that is by no means the case, for several reasons.

First, when it decides to manufacture a drug, Far Manguinhos has to develop expertise and tools for controlling the quality of the raw material it buys. Second, in order to meet ANVISA standards for approval of generic drugs, it has to establish standards of purity and quality of the various molecules it uses. Note that in the case of most ARV these standards are currently not available in international pharmacopoeia since patent holders refuse to disclose them. Far Manguinhos has therefore had no alternative but to reformulate them in order to be allowed to produce generic drugs. Third, Far Manguinhos has developed a strategy of systematic acquisition of knowledge on these molecules, particularly their synthesis, in order to be able to transfer it to Brazilian private-sector laboratories that either are, or might be, able to develop production of the active principles of the relevant drugs. The laboratory's aim here is to organize technology transfer towards Brazilian private-sector industry. Fourth, acquisition of knowledge on drugs, that is, on their formulae, on molecule standards and on synthesis processes, is a key element in Health Ministry negotiations with international laboratories. The Ministry can use this knowledge, and the potential ability to manufacture drugs locally, as a real threat when bargaining to obtain price reductions. Fifth, Far Manguinhos does not intend to limit itself to reproduction of existing drugs. Apart from reverse engineering on existing products, the laboratory is developing research on combinations of molecules, on the polymorphic molecules of ARV and on new molecules for treating AIDS.

To acquire this knowledge base on AIDS molecules and drugs, Far Manguinhos has developed a proven reverse engineering methodology now formalized in computerized management of projects. We shall now examine

the different areas of expertise and the reverse engineering methods used by Far Manguinhos chemists.

We first consider the three areas of expertise directly related to local drug production, *i.e.* characterization of raw materials bought elsewhere, formulation of drugs, and development of standards to be added to the pharmacopoeia. We then look at research on molecule synthesis processes. The results of this research exceed the needs of Far Manguinhos itself; they are transferred to Brazilian pharmaceutical firms and used by the Health Ministry in negotiating price reductions with the pharmaceutical laboratories that own the patent rights. Finally, we consider research on the design of new combinations of existing molecules and the identification of new ARV.

The first kind of knowledge that the laboratory needs to acquire on the drugs it wishes to manufacture concerns the characterization and quality control of the raw material it buys, primarily from foreign suppliers – Indian, Chinese and Korean – and secondarily (about 20%) from Brazilian suppliers. Quality control is a matter of strategy. The idea is to guarantee the reputation of drugs manufactured in the public sector, on which the Health Ministry's AIDS programme relies. To this end, Far Manguinhos recruited a chemist who previously worked in the federal food and drug agency laboratory, and entrusted him with the task of setting up a testing department. The number of staff employed in this analytical chemistry department has risen from 8 to 20 in the past five years. The department has also acquired new equipment – especially two sets of Nuclear Magnetic Resonance apparatus used to identify chemical substances – and is recruiting young chemists with a PhD to develop new analysis techniques. It has simultaneously formed partnerships with university laboratories which perform complementary analyses.

Chemists in the analytical department use several knowledge acquisition techniques in characterizing raw material purchased elsewhere and in formulating quality standards. They start off by analysing available information on the drugs in question: patents and publications. They then acquire samples of raw material to test, and draw comparisons with the proprietary drug. When the programme was launched in 1998 the director of the analytical department went on two trips to India. He wrote follow-up reports containing technical information gathered during visits to several pharmaceutical factories. The aim was to get to know suppliers, to assess their competencies, to inquire into certain problems of quality encountered – which sometimes helped to solve irregularities in batches of raw material, as in the case of Indinavir – and to obtain information on the synthesis processes used.

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The analytical department's work has resulted in the development of quality standards and of methods for analysing the structure of molecules and the purity of material. These are used routinely to check batches of raw material used in manufacturing the drug on site. This knowledge is thus applied directly in the production process⁶. Characterization of raw material also produces knowledge for research. For example, by means of reverse engineering, contaminants found in raw material can be used to find the synthesis process of a particular supplier. This information is transmitted to the relevant research laboratory which thus enhances its expertise on the synthesis processes used. These results also serve in negotiating or cooperating with suppliers. On several occasions the analytical department established that the synthesis routes stated by Indian suppliers did not correspond to the ones they actually used, for the contaminants identified differed from the process disclosed by the suppliers. The department has sometimes even informed suppliers about contaminants of which they were unaware. In such cases Far Manguinhos asked the suppliers to change their synthesis processes in order to avoid the production of dangerous contaminants. Thus, the analytical department produces data that are useful to suppliers, to Far Manguinhos production managers, and to researchers in the synthesis department.

Local production of drugs also entails working on their formulation, and Far Manguinhos has a group of chemists devoted to the task. The laboratory director is herself a chemist specialized in formulation, who for many years worked in a large international laboratory. Her team consists of twelve chemists and pharmacists, and a PhD student. It is about to employ a further three pharmacists. This team has developed the formulae of 50 drugs since 1996 and is currently working on 35 projects. It also developed the project management software that is now used in the other departments. The formulation of molecules used in AIDS drugs is also based on reverse engineering from information and proprietary drugs, to identify the excipients used. Formulation furthermore involves frequent interactions with the synthesis and analytical chemistry departments to select the appropriate raw material. Chemists working on formulation ask for a particular raw material or synthesis: "we want that product in that way; our aim is to formulate and produce but we know which raw material we want and therefore which synthesis" (chemist, formulation group). This choice also incorporates financial parameters in so far as the aim of reducing

6. The analytical department's expertise has thus made it possible to detect batches with defects and unreliable suppliers.

prices is essential to the AIDS programme. Several formulae are tested (often four or five) in order to evaluate their performance in the production stage. The final product is compared to the reference drug during bio-equivalence tests undertaken by outside laboratories.

One of the most remarkable results of the formulation group is their discovery of a ddi formula that was more effective than the one invented by the original manufacturer Bristol Myers Squibb (BMS). During bio-equivalence tests on ddi at Sao Paulo University, researchers discovered that the Far Manguinhos product was not bio-equivalent to the original product. Its bio-equivalence curve was substantially better! BMS congratulated the Far Manguinhos chemists who did not patent their result since the new formula had been disclosed in a conference. The Far Manguinhos officials in charge of industrial property rights are now more careful and will ensure that any new improvements are patented.

The third area in which reverse engineering is practised concerns the creation of molecule references to be added to the pharmacopoeia. The creation of these standards became a necessity when Far Manguinhos embarked on the production of generic drugs⁷. Purity standards for chemical substances listed in the pharmacopoeia are a compulsory reference for any generic drug manufacturer wanting to reproduce the molecule. As soon as they are recorded in a pharmacopoeia, for example the European one, these references are accessible to any potential user. In the framework of the AIDS programme, Brazilian government laboratories were, however, faced with a major problem. The substances that they decided to reproduce were patented abroad and their purity standards were not available in international pharmacopoeias – with the exception of the standards and samples of two molecules, including AZT, that Far Manguinhos was able to obtain from pharmacopoeias. With the other molecules, when the Health Ministry's laboratory wanted to obtain authorization to produce generic drugs, it had to recreate these references by reverse engineering. After being approved, such standards are added to the Brazilian pharmacopoeia.

For its standards production programme, Far Manguinhos was supplied with new equipment financed by the Brazilian Food Safety Agency, ANVISA. This programme has benefited from computerized management of reverse

7. ARV produced by Far Manguinhos are currently being registered with ANVISA as generic drugs. Until now Far Manguinhos has produced "similar" drugs that contain the same active principle and have the same pharmaceutical form and therapeutic result as the reference drug but do not necessarily have the same bio-equivalence.

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engineering which sets out the steps in the creation of standards for each molecule. The first step consists in the collection of data from patents, scientific publications and other documents; the second concerns the choice of methodology: extracting the molecule from capsules of proprietary drugs, working from raw material bought on the market, especially from Indian generic drug producers, and reproducing the molecule by laboratory synthesis; the third step is that of extraction and purification of the molecule; the fourth consists in approval of the reference; and, lastly, the fifth consists in its registration in the pharmacopoeia. For each step the software records the time spent and the financial value of the work. Far Manguinhos has a small manual for each molecule listed, which recapitulates all the data produced.

Creation of standards is a particularly complex task, for the exact molecule used by the manufacturer has to be identified. Although it is possible to use a different synthesis pathway to that of the manufacturer, for example one that is more efficient and/or safer, when it comes to the original molecule it is essential to find the exact structure and standards of purity. The elaboration of standards must furthermore comply with guidelines established by the WHO which specify analyses to perform and purity thresholds to meet. The process of purification of substances is arduous. It involves extraction of the active principles from the manufacturer's capsules and from raw material purchased, and comparisons between the two: "And it's a huge job, complicated, we have to extract the substances from the capsules, purify, purify, purify, and buy raw material in India and purify that to compare it with the capsules." (Director of the Synthesis Department). Even when the active principle has been extracted from the original drug, there is no guarantee that the right structure has been isolated, for it can change during the extraction process. The second difficulty concerns the existence of several polymorphs for the same molecule⁸. It is essential to identify the right polymorph used by the patent-holding laboratory commercializing the substance: "Sometimes we discover that there are different polymorphs and it is difficult to know which is the right one, which is the company's polymorph; it's a challenge but we learn." (Director of Synthesis Department). Once the Far Manguinhos chemists have isolated the right substance it has to be tested externally by university laboratories, by the federal drug agency and by the pharmacopoeia. The average time taken to create a standard is around six months.

8. Differences of crystallisation can occur with the same molecule prepared according to the same synthesis processes. These differences can result in very different properties and effects in the final product.

The acquisition of knowledge on synthesis processes is also crucial in the laboratory's technical and economic strategy. First, knowledge on synthesis processes enables it to check the quality of raw material and, when necessary, to ask suppliers to adjust their processes. Second, acquisition of synthesis expertise by Brazilian public-sector laboratories, combined with the possibility of demanding a compulsory licence for public health reasons, carries a lot of weight in negotiations with international laboratories: "A way of exerting pressure is by doing synthesis ourselves and showing that we can do it, that we know how to." (researcher, Far Manguinhos). Third, the fact of mastering synthesis makes it possible to envisage technology transfer from the public laboratory to Brazilian industry, in keeping with an industrial policy of replacement of imported active principles by local production. This process can be introduced gradually: Brazilian laboratories can initially limit themselves to the last steps in the synthesis process, before integrating the entire cycle.

The reverse engineering policy regarding synthesis draws on several sources. Apart from the knowledge produced during the process of characterization of imported raw material, chemists collect information from available sources – patents, scientific and trade publications – which they then test in their laboratory. During this process the 35 chemists in the synthesis department frequently interact with the analytical department. In 1999 Far Manguinhos management requested a chemist to review available information on five molecules used in the treatment of HIV/AIDS: "I spent three months reading patents and the literature and giving my opinions on the difficulties involved in synthesis." Patent analysis alone enabled him to perform an initial assessment of synthesis processes and above all to show the difficulty of synthesizing anti-proteases. But conclusions drawn from descriptions contained in patents are not enough to reproduce laboratory synthesis. Despite the obligation to provide an adequate description of the invention, the knowledge described in patents is fundamentally incomplete: "A patent is supposed to say everything and experience has proved that everything is not said." It is therefore essential to perform laboratory tests on knowledge collected from patents: "If they are hiding something, it's something that's not going to be noticed in the patent but that will be missed if the reaction is to be achieved. So one has to actually test it to see if it works." The incompleteness of knowledge recorded in publications is not peculiar to invention patents. Researchers are confronted with the same problem when they wish to reproduce an experiment described in a scientific article. But control of disclosure in a patent reinforces the phenomenon. This gap between the description in the patent and the knowledge needed to reproduce the molecule obviously

complicates the task of chemists in the Brazilian laboratory. They lack access to know-how not disclosed by the inventor who owns the patent.

Chemists in the synthesis department emphasize this incompleteness of knowledge contained in patents. For example, the synthesis path described in a patent may be deficient, the addition of reagents may not be fully specified, reaction time may be defined very imprecisely, or contaminants from the synthesis reaction may simply not be mentioned. Such omissions can be particularly serious in the case of a molecule such as Indinavir, for at a certain temperature its synthesis produces a toxic molecule. It is therefore essential to validate knowledge drawn from patents, through laboratory tests: "Sometimes it is stated that reagents are added, but in fact that doesn't work: the quantity isn't right; it's necessary to analyse, to see the processes, to evaluate in detail, to see if it's necessary to heat it; the reaction is supposed to happen at that temperature, but it's not true; or in a very wide interval, so it's necessary to rediscover." (chemist, responsible for ARV).

Chemists in the synthesis department have undertaken laboratory scale development of the synthesis processes of several ARV copied by Far Manguinhos, as well as of two patented ARV not produced on site, Efavirenz and Nelfinavir. In the case of the latter two patented molecules this knowledge has been used in negotiations with manufacturers to obtain price reductions. During the summer of 2001 the Brazilian Health Ministry was able to threaten Roche that they would produce its molecule on site if the company did not reduce its price sufficiently. For every molecule studied, Far Manguinhos has a document setting out its synthesis path. This knowledge is likely to be transferred to Brazilian private-sector laboratories.

Reverse engineering on synthesis processes of AIDS molecules is described by our interlocutors as a learning process. The task of Far Manguinhos chemists was particularly difficult in the case of Indinavir: information contained in the patent was incomplete; Indian suppliers failed to disclose their synthesis processes; and Far Manguinhos chemists were discovering the chemistry of anti-proteases whose synthesis is difficult to control. Gradually their knowledge base expanded, through the collection and systematic analysis of a growing number of publications (patents and articles), through information gathered during tests on raw material purchased, through experiments run in their laboratories, and through interaction with Brazilian universities. As a result, reverse engineering can now advance faster. It is often the time spent buying reagents that is the most constraining element in the process. Brazilian chemists have, in a sense, become "the consultants of Indian manufacturers" (chemist, responsible

for ARV)⁹. It was the Far Manguinhos synthesis department that showed that the last step in the synthesis of Indinavir could produce a dangerous contaminant. The laboratory's chemists gave their Indian supplier specifications for synthesis and: "Since then they've done it according to our specifications." (Far Manguinhos chemist). It has therefore become possible to draw on this knowledge base to fill in the gaps of incomplete descriptions of synthesis processes in patents, or to assess synthesis processes kept secret by a supplier: "one needs a theoretical base from the literature as a basis for discussion: it's not path X that they sent us, it's something else" (chemist, Synthesis Department).

To conclude on this process of knowledge acquisition by reverse engineering, we wish to underscore the following points.

First, this process requires reliable knowledge management, from trips to suppliers to consultation of patent data bases and scientific publications, testing of knowledge collected through laboratory experiments, and reverse engineering starting from capsules of reference drugs or raw material bought elsewhere. This learning process involves the combination and comparison of external and internal knowledge, as well as interactions between the laboratory's different specialized departments: analytical chemistry, synthesis, formulation and production.

Second, this learning process is gradual and cumulative. The knowledge base that has been built up currently serves for evaluations, comparisons, and the design of improvements to processes and products. Work on several copying projects undertaken simultaneously has also facilitated comparisons and added to experience. The Health Ministry now readily entrusts Far Manguinhos chemists with the evaluation of synthesis processes of a new molecule before negotiating its acquisition, including in fields other than AIDS. This is what happened recently with a very expensive drug used for treating leukaemia.

Third, knowledge acquired by Far Manguinhos is partly public – ARV standards are put into the Brazilian pharmacopoeia – and partly confidential – for instance the discovery of new polymorphs or elements not described in the literature. By publishing the latter type of result the government laboratory would be giving information to patent holders who refuse any technology transfer to the Brazilian laboratory. According to the head of organic synthesis, this is "internal knowledge".

9. Far Manguinhos chemists also highlight the contribution of their Indian counterparts: "The Indians have all studied in American universities and are excellent chemists. They publish a lot in order to optimize these steps, to reduce costs and to use less expensive reagents. I'm amazed by the literature they produce in this field" (researcher).

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Fourth, drug copying projects incorporate more and more cost variables, for example for choosing between different possible synthesis routes.

Fifth, the reproduction of patented molecules is not simply an exercise in copying, in so far as the Brazilian chemists do not start off with a complete list of the knowledge that needs to be applied. Patents are fundamentally incomplete and the chemical references of ARV were not available in pharmacopoeias. Chemists therefore have to combine the copying of available knowledge with the rediscovery or reinvention of other data, such as standards for pharmaceutical molecules, that they have had to recreate, or synthesis procedures imperfectly described in publications, that they have had to rediscover or develop.

Sixth, this learning process extends beyond the copying of existing drugs. In the course of the reverse engineering process chemists discover new entities or introduce variations or improvements. During work on synthesis routes of a particular existing molecule they sometimes propose improvements: "How can we do the synthesis of this? We can find it in the literature, and we can do some innovation because we have some experience here; we can change certain things." (Head of Synthesis). The same applies to the new formulation proposed for ddI. New polymorphs discovered during reverse engineering are now systematically studied, and this research could lead to new patents. The formulation group has a research programme on combinations of existing molecules. Finally, Far Manguinhos chemists run research programmes on new molecules for AIDS drugs. For instance, the young head of the ARV programme has moved from copying to doing R&D on a new molecule. This chemist's individual progression illustrates possible passages between copying and creation of molecules¹⁰. The development of research activities, apart from copying, is a challenge for this government laboratory which is recruiting more and more young PhD students.

10. One chemist told us about someone whose career was the opposite. A young researcher who did his PhD in France and a post-doc in the US, during which he invented several patents, is currently copying patents at Far Manguinhos. The prospect of developing new molecules would be far more attractive to him.

III
AN R & D LABORATORY FOR BUILDING UP
PHARMACEUTICAL INNOVATION NETWORKS IN BRAZIL

Whereas the Far Manguinhos government laboratory started out by copying existing drugs used to treat HIV/AIDS and manufacturing them in the final pharmaceutical production stage, from raw material bought primarily from Indian or Chinese companies, the technological learning process thus triggered off has now enabled it to plan industrial integration higher up in the process. The Health Ministry's laboratory is equipped to transfer knowledge acquired on molecule synthesis processes to Brazilian companies, thus enabling them progressively to produce intermediates and then active principles. In the future Far Manguinhos is expected to play a strategic part in this industrialization process, starting upstream with a policy of systematic acquisition of knowledge and R&D, right down to technology transfer.

This strategy is clearly apparent in the field of ARV. It explains the reverse engineering carried out by Far Manguinhos chemists on ARV synthesis processes even though the laboratory's mission does not include production of active principles. Far Manguinhos started to implement the strategy by signing a technology transfer agreement with the Brazilian laboratory Nortec, for the production of raw material according to a process specified by the government laboratory's chemists. The private company, with which the Far Manguinhos synthesis department maintains close ties, pays for the technology transfer in the form of raw material. More generally, Far Manguinhos has a policy of systematic technology transfer towards private industry. Processes developed on a laboratory scale – on a scale of one liter – are simultaneously sent to the companies concerned: “We have three molecules which are developed on a laboratory scale, afterwards they are sent back to the customer firms who want the technology.” (Far Manguinhos chemist). Far Manguinhos has also transferred technology on the final stage of AIDS drug production to other Brazilian government laboratories.

At the same time, Far Manguinhos is developing its R&D activity, both inhouse and in collaboration with universities. The laboratory has used income from the sale of drugs to the Health Ministry to build new research premises designed to house research in partnership with universities (PhD research, research contracts). Academics thus have access to premises and equipment that is often unavailable at their university. One of the recent results of this

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cooperation is a patent filed on an anti-protease, owned jointly by Far Manguinhos and the university.

Several engineers and one research chemist are responsible for intellectual property rights, research agreements with university, and technology transfer. The new accent on intellectual property relates to the laboratory's internal and external research programmes on polymorphs of existing molecules, combinations of ARV, and the discovery and development of new molecules for treating AIDS and other pathologies. For Far Manguinhos, patenting is a form of protection against opportunistic appropriation, a way of guaranteeing the transfer of innovations to outside partners, and a means for regulating prices and supply in the medicinal drug market¹¹. The aim is also to develop different types of technology transfer contracts with industry, generally from Far Manguinhos towards industry (*cf.* the contract with Nortec). On two occasions Far Manguinhos has negotiated with Indian and Brazilian suppliers for access to their synthesis processes. In these cases the raw material purchase agreement was combined with a technology transfer contract from the seller (the Brazilian laboratory Cristalia) to the buyer (Far Manguinhos).

The Health Ministry laboratory is busy building technical-economic networks with multiple actors: Brazilian universities, for testing its products and searching for new molecules; other pharmaceutical laboratories in various Brazilian states – Far Manguinhos transfers to them the technology of final production stages of the drugs it develops; and Brazilian private-sector industry, regarding both the production of the drugs – the public laboratories purchase the raw material from the private companies and manufacture the final product – and the transfer and development of the synthesis processes of the active principles of these drugs – in the framework of Brazil's industrialization policy.

This industrialization process is nevertheless confronted with a major stumbling block: during the 90s the Brazilian pharmaceutical chemical industry declined considerably. The number of firms able to receive and implement Far Manguinhos technologies today is relatively limited¹².

11. Interview with the person in charge of Intellectual Property.

12. The head of technology transfer to industry knows of only nine Brazilian pharmaceutical chemicals firms.

Conclusion

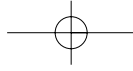
The first encouraging results of the Brazilian Health Ministry's AIDS programme launched in 1996 are well-known, both in terms of medicinal drug prices and public health. The launching of Brazilian production has resulted in the plummeting of the cost of ARV per patient in Brazil and in a regulatory effect reducing prices in the world market. The originality of this experience is based on the combination of a favourable industrial property policy for drugs until 1996 (*i.e.* non-patentability of pharmaceutical products and processes), a public health policy (the 1996 decree on universal access to ARV), and an industrial policy that allows the copying of existing drugs. The Rio de Janeiro Health Ministry laboratory Far Manguinhos has played an essential part in this system, even though it was a small private laboratory that initiated the copying of AZT in 1993. Far Manguinhos is also part of the Oswaldo Cruz Foundation, the largest scientific and technological institution in Latin America in the health field. It has a long history, starting in 1938 on the Manguinhos site which mass-produced yellow fever vaccine [3].

In our opinion, the launching of the copying of ARV has had an essential effect in terms of economics of knowledge and industrial economics. It triggered a process of technological learning and acquisition of knowledge relative to the molecules copied, especially in the Health Ministry's laboratory in Rio, a process that is now being continued in the form of projects to discover new drugs. This can be explained primarily by the fact that the Brazilian chemists who embarked on copying the molecules from 1997 were forced to partially rediscover the quantitative and qualitative composition of the active principle of these drugs, as well as their pharmaceutical form. They did not have access to the knowledge that the owners of patented molecules held or transferred to their licensees. Nor could they rely on references in pharmacopoeia on the components of these drugs since they were not disclosed. These chemists therefore reinvented tests to identify drug components, consisting of reverse engineering to find their formulae and synthesis processes. The knowledge acquired exceeds the industrial capacities of the government laboratory which is equipped only to produce the pharmaceutical form of the drug. Yet Far Manguinhos has developed a strategy for the acquisition of knowledge on synthesis processes, by increasing its in-house and external research and by acquiring technology from its suppliers. The laboratory is therefore currently able to transfer the synthesis processes that it develops to Brazilian industry, provided it can solve the problem of switching from a laboratory to an industrial scale. The challenge is also to go

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beyond copying, to develop new molecules, both in-house and in cooperation with Brazilian academics. During this experience, the copying process spawns the creation of a local knowledge base and an R&D dynamic. The two development strategies identified by Paul Romer, “Using ideas and Producing ideas” [1] are thus closely combined here. Yet, even though Far Manguinhos has started to launch research that goes further than simply copying existing molecules, the development of a new molecule, from initial research down to industrial production, is still a challenge in areas like AIDS and tuberculosis.

This process of acquisition and creation of knowledge around the copying of ARV has been facilitated by the non-patentable status of drugs in Brazil before 1996. The copying of new ARV patented since 1996 would require Brazil to use compulsory licensing provided for in its 1996 industrial property law and in the 1994 TRIPS agreement. This is what the Far Manguinhos chemists that we interviewed want – and they have already done the reverse engineering of these drugs. It is also what the patients’ associations and NGOs (*e.g.* Médecins sans Frontières – Brazil) that support their work want. This experience provides an outline of some of the amendments that could be made to patent laws – especially free use of drug inventions in countries of the South – to solve public health and industrial development problems in those countries. How many of us remember that the French pharmaceutical industry enjoyed a non-patentable status of drugs in France from 1844 to 1959 and was therefore able to copy German patents freely?



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