Biodiversity and Technological Development: Opportunities for Developing Countries and the Case of Brazil

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Abstract

A significant percentage of world's prescription medicines are derived from natural products. There has also been a steady increase in the natural medicines market. These trends may provide an opportunity for developing countries with large biological resources to implement industrial and technological development strategies based on those resources. Developing countries face several problems in the pharmaceutical sector due to technological dependency, precarious access to medicines and the fact that research-based companies do not direct efforts toward diseases that are prevalent in those countries.

To fully understand the opportunities biological resources might present, it is necessary to conduct a careful analysis of the industrial, technological, and regulatory environments, both at national and international levels. While developing countries do share some common characteristics in terms of their integration into the world economy not all of them have industrial and technological capabilities in the pharmaceutical sector.

Brazil provides an interesting case study for the analysis of natural products and pharmaceutical development opportunities. Brazil is among the world's five richest countries in biodiversity, has an established pharmaceutical industry, is among the top ten pharmaceutical markets in the world, and has a good science and technological infrastructure for natural products research. Yet Brazil is also dependent upon importation of inputs and products from the world's most developed countries, and access to medicines is a public health problem throughout the country.

The ultimate aim of this paper is to discuss the extent to which a developing country can benefit from windows of opportunity in the pharmaceutical industry related to biodiversity, with special attention given to the case of Brazil.

Keywords: biological resources, economic development, medicinal plants, pharmaceutical industry, Brazil

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Introduction

The pharmaceutical industry is a highly internationalized industry, with leading companies from the developed world dominating most markets (except in a few countries such as India) and a market that is heavily geared toward therapeutic classes of drugs. Pharmaceutical innovation, production, and trade are also concentrated in developed countries, where leading firms are based. This geography of innovation and production reflects the dynamics of knowledge production in the pharmaceutical industry and their relationship with other factors, such as the industry's development and organization at national and international levels.

These characteristics pose several challenges for developing countries, where access to medicines is a problem. Most pharmaceutical companies in the developing world (either domestic or foreign) do not invest (or invest very little) in research and development (R&D), especially for diseases that pose serious public health problems in developing countries — such as malaria, schistosomiasis, leishmaniasis, etc.

While the majority of the world's population lives in developing countries, these countries represent a small share of the international pharmaceutical market — although a few developing countries such as Brazil, Mexico, and Argentina are among the world's top ten markets. A handful of developing countries have advanced technological and industrial capabilities for the production of fine chemicals[1] and finished medicines but the vast majority of them do not. Thus, these countries are generally dependent upon fine chemicals, processes, or products developed by leading pharmaceutical companies located in developed countries, either through these companies' in-house efforts or their licensing of rights to other companies

[1] Fine chemicals are active substances responsible for therapeutic action and chemical intermediates that are used in the formulation of medicines.

located in developed countries. Even in the developing countries that have managed to establish local production abilities in fine chemicals and finished medicines, efforts directed toward the development of new molecules have been modest compared to what is happening at leading firms in developed countries. Besides, developing countries' pattern of integration into the world economy is characterized by higher vulnerability and lower bargaining power in international trade negotiations (Fialho et al. 2003).

It has been argued that developing countries that are rich in biodiversity should implement strategies geared toward pharmaceutical innovation, such as:

(1) Technological and industrial development policies to stimulate a country's domestic pharmaceutical industry and reduce its technological dependency

(2) Encouraging the development of natural medicines and taking advantage of the market potential of phytomedicines

(3) Stimulating the development of medicines for diseases that are prevalent in the developing world but tend to be neglected by leading international pharmaceutical companies

The main reason such possibilities exist has been the fact that of the 250,000 to 500,000 estimated plant species on the planet, less than 15 percent have been studied in terms of their phytochemical properties and less than 6 percent in terms of their therapeutic properties. In the case of microorganisms, less than 1 percent has been studied (Harvey 2000; Fabricant and Farnsworth 2001). With other natural products such as marine organisms and insects, research has begun only as recently as the mid 1970s, and although no product has been introduced into the market, this is a promising field. In addition, despite the substitution of natural medicines by synthetic or semi-synthetic medicines beginning in the first quarter of the twentieth

century, several of the world's current prescription medicines were developed through natural products research (Farnsworth et al. 1985; Nisbet and Moore 1997; Cragg et al. 1997; Cragg et al. 1999; Shu 1998; Young 1999; Harvey 2000).

In the late 1970s, several medicinal plant initiatives were put in place by countries and multilateral organizations. In 1978, the World Health Organization (WHO) created the Traditional Medicines Program (TRM) to support the use of traditional medicine in the international health system (and particularly in developing countries).[2] There has also been an increasing interest in alternative medicines and natural medicines, especially in developed countries. This trend reflects rising concerns about the efficiency of conventional therapies; problems related to the irrational use of synthetic medicines and their adverse effects; and the belief that natural medicines are less dangerous.[3]

In addition, advances in modern biotechnology have allowed overcoming some technological bottlenecks in natural products research. Similar advances have occurred in cultivation techniques and production of phytomedicines, which have improved the quality, safety, and efficacy of natural medicines. In the beginning of the 1990s, it was recognized by the Convention on Biological Diversity (CBD) that individual nations should have sovereignty over (and access to) the biological resources in their territories, and that equitable benefit sharing and transfer of relevant technology should be facilitated. At the same time, changes in international intellectual property rights regimes have allowed living organisms to be patented

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[2] In the 1980s, Farnsworth et al. (1985) collected information from the World Health Organization's collaborating centers for the TRM program about the role of ethnomedical knowledge in drug development. Farnsworth et al. indicated that the TRM study identified 122 compounds derived from 94 plant species (Fabricant and Farnsworth 2001).

[3] ,Although toxicity is not a matter of whether a compound is natural or synthetic, some natural products can be highly toxic (Topliss et al. 2002).

(Duttifield 1995; Silva 1995; Hoareau and Silva 1999; ten Kate and Laird 1999; Michael 2000; Rates 2001).

According to Abramovitz (1979, 1986, 1989) and Abramovitz and David (1996), the greater a developing country's "technological gap" from the developed world, the greater chance it has to "catch up" and reduce this gap. In this catch-up process, the most important elements are the country's "social capability" in relation to the institutional framework and its relationship to the resources that are needed for technological progress in a given period. However, it has been observed that these assumptions about catch-up development may only hold true for the trajectory that was followed by some countries that are already developed. The same dynamics may not be possible in current developing countries, given that the technology gap has been widening among developed and developing countries and despite considerable improvements observed in some newly industrialized countries over the last 30 years (Lau 1996).

Changes in the techno-economic paradigm with microelectronics, biotechnology, and automation, and institutional changes in the 1980s created a more favorable environment for technologically backward countries to stimulate industrial, economic, and technological development (Perez 1985). In order words, these changes opened "windows of opportunity" for the countries that were not committed to the previous paradigms to stimulate industrial and technological development within the new paradigm. The idea of "windows of opportunities" is based on the assumption that during periods of change, learning would be relatively homogenous for all countries for a certain period of time (Perez and Soete 1988).

Yet the ability to take advantage of such opportunities depends upon several factors, including a country's capability to actively absorb foreign technology, its endowment of

qualified human resources (especially in the new technologies), its level of involvement in research and development efforts, and the existence of reasonable productive capabilities beyond those capabilities that are presented by location advantages (Soete 1985; Perez 1985; Freeman and Perez 1988; Perez and Soete 1988). However, one cannot forget that technological change is a cumulative process. The ability to benefit from a "window of opportunity" is generally related to factors at the national level, as one can observe from studies based on the concept of national innovation systems (Freeman 1987; Lundvall 1992; Nelson 1993). Yet in all of these studies, non-local factors such as the geopolitics of competition among nation-states are poorly addressed. Recently, some scholars have attempted to incorporate the role of non-local factors into the analysis of development trajectories (Freeman 1997; Cimmoli 1998). But, as Lundvall (2002) suggests, these aspects have still not been sufficiently addressed.

In the pharmaceutical industry, a country's chances of benefiting from a "window of opportunity" during periods of technological change depends upon local factors, such as the country's pharmaceutical industry structure and the behavior of individual companies; its science and technology infrastructure; its domestic market dynamics; its industrial and technology policies and regulatory environment; and its technological learning and absorption capacity (Fialho et al. 2003). However, these opportunities also depend on a country's integration into the world economy, the dynamics of industrial competition at the international level, and the international regulatory environment.

This working paper discusses the possibility of developing countries benefiting from the window of opportunity related to biodiversity in the pharmaceutical industry. Section 1 presents the elements that allow the characterization of these windows of opportunity in

respect to the international institutional environment and the dynamics of technology, industry, and regulation. Section 2 discusses the specific case of Brazil. Brazil is one of the world's five richest countries in terms of biodiversity, has an established pharmaceutical industry, is among the world's top ten world pharmaceutical markets, and has a good science and technological infrastructure for natural products research. But Brazil is dependent upon importation of inputs and products from more developed countries, and access to medicine is a problem. Thus, as it is a laggard country with large biological resources, Brazil is an interesting case for the analysis of windows of opportunity associated with biodiversity's potential for the pharmaceutical industry. The last section of this paper is devoted to conclusions.

1. Opportunities in Natural Products

The central argument of this study is that developing countries' biodiversity presents some windows of opportunity for their pharmaceutical industries: finding and using active biological compounds for the development of medicines; expanding the potential of natural medicines (in particular, phytomedicines); and developing medicines for neglected diseases. The emergence of such opportunities is related to several factors: changes in the international institutional environment regarding access to and use of biological resources; technological changes in drug discovery processes and their consequences for the search for new medicines; and the growth of a market for natural medicines (which are now competing with synthetic medicines). Consequently, a careful analysis of these opportunities must consider developing countries' institutional, economic, and technological environments.

1.1 Access to Biological Resources: The Convention on Biological Diversity (CBD) and Trade Related Aspects of Intellectual Property Rights (TRIPS)

Historically, developing countries have not received many returns from pharmaceutical companies' marketing of the medicines developed from research on biological resources found in these countries (Juma 1989; Reid et al. 1993). Until the end of the 1980s, these resources were considered "the common heritage of mankind" and seen as universally accessible. But after the Convention on Biological Diversity (CBD) was signed in 1992 during the United Nations Conference on Environment and Development (UNCED) in Rio de Janeiro, nation-states' sovereignty over these resources was recognized (Reid et al. 1993; Blum 1993; ten Kate and Laird 1999; Srividhya 2000; Strauss 2000; Dalton 2004).

The CBD is an international treaty that resulted from discussions that occurred at different international forums beginning in the 1970s. These discussions addressed several issues: environmental concerns (the extinction of species, conservation, and access to biodiversity resources); intellectual property rights; benefit sharing; sustainable development; and the transfer of technology. Of the 188 countries present at the 1992 UNCED Conference, 160 countries (plus the European Community (EC)) signed the CBD, which entered into force in 1993 after 39 countries had ratified it in their national legislatures. In 1993, 5 other countries, including the United States, signed the CBD.[4] Of the 188 current UNCED members, 37 (including the United States, Japan and the Netherlands) have not ratified the convention in their national legislatures.[5] Although the EC signed the CBD in 1992 and most EC countries have individually ratified the CBD, the EC as an entity has not ratified it. The deadline for CBD ratification is 2010.

The United States' refusal to sign the CBD in 1992 was related to some of the main issues that have been debated since the convention was first signed: access to resources, intellectual property rights, access to and transfer of relevant technology, and benefit sharing. In terms of access to resources, it has been argued that the CBD could result in national laws that may inhibit access to biological resources and create obstacles to technological development. In terms of intellectual property rights over the results based on access to those resources and benefit sharing, the main problems are related to the valuation of resources, their

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[4] The four other countries are the Czech Republic, Slovakia, Syria, and Vietnam.

[5] The following countries are signatories of the CBD, but have not ratified it yet: Armenia, Azerbaijan, the Democratic People's Republic of Korea, Finland, Japan, Netherlands, Togo, the Czech Republic, Slovakia, and the United States of America.
The following UNCED countries have neither signed nor ratified the CBD: Albania, Andorra, Bosnia and Herzegovina, Brunei Darussalam, Cambodia, Equatorial Guinea, Eritrea, Georgia, the Holy See, Iraq, Kiribati, Kyrgyzstan, Lao People's Democratic Republic, Niue, Palau, Saint Lucia, Saint Vincent and the Grenadines, Saudi Arabia, Sierra Leone, Somalia, Tajikistan, the Former Yugoslav Republic of Macedonia, Timor-Leste, Tonga, Turkmenistan, and Uzbekistan.
Only two countries that did not sign the CBD in 1992 have since ratified it (the Dominican Republic and South Africa in 1994 and 1995, respectively).

role in the development of products and processes, and the monitoring and proprietorship of future developments based on access to a given resource.[6] Developed countries do not agree that all developing countries should have preferential treatment in technology transfer agreements. Another important issue is that the CBD's objectives are to facilitate access to biological resources, and to promote protection, conservation, and sustainable development with fair and equitable benefit sharing. Since the CBD is a framework treaty, its provisions are basically recommendations, and there are no sanctions for those countries that bypass the convention's provisions through practices such as "biopiracy"[7] that are not explicitly mentioned by the CBD (Burgiel 2004).

Since 1992, the implementation of CBD recommendations — especially regarding intellectual property rights and transfer of technology — have been at the center of debates about the treaty and no consensus has been reached between developing and developed countries on these issues. In the light of these problems, the CBD Secretariat put forward the *Bonn Guidelines*. These guidelines were intended to address demands from developing countries regarding the disclosure of the origins of resources, including traditional knowledge, evidence of PIC (*prior informed consent*), MAT (*mutually agreed terms*) and ABS (*access and benefit sharing*) in patent applications. Since the *Bonn Guidelines* were passed, the associations representing the pharmaceutical (IFPMA 2003) and biotechnology industries (Bio 2004) have consistently claimed that such recommendations — if widely implemented by countries in their national laws — would run counter to CBD objectives, since companies would no longer be willing to undertake R&D efforts under such requirements.

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[6] For example, according to Turner (1996), Glaxo Smithkline would share ownership over active compounds resulting from research in natural products with the resources' country of origin, but would not share ownership in the case of lead compounds or analogues.

Another issue that has been raised is related to the difficulties national patent offices face in verifying CBD requirements, a process that will require a collective effort of gathering and sharing information. One option would be support for the creation of databases on biological resources, such as the Global Biodiversity Information Facility.[8] However, some developing countries have been reluctant about such initiatives. They fear that making this kind of information available would allow companies to develop products without necessarily sharing benefits, or that sharing such information would facilitate the smuggling of species, especially endangered species with higher value. Another concern involves *ex situ* collections to which the CBD provisions do not apply (Strauss 2000; Sharma 2004; Sterckx 2004; Masood 2004).

In 2003, during the Fifth Ministerial Conference of the World Trade Organization (WTO) in Cancun, a group of fifteen developing countries[9] created the Group of Like-minded Megadiverse Countries, with the goal of coordinating their efforts concerning CBD recommendations, technological capability efforts, and technology transfer involving the exploitation of biological resources. At the same time, twenty-one developing countries (some of them also belonging to the new Group of Like-minded Megadiverse Countries) formed the Group of 21 Coalition (G21),[10] in order to coordinate negotiations on agriculture and biopiracy issues at the WTO. During the Cancun Conference, developed countries believed that the G21 was "a marriage of convenience" since all of these countries has many different interests.

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[7] Defining biopiracy is itself problematic. Here, biopiracy means the appropriation of biological resources for commercial purposes without the authorization of, or compensation to, the entitled owners.

[8] This is an intergovernmental organization that shares information about biological resources, such as botanical descriptions, through the Internet.

[9] These fifteen countries are Bolivia, Brazil, China, Costa Rica, Colombia, Ecuador, India, Indonesia, Kenya, Mexico, Malaysia, Peru, Philippines, South Africa, and Venezuela.

[10] These twenty-one countries are Argentina, Bolivia, Brazil, Chile, China, Colombia, Costa Rica, Cuba, Ecuador, Egypt, Guatemala, India, Indonesia, Mexico, Nigeria, Pakistan, Paraguay, Peru, the Philippines, South Africa, Thailand, and Venezuela.

These divergences, however, do not invalidate developing countries' attempt to create a level playing field in international trade negotiations regarding biological resources (van de Ven 2003).

It has been observed that most discussion of the CBD that is not about agriculture is related to the pharmaceutical and biotechnology industries, since prior to the CBD, the commercialization of medicines based on natural products found in developing countries had not resulted in benefits for these countries. It is also important to note that the technology gap that exists between developed and developing countries (especially in biotechnology) and the strengthening of intellectual property rights (especially regarding the patenting of living organisms) may create obstacles to the sustainable use of biological resources in developing countries.

Since patent protection is seen as an important element in obtaining the benefits accruing from the marketing of the results of R&D efforts in pharmaceutical and biotechnology industries, it is important to note that this discussion about natural medicines development is affected by recent changes in intellectual property rights regimes. Patent protection provides temporary monopoly rights that allow the patent holder to also establish prices, which are generally set at high levels in order to recoup costs related to inventing a product and bringing it to market. Therefore, patent protection supposedly creates economic incentives for the introduction of the patented invention into the market, since it allows the applicant to forbid third parties to use or commercialize the invention.

The role of patents as a mechanism to protect inventions and a means of promoting economic returns differs from industry to industry, but is particularly important in the case of pharmaceuticals. This is due to the fact that within the pharmaceutical industry, it would be

relatively easy for people with sufficient knowledge to design around a patent. Gaining sufficient knowledge, however, is not an easy process. Therefore, during the evolution of the pharmaceutical industry, countries have taken different positions regarding patent protection for processes and products. In general, countries introduce product patents after reaching a certain level of technological capability, which allows them to reduce their technological dependency.

Although there have been international treaties regarding intellectual property rights since the end of the nineteenth century, countries have had certain freedom to establish national laws regarding pharmaceutical products and processes that were not subject to patent protection. Until the 1970s, both developing countries and some developed ones did not protect pharmaceutical products and processes through patents. Such policies were intended to reduce technological dependency and stimulate local industry development. By the end of the 1970s, however, intellectual property rights protection for pharmaceutical processes and products had been established in most developed countries.[11] In most developing countries, on the other hand, weak intellectual property rights regimes for pharmaceuticals still prevailed through to the beginning of the 1980s.

The United States[12] managed to introduce services, intellectual property rights, and investment onto the agenda of the General Agreement on Tariffs and Trade (GATT) during the 1986 Uruguay Round, despite the initial reluctance of other developed countries (including

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[11] The United Kingdom introduced process and product patents for pharmaceuticals in 1949, Japan in 1976, and Switzerland in 1977; France introduced process patents in 1944 and product patents in 1960; West Germany introduced product patents in 1968; and Sweden and Italy introduced product patents only in 1978.

[12] According to Tachinardi (1991), the defense of intellectual property rights became the main issue on the agenda of the U.S. Pharmaceutical Manufacturers Association (PhRMA). It also worth mentioning that in 1974 the United States introduced Section 301 to the United States Trade Representative's (USTR) responsibilities. According to this section, the USTR is responsible for monitoring intellectual property rights around the world, and those countries whose intellectual property regimes are considered by the USTR to be unsatisfactory enter a "Priority Watch List" and are subject to U.S. economic sanctions.

EC countries and Japan) and of developing countries. So at the same time that the sustainable use of biological resources was being discussed during the CBD negotiations, the enforcement of intellectual property rights was being discussed within the GATT negotiations. Developed countries' argument was that the harmonization of intellectual property rights was necessary for technology transfer efforts to be successful. On the other hand, developing countries expected developed countries to lower tariffs, non-tariff barriers, and export subsidies in agriculture and textiles (Pereira 1993).

Although there have been some slow advances in the reduction of international trade barriers in agriculture and textiles since the end of the Uruguay Round, intellectual property rights, on the other hand, have been rigorously enforced at international level, after the Trade Related Aspects of Intellectual Property Rights (TRIPS) was signed by 123 countries in April 1994 and entered into force in 1995.[13] After the TRIPS, countries have had less discretion to set the terms of patent rights such as to restrict patent protection to pharmaceuticals.

Despite developing countries' the lower bargaining power in international trade negotiations, these countries expected that the TRIPS would stimulate technology transfer agreements. This hope was based on the fact that according to TRIPS Article 7, one of the objectives of protection and enforcement of intellectual property rights is to "contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations." However, as we approach 2005, the opening of international trade, especially agricultural trade, is still stalled on the WTO agenda. Meanwhile, most developing countries have

implemented or are about to implement strong intellectual property rights regimes, but they are still technologically dependent on developed countries and north-south technology transfer is still very low. (CIPR 2002) It is worth noting that recent discussions at the WTO create a more favorable environment for the elimination of trade barriers in agriculture and for enhancing technology transfer. But the effective implementation of recent decisions depends on further negotiations among WTO member countries.

One fundamental aspect of the intellectual property rights discussion is patentability criteria, since there is no consensus on whether results of research using living organisms are inventions (and therefore patentable) or discoveries (and therefore not patentable). According to TRIPS Article 27.3(b), member countries have to grant patent protection to microorganisms, non-biological and microbiological processes, plant varieties,[14] and objects resulting from genetic engineering — except in cases in which it is necessary to "protect public order or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by [these countries'] laws."

In this sense, results from biotechnology and natural products research, in the form of isolated compounds, may be subject to patent protection, even if the structure is identical to the original natural product (Strauss 2000; Bermudez et al. 2000; Sterckx 2004). It is noteworthy that the TRIPS does not define technology or discovery. Considering the difficulties in reaching consensus in respect to the patentability of biological matters and other

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[13] WTO members and WTO aspirants have to bring their intellectual property laws in accordance with the TRIPS by 2005.

[14] In 1961, the International Convention for the Protection of New Varieties of Plants (UPOV), an independent intergovernmental organization, was created. The UPOV secretary is the World Intellectual Propery Organization (WIPO) director general, and the WIPO provides administrative and financial services to the UPOV. Currently, fifty-four countries are parties of the UPOV (UPOV 2004).

issues, TRIPS Article 71 established the year 2000 as the initial date to begin reviewing and discussing amendments to the agreement. However, no consensus has been established, and changes are still being discussed (Sterckx 2004).

Another important concern is that the TRIPS does not mention or define "biopiracy." In March 2004, the World Intellectual Property Organization (WIPO) convened a meeting to discuss biopiracy, the protection of genetic resources, and traditional knowledge. But no consensus was reached between developed and developing countries on these issues. Both the United States and EC countries are against the discussion of biopiracy in international forums like the WTO (Vidal 1999). However, developing countries have proposed that patent applications should specify the country of origin of genetic resources and traditional knowledge, and eventually evidence of PIC, as recommended by the recent CBD provisions put forward by the *Bonn Guidelines* (Chade 2004).

Besides the discussions involving the compliance between the TRIPS and the CBD, increasing attention has been directed toward the implications of the TRIPS for public health, especially regarding TRIPS' impact on developing countries' access to medicines. In the case of pharmaceuticals, a strong intellectual property rights regime may result in insufficient access to medicines, especially in countries where the population has a low purchasing power. However, it should be emphasized that the absence of patent protection does not necessarily mean greater access to pharmaceuticals, since other factors must also be taken into account, including:

- A country's model of acquiring and financing medicines, and the public and private resources available for these tasks

- The existence of local pharmaceutical production capabilities and the local pharmaceutical industry's integration into the world pharmaceutical industry
- Problems related to geographical access
- A country's level of income distribution and price regulation

Nevertheless, this does not mean that the existence of patent protection has no influence on access to medicines. In many countries, especially developing ones, medicines are supplied through importation. Hence, the existence of intellectual property rights in other countries may influence developing countries' own level of access to medicines (CIPR 2002).

Recent debates about TRIPS and access to medicines have often focused on the impact of strong intellectual property rights on the fight against the HIV/AIDS epidemic, especially in developing countries where access to medicines is a problem. One prominent example of this debate about intellectual property rights and HIV/AIDS is the dispute at the WTO between Brazil and the United States with respect to Brazil's intellectual property law (Law 9.279 of 1996) and the issue of compulsory licensing.[15]

The Brazilian case is an example of how the absence of intellectual property rights for pharmaceuticals allowed a country (Brazil) to support a pharmaceutical assistance program that provided guaranteed access to antiretroviral medicines at lower costs. This was possible not only because public procurement by Brazilian public health authorities (such as the Ministry of Health) of products not subject to exclusivity (such as medicines not protected by patents) based on a tendering process according to the lowest price offered. It was also

[15] It is important to observe that the TRIPS does not explicitly mention "compulsory license"—a government permit to allow third parties to produce a patented product or process without the consent of the patent holder. In the TRIPS, Article 31 refers to "other use without the authorization of the right holder"—and compulsory license is one of those uses (WTO 2003a).

possible because once antiretroviral medicines were guaranteed in Brazil with the passage of Law 9.313 in 1996, domestic companies saw that they could invest in and profit from technological learning in antiretrovirals despite competition based on low prices.

In addition, Brazilian public laboratories that are committed to public health policies have supplied finished medicines at low costs, based mainly on imported inputs from India and China.[16] However, the enforcement of intellectual property rights after Brazil passed Law 9.279 has pointed to limitations for the antiretroviral program's sustainability, since the public procurement law obliges the government to purchase products that are exclusive (like patented medicines) from the original manufacturer or its licensee. Given the power of the patentees to fix prices due to temporary monopoly rights granted by patents, the Brazilian government has been systematically negotiating price reductions with pharmaceutical companies. In these negotiations, the Brazilian government, taking the capabilities of local companies in antiretrovirals into account, has signaled its intention to apply compulsory license, based on Article 71 of Law 9.279 and in accordance with TRIPS Article31(b). However, given the recent changes in Brazil's procurement policy regarding antiretrovirals, there has been some discussion about the extent to which this application of "compulsory license" is actually a credible threat, especially due to the reliance upon importation of active substances from China and India[17] that will be subject to TRIPS provisions after 2005 (Hasenclever 2003).[18]

The WTO addressed this discussion about the impact of TRIPS on access to medicines at the Fourth Ministerial Conference in Doha (Qatar) in November 2001. This meeting led to

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[16] For a discussion about the Brazilian experience in the production of antiretroviral medicines in Brazil, see Hasenclever (2003).

[17] In the case of patent applications filed in India between January 1, 1995 and December 31, 2004, these will be examined under the new law according to the TRIPS provisions after 2005. A very simple example is the case of the GlaxoSmithKline antiretroviral Combivir. If a patent application were filed for this drug under the new system, it is uncertain that it would be issued (MSF 2004).

the "Declaration on the TRIPS Agreement and Public Health" (WTO 2001), generally referred as the Doha Declaration.[19] The main objective of the Doha Declaration (Paragraph 6) is to ensure that countries can adopt any measure in order to protect the public health of their citizens. According to TRIPS Article 31(f), the use of patented objects without the authorization of the right holder (e.g., compulsory license) must be predominantly for the domestic market and there are "limits [to] the amount they [countries producing under compulsory license] can export…" (WTO 2003a).

Since the Doha Declaration, the WTO has addressed two other important issues regarding TRIPS and public health: (1) The attempt of developed countries to limit the type of diseases that would fall under the declaration, and (2) The countries to which these public health provisions should apply.[20] These limitations were rejected by developing countries — especially the least developed countries that do not have sufficient pharmaceutical manufacturing capabilities to be able to apply compulsory license (CIPR 2002). In 2003, at the end of the Fifth Ministerial Conference in Cancun, WTO members agreed to facilitate the importation of "cheaper generics made under compulsory license if they [less developed or developing countries] are unable to manufacture medicines themselves"[21] through the Decision WT/L/540 (WTO 2003b), concerning the implementation of Paragraph 6 of the Doha Declaration on TRIPS and Public Health. According to this decision, countries can

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[18] The Brazilian government recently passed a Decree n.4380 of December 2003 allowing the importation by the government of medicines produced elsewhere through compulsory license based on Article 71 of the Brazilian Patent Law.

[19] The Doha Declaration contains declarations and decisions concerning other issues besides public health.

[20] A major concern regarding the Doha Declaration is the avoidance of "parallel imports" by rich countries. Parallel imports refer to the exportation of products protected by patents without the patent holder's permission. The rationale behind parallel imports is the idea of "exhaustion" of rights, according to which patent rights are exhausted after a product has been sold. it is important to observe that under TRIPS, the principle of exhaustion can be subject to dispute only if "fundamental principles of non-discrimination are involved" (WTO 2003).

[21] This decision, however, is not limited to medicines, since it defines pharmaceutical products as "any patented product, or product manufactured through a patented process, of the pharmaceutical sector needed to address the public health problems as recognized in Paragraph 1 of the Declaration. It is understood that active ingredients necessary for its manufacture and diagnostic kits needed for its use would be included."

import generic medicines from other countries that are producing these medicines under compulsory license, and hence the limitations of the TRIPS Article 31(f) are waived for exporting countries in these instances.

This decision does not limit which countries could use the system. However, a group of twenty-three countries[22] voluntarily announced that they will not use the system to import pharmaceuticals, while ten other countries[23] that are about to enter the European Community said they would use the system only in the case of a national emergency and only before entering the EC; and another twelve countries[24] said they would use the system only in cases of national emergency. Least developed countries do not have manufacturing capabilities in pharmaceuticals and are thus eligible to use the system, but other countries are also eligible, except for those twenty-three countries that indicated they will not use the system. To become eligible to use the pharmaceutical import system, a country must communicate its intentions to the WTO and affirm either the non-existence of local capability or demonstrate that local capabilities (not taking into account the original manufacturer's capability) are insufficient to meet the demand. But according to Decision WT/L/540, as soon as this capability exists, a country can no longer use this system. In general, WTO member countries agreed that:

- This mechanism must be used only to protect public health and would not be used for commercial and industrial policy goals

[22] The twenty-three countries that announced that they would not use the system to import medicines are Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, the United States, and the United Kingdom.

[23] The ten countries that are about to enter the EC and have announced that they would not use the system to import medicines except in national emergencies are the Czech Republic, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia.

[24] The twelve countries that have announced that they would only use the system in a national emergency are Hong Kong, China, Israel, South Korea, Kuwait, Macao China, Mexico, Qatar, Singapore, Taiwan, Turkey, and the United Arab Emirates.

- There would be packaging systems in order to avoid re-exportation of pharmaceuticals to rich countries at lower prices
- The adequate use of the system would be monitored by the TRIPS Council

Some NGOs have criticized Decision WT/L/540, calling it a step back from the Doha Declaration, since Paragraph 1 of the Doha Declaration emphasized that its provisions apply to problems recognized in "HIV/AIDS, tuberculosis, malaria and other epidemics." But it is worth remembering that the Doha Declaration does not limit the type of diseases to which compulsory license can apply (CIPR 2002).

While the implications of the TRIPS for capacity building in the pharmaceutical and public health industries in developing countries were being discussed, so was the issue of compliance with the TRIPS and the CBD. The Doha Declaration also indicated that a TRIPS Council should be established to examine the compliance of the TRIPS provisions and CBD recommendations. This issue is supposed to be discussed at the next WTO Ministerial Conference (on December 2005 in Hong Kong, China). While the CBD's objectives are to promote conservation and sustainable use as well as promote access to technology transfer, TRIPS' strong protection of intellectual property rights is designed to limit access to technology. Another important issue is related to the protection of traditional knowledge.[25] This kind of knowledge cannot be protected by patents because it is not possible to attribute novelty criteria to it and it cannot be recognized as a pre-existing art unless it has been published elsewhere (Strauss 2000).[26]

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[25] In 2000, the WIPO created the *Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore*. In 2002, this committee began to discuss the disclosure of PIC, ABS, and origin of resources in patent applications, but there have not been any significant advances in this regard at this time.

[26] The idea that traditional knowledge may be protected by a *sui generis* intellectual property regime has been discussed by the WIPO. However, even on this issue there is no consensus.

Dedeurwadere (2004) argues that the current system of incentives for R&D in biodiversity resources, intellectual property rights, and the recommendations of the CBD (such as ABS and IPC) do not have positive externalities along the value chain. There are also difficult problems—such as moral hazard, opportunism by either companies or stakeholders of biological resources, and traditional knowledge—that have not been addressed efficiently by current legal mechanisms. These problems may lead to underinvestment in activities related to protection, conservation, and exploitation of biodiversity, as well as to the issuing of patents on an unforeseen scale and not necessarily to those parties that would most likely to be entitled to these privileges (Sterckx 2004).

Another important question related to access to biological resources and intellectual property rights is the issue of neglected diseases. In pharmaceutical companies' decision-making about drug development, substantial attention is paid to a drug's market potential, both from the point-of-view of the purchasing power of potential consumers (either individuals or governments) and from the point-of-view of the disease's prevalence. These aspects have led to the identification of a group of diseases considered to be "neglected" or "orphans" due to the underinvestment in R&D efforts directed toward them — given the lower purchasing power of the affected population[27] and the diseases' lower level of prevalence.[28] According to the International Federation of Pharmaceutical Manufacturers (IFPMA), which represents research-based pharmaceutical companies, the existence of strong intellectual property rights in developing countries would create incentives for R&D investments, especially for neglected diseases (IFPMA 2003). However, it has been observed that there are no indications that the

[27] This is the case with the most prevalent diseases in developing countries (e.g., malaria, leishmaniasis, etc.), except for those diseases that are also prevalent in developed countries and therefore have significant market potential (e.g., cardiovascular diseases, diabetes, etc.).

enforcement of intellectual property rights in developing countries has any effect upon research-based pharmaceutical companies in respect to R&D on diseases prevailing in developing countries, except for those diseases that also represent larger markets in developed countries such as cardiovascular diseases (Pecoul et al. 1997; CIPR 2002).

1.2 Technology and Industry: Natural Products Research

In 2003 the pharmaceutical industry recorded worldwide sales of around US$315 billion, primarily concentrated in developed countries. Leading pharmaceutical companies based in developed countries have been responsible for the largest portion of sales.

In the early days of the pharmaceutical industry during the nineteenth century, the development of medicines was based mainly on plant and animal extracts. These were used for the preparation of fluid extracts (tinctures and syrups), powders, and solid extracts (pills or tablets). These medicines were created in accordance with certain ideas about the systematic use of certain plants for some health conditions and "beliefs" about their use. Given that the scientific bases of chemistry and pharmacology were not yet in place, most pharmaceutical products had no proven efficacy and many of them were simply not effective. With the development of pharmacology and organic chemistry in the first half of the nineteenth century, it became possible to isolate the active substances of plant extracts, identify the active mechanism of some compounds, and develop medicines based on those active substances (mostly alkaloids). During this same period, advances in chemical synthesis allowed scientists to create synthetic dyes; the development of bacteriology changed the base of knowledge about certain diseases; and the founding of the chemotherapy paved the way for the

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[28] Developed countries have established comprehensive lists of diseases that are considered neglected and provided mechanisms to stimulate R&D on these diseases (Meyers 1997).

development of synthetic medicines stemming from synthetic dyes in the early twentieth century.

At the end of the 1920s, the discovery of penicillin, manufactured on an industrial scale in the 1940s, gave a new direction to the search for active compounds. At that time, the structure of the world pharmaceutical industry changed considerably with the emergence of large companies competing on the international level. Since the 1930s, but mainly since World War II, efforts by pharmaceutical companies, which became the locus for product development, were directed toward the search for synthetic compounds or toward full or partial synthesis of active substances obtained from natural sources (mostly medicinal plants and microorganisms). In addition, advances in computational chemistry in the 1980s made it possible to speed up the synthetic compound design process based on chemical libraries developed over time by pharmaceutical firms during their search for synthetic drugs or drugs based on natural sources (Drews 1998).

Despite the general trend of pharmaceutical companies to look for synthetic compounds, the majority of new drugs approved for use in the United States and other countries are derived from natural sources. According to Cragg et al. (1997), of the 520 new drugs approved either in the United States between 1983 to 1994, 28 were large molecules (vaccines, monoclonal antibodies, and materials derived from mammalian sources), and 492 were small molecules. Of these 492 drugs derived from small molecule sources, 30 derived from a unmodified natural product source; 127 derived from a natural product (e.g. semi-synthetics); 46 derived from a synthetic source that was originally modeled on a natural product parent; and 289 were exclusively from a synthetic source. This means that of the 492 small molecules drugs, 41.26 percent derived from natural products. In respect to the

therapeutic classes of drugs, 64 were antibacterials and 31 were anticancer medicines; of which 78 percent of antibacterials and 61 percent of anticancer medicines derived from a natural product (modified or not).

Newman et al. (2003) observed that of the 1,031 new chemical entities introduced between 1981 and 2002, only 33 percent were fully synthetic medicines; 23 percent derived from a natural product (usually a semi-synthetic medicine); 10 percent were synthetic compounds "designed from knowledge gained from a natural product (...) or (...) discovered by using an assay whereby the compound is designed to displace the natural substrate in a competitive fashion"; 5 percent derived from a unmodified natural product source; and the remaining 15 percent were biological products. In respect to the therapeutic classes of drugs, there were 159 anti-infective medicines (90 antibacterial, 23 antifungal, 13 parasitic, and 33 viral), of which only 30.2 percent were fully synthetic medicines; and 65 anticancer drugs, of which only 26 percent were fully synthetic.

It also important to note that according to Young (1999), modern biotechnology has allowed the development of medicines based on natural products with lower adverse effects, as illustrated by the case of ergotamine. Between the seventeenth and nineteenth centuries, *ergot* extracts (obtained from the mold that grows in rye, *Claviceps purpurea*) were used for pain relief, after child birth, and for headaches. In 1918, Arthur Stoll synthesized the ergotamine tartar marketed by Sandoz as Gynergen and prescribed for bleeding control after child birth. Between the 1920s and 1930s, ergotamine also began to be used for migraines. In 1943, Stoll synthesized another drug derived from *ergot* — the dihydroergotamine marketed

by Sandoz as Dihydergot or Orstanorm for migraines.[29] During the 1990s, stemming from research on ergotamine and its effects on the central nervous system, Burroughs Wellcome developed the sumatriptan commercialized as Imitrex and Merck & Co. developed the rizatriptan marketed as Maxalt.

In their search of active substances, pharmaceutical companies involved in R&D activities have generally followed two strategies: development (or acquisition) of chemical libraries, and natural products research.

In the 1980s, advances in molecular biology and molecular pharmacology improved the knowledge about the interaction between therapeutic targets and compounds. This allowed companies to move from *random screening* ("trial and error" methods of screening molecules against therapeutic targets) to *rational drug design*. Before rational drug design, most pharmaceutical compounds under development did not reach the market either because they were tested against the "wrong" therapeutic targets or because of unexpected adverse effects. With rational drug design, the challenge became to identify a relevant drug target that would make R&D investments worthwhile. The development of combinatorial chemistry in the 1990s opened the possibility of designing molecular structures more rapidly based on existing chemical libraries.

In addition, the development of automation and miniaturization technologies allowed the development of *high-throughput* screening (HTPS), and more recently *ultra high-throughput screening* (UHTPS) — techniques that dramatically reduced screening times. And the development of genomics research considerably increased the number of potential

[29] Between the late 1930s and the 1970s, Sandoz developed other two medicines based on ergot:: metisergide (Deseril) and bromocriptine (Parlodel) (Tepper 1997).

therapeutic targets and opened new possibilities for the search of active compounds, although the discovery of therapeutic targets does not necessarily lead to new drug targets (Rates 2001; Montanari and Bolzani 2001; Moore 2003). As a result of these new developments, many pharmaceutical companies withdrew from natural products research in the 1990s and directed their efforts toward combinatorial chemistry and partnerships with biotechnology companies (Cragg et al. 1997). After identifying a drug target, the drug discovery process is followed by the "design" of the appropriate molecular structure. Then, with the help of computational techniques, researchers look for the real chemical structures in their chemical databases (Rates 2001; Montanari and Bolzani 2001).

In their search for fully synthetic compounds, pharmaceutical companies have not yet taken full advantage of combinatorial chemistry's potential to increase the number of new chemical entities. This is reflected in the *innovative deficit* observed in the pharmaceutical industry since the end of the 1990s (Drews and Ryser 1996; Drews 1998b; Class 2002). Different reasons have been pointed out for this shortcoming, including the fact that existing chemical libraries are not intrinsically useful (since synthetic chemical compounds found in those databases are simple structures highly similar to each other) and that combinatorial chemistry is a relatively new technology (Rouhi 2003a). Another reason for the lower productivity levels in terms of new chemical entities that have been introduced has been related to pharmaceutical companies' departure from natural products research, since *high-throughput screening* techniques require greater molecular diversity, which is found mainly in natural sources (Cragg et al. 1997; Newmann 2003; Rouhi 2003a).

With respect to natural products research, there is a distinction between its potential for the development of pharmaceuticals[30] and its potential for the development of exclusively natural medicines. In the case of research in plant extracts, one might distinguish between:

- Research to obtain unmodified isolated active compounds or obtain active ingredients with unknown structures, *leading* to medicines by synthetic or semi-synthetic routes
- Product development based on the plant as a whole (phytomedicines)

In the case of plant-derived pharmaceuticals, the first step is to choose the plant to research for medicinal properties. This can be done by utilizing different, but not mutually exclusive, resources (Fabricant and Farnsworth 2001):

- Ethnomedical knowledge, such as traditional knowledge[31] or knowledge about uses of medicinal plants by organized systems of traditional medicine[32]
- Databases such as the "Natural Products Alert (NAPRALERT)
- Random collection followed by one or more bioassays or chemical screening[33]
- Ethnobotanic knowledge

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[30] According to Harvey (2000), natural products that are biologically active are generally small molecules with *drug-like* properties. This means that drug development for biotechnology products or natural products making use of combinatorial chemistry techniques should be relatively low.

[31] The best known example is that of the U.S. company Shaman Pharmaceuticals, created in 1989, whose search for biologically active substances was based on traditional knowledge of healers or shamans from indigenous communites in South America (Brazil and Argentina). At the begining of the 1990s, Shaman had two medicines undergoing clinical trials (Blum 1993). However Shaman halted operations in 1999. According to analysts, one of the reasons for the company's decline was that it was not able to introduce any medicine into the market after failures at the clinical trials stage. This would be, alas, a problem faced by most research specialized companies, generally of a smaller size, since these companies are not as well-skilled as large pharmaceutical companies in the drug approval process (Moore 2003).

[32] Examples of organized systems of traditional medicine include the Ayurveda in India and traditional Chinese medicine.

[33] Generally the pharmaceutical industry tends to focus in *chemical screening*, and universities and research institutes in biological assays. (Fabricant and Farnsworth 2001).

After this step, it is necessary to assure an appropriate botanical characterization and register the time and place where the sample was collected, and then to conduct stabilization procedures. Next, the material must be transformed into a powder and subjected to appropriate extraction processes in order to obtain higher purity levels from the extracts. To isolate the active compound, it is necessary the fractioning of the plant extract, which is then submitted to bioassays (using microorganisms, mollusks, insects, enzymes, receptors, cell tissue cultures, isolated organs, or *in vivo*).

After purification, it is necessary to determine the chemical structure of the isolated compound. Then it is possible to consider whether full synthesis or semi-synthesis will be pursued in order to analyze the biological activity of the isolated compound. These processes are then followed by increasing the size of the sample set (sometimes it is necessary to collect more samples) in order to begin pharmacological evaluation in pre-clinical, toxicological, and clinical trials. Despite the complexity involving screening of medicinal plants and the fact that secondary metabolites (the focus of pharmaceutical companies' research) are not produced by plants in sufficient amounts from an economic point-of-view, medicinal plants are still the main source of natural-products-based medicines, followed by microorganisms, marine organisms, fungi, and insects. The fact that bacteria and fungi are easier to cultivate and scale up than plants may lead companies still involved in natural products research to the search for drug leads in other biological resources besides plants (Borris 1996; ten Kate and Laird 1999; Young 1999; Rates 2001; Rajasekharan 2002).

Between 1980 and 1990, the search for active compounds in natural products was based on traditional methods. These methods included exposing crude extracts to therapeutic targets, and when evidence of biological activity was detected, fractioning and isolating the

active compound. This was a relatively lengthy and labor-intensive process, and more expensive in relation to the possibilities recently opened by combinatorial chemistry. Besides, it was difficult to ensure that the drug would be chemically workable or patentable, especially after the 1990s due to the discussions leading up to the TRIPS and the CBD. This reason has been cited for some pharmaceutical companies' withdrawal from natural products research (Cragg et al. 1997; Breinbauer et al. 2002; Newmann 2003; Rouhi 2003b).

The identification of the lead molecules (through any of the methods described in the previous paragraph) is followed by drug development that involves changes in the chemical structure of the lead molecules (in order to obtain analogues that are more potent, less toxic, have smaller structures, and if possible a new mechanism of action), pharmacological tests in animals, and safety studies. Pre-clinical (biological and pharmacological) tests use laboratory animals, cell cultures or cell tissue cultures, enzymes, and so forth in order to evaluate toxicity, bioavailability, and pharmacokinetics. Along with pre-clinical trials, it is necessary to decide which compounds are most likely to become drug candidates in order to pursue Phase I, Phase II, Phase III, and Phase IV clinical trials[34] in human beings[35]. These trials involve higher costs and complex structures, and take around seven years to complete (Hilleman 2002). Pharmaceutical R&D may seem like a linear process, but it is not.

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[34] In general, these four phases of clinical trials are considered the FDA standard. According this standard, after pre-clinical trials, it is possible to fill an Investigational New Drug Application (INDA) with research protocols for clinical trials in human beings. Phase I clinical trials involve toxicity tests in healthy volunteers for approximately 18 months. Phase II clinical trials are designed to determine the medicine's effectiveness in around 100 to 500 volunteer patients over approximately two years. In Phase III trials, the medicines are administered to around 1,000 to 5,000 volunteer patients for almost three and a half years. After Phase III, companies can fill a New Drug Application (NDA) for commercialization approval from the FDA. After the medicine is introduced to the market, companies generally submit approved medicines to Phase IV trials, in which they explore new uses and long-term effects for a given medicine (Hilleman 2002).

[35] Historically, most of these phases have been conducted by pharmaceutical companies. However, the creation of companies specialized in drug discovery and companies specialized in managing clinical trials have led pharmaceutical companies to contract out some of these phases. But this trend has been observed mainly in the United States (Gambardella et al. 2000). Some pharmaceutical companies also contract out the manufacturing of pharmaceutical intermediates (McCoy 2002).

In the early 1990s, estimates for the R&D costs for a new medicine[36] varied between US$65 million and US$231 million for each new chemical entity (OTA 1993). Since the mid 1990s, industry's estimates have varied between US$500 million and US$800 million. (PhRMA 2004) However, NGOs have claimed that these statistics are overestimated (the accurate number would around US$ 57 millions and US$ 71 millions), since they consider opportunity costs, and most companies do not appropriate R&D expenses for individual projects but for the R&D department as a whole (Public Citizens, 2001).

While some pharmaceutical firms (e.g., Abbott, Pfizer, and Bristol-Meyers Squibb) have shutdown their respective research centers in natural products, others (e.g., Merck & Co., Novartis, Bayer, and Wyeth) are still investing in this area. These companies conduct natural products research at their in-house facilities or in partnerships with botanical gardens, universities, research institutes, small biotechnology companies located mainly in developed countries, and (to a lesser degree) with institutions located in developing countries. Some companies, such as Eli Lilly, have licensed their natural compounds libraries to small specialized biotech companies and have made joint R&D agreements.

As a matter of fact, R&D agreements between pharmaceutical and biotechnology companies have been a characteristic of the pharmaceutical sector since the emergence of modern biotechnology. This has been a two-way relationship, since the greatest obstacles in drug development have been the drug approval processes for new chemical or biological entities and marketing. This has been a major obstacle for small biotech companies working on the edge of scientific discovery. Meanwhile, large research-based pharmaceutical

[36] Pharmaceutical companies claim that patent protection is fundamental so that they can recoup high R&D investments that tend to increase each year. Bseides the number of chemical compounds screened are significantly higher than the number of

companies have been pressured by stockholders and greater competition to increase productivity levels and the number of new products introduced. Since neither combinatorial chemistry nor the recent wave of pharmaceutical mergers and acquisitions have led to the expected increase in productivity, and since a great portion of newer drugs are biotechnology drugs, pharmaceutical companies have also been willing to establish partnerships with biotech companies (Moore 2003).

In the case of the biopharmaceutical companies, several new companies specializing in natural products research have been created. It also important to note the foundation of bioinformatic specialized, for example, in databases and screening techniques (Shu 1998; Young 1999; ten Kate and Laird 1999; Newmann 2003; Rouhi 2003c).

Despite the trend of pharmaceutical companies' withdrawing from natural products research due to technological and economic factors[37] and the higher uncertainties regarding the international institutional environment, the difficulties in increasing the number of new chemical entities through combinatorial chemistry and the complexity involving the scaling up biotechnology drugs may change this scenario. The most likely explanations for the recent revival of natural products research among pharmaceutical companies include (Borris 1996; Giddins et al. 2000; Montanari and Bolzani 2001; Pinto et al. 2002; Rajasekharan 2002; Rouhi 2003a):

- The intrinsic utility of natural products

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new chemical entitites introduced into the market. But the pharmaceutical companies spend around 38 percent of sales in marketing, and from 14 percent to 20 percent of sales on R&D. (Drews 1998a)

[37] Eisner (2004) observed that several factors may create challenges for drug discovery in the near future. These factors include the departure of pharmaceutical companies from natural products research (consequently reducing their hiring natural products chemists), the fact that natural products chemistry is no longer seen as priority in the chemical field, and that the teaching of natural chemistry may disappear in some universities because of these trends.

- The greater diversity of natural products, which can help to fulfill the needs of expensive high-throughput screening technologies
- Advances in separation technology and structure elucidation that have allowed scientists to overcome several bottlenecks in natural products research; these advances include identifying biologically active molecules in small samples at low levels

Pharmaceutical companies and research groups still involved in natural products research have pursued three main strategies (Newmann et al. 2003; Rouhi 2003d):

1. Combining the diversity of natural products and the potential of combinatorial chemistry
2. Building around natural products scaffolds using combinatorial chemistry and assembling natural-product-like compounds through synthesis
3. Creating new natural products derivatives. Despite the complexity involving natural products research, new medicines based on natural products have been introduced into the market (Nisbet and Moore 1997; Cragg et al. 1997; Shu 1998; ten Kate and Laird, 1999; Young 1999; Newmann et al. 2003).

With respect to engagement in natural products research for the development of new chemical entities, developing countries face great obstacles. Most of them do not have industrial and technological capabilities in either finished medicines or fine chemicals (active compounds or intermediates). Only a small group of developing countries (like India, South Korea, and China) have the ability to manufacture inputs and finished medicines at domestic integrated companies and several small, specialized fine chemical companies. In countries

such as Brazil, Mexico, and Argentina, fine-chemical companies are struggling to survive due to several factors, and imports of finished medicines have been rising recently. More importantly, developing countries as whole are highly dependent on products developed by leading multinational companies, and only a small number of leading firms have begun to invest in R&D for new product development.

This does not mean that developing countries should not devote efforts to enhance and strengthen technological capabilities in pharmaceuticals. To the contrary, these countries must take these issues seriously, especially those regarding partnerships with research-intensive companies interested in access to biological resources. It is fundamentally important that access to those resources results in technology transfer and creates incentives for future technological development and not only economic returns. These developing countries must also observe that most multinational pharmaceutical and biotechnology companies are not directly involved in collecting samples (some of them have natural compounds libraries that existed prior to the CBD). Rather, they prefer to establish partnerships with botanical gardens and universities in their own countries, although some companies may seek partnerships with other small biotech companies in developing countries for compound screening.

Nevertheless, an important window of opportunity can be seen in antiinfectives, since (as observed above) most of the antiinfectives (especially antibacterials) introduced since the 1980s have been based on natural products. However, infectious diseases, which are one of the leading causes of death in the world, cover a wide spectrum — from HIV/AIDS to other diseases with lower market potential, such as malaria. In the antiinfectives segment, antibacterials may provide an opportunity for developing countries, since pharmaceutical companies are leaving this segment of the industry. There is an increasing need for new

medicines not only due to increasing resistance to current drugs, but also due to biosafety concerns (Iwu et al. 1999; Projan 2000, 2003; Schuster 2001; Newmann et al. 2003). Besides, most antibacterials have been based on medicinal plants, and only a small percentage of plant species have been studied to determine their therapeutic effects. Hence, developing countries, such as Brazil (which holds 22 percent of all plant species on the planet) may benefit from this window of opportunity. Yet it should be noted that regulatory agencies, like the United States Food and Drug Administration (FDA), have imposed several requirements on the approval of new antibacterials, especially the need to demonstrate efficacy in relation to current medicines (Projan 2000, 2003).

Medicinal plants' potential is not restricted to the new chemical entity discovery process. There is a great potential, especially for developing countries, in the phytomedicines segment. This segment has shown increasing growth rates in the last several years, especially in developed countries that represent the world's largest pharmaceutical markets. Gruenwald (1995) estimated that the consumption of phytomedicines in 1994 was around US$12.4 billion, of which European Community countries accounted for almost 50 percent of this, Asia 35 percent, and United States 11 percent. It was estimated that in the year 2000 the world consumption of phytomedicines market amounted to around US$22.3 billion (almost 13 percent annual growth rate). Europe was still the largest market (35 percent), Asia accounted for 28 percent, and the United States increased its share to 18 percent of the total (Hong Kong Trade Development Council 2002).

It is important to observe that it takes from two to five years — and between US$2 million to US$5 million — to develop a new phytomedicine that may lead to products with synergic (and less adverse) effects. However, the chemistry of exclusively natural products is

more complex because it is more difficult to identify the compound responsible for a given effect. This is because several active ingredients can be found in the same plant at different concentrations, and the effect may lie in the plant as whole and not in a single compound. It is also more difficult to obtain higher levels of potency. In addition, it is important to observe that phytomedicines are not subject to patent protection since they are based on the whole plant and thus are not inventions. Nevertheless, the costs of entering the phytomedicines segment of the pharmaceutical market are basically those involved in product registration and commercialization. But countries differ widely in this respect — some have classified phytomedicines as medicines, while others have classified them as dietary supplements or nutraceuticals, depending on the medical claims they make (Iwu 1998; ten Kate and Laird 1999; Rajasekharan 2000; Yunes et al. 2001; ABIFITO 2003).

Thus, depending on the country and how it regulates product commercialization, the "newness" of the phytomedicine, and the claims it makes, phytomedicine registration may begin with clinical tests — including toxicity, safety, pharmacological, and biochemistry tests. Following the recommendations of the World Health Organization (WHO), some countries have used traditional knowledge as an element for product registration, while others (such as the European Union and Canada) have developed more specific and stringent regulations. In EC countries,[38] phytomedicines are considered medicines, but each country differs in respect to how they define phytomedicines. The European Community phytomedicine guidelines, for example, require Good Manufacturing Practices (GMP); clinical, toxicological, and

[38] The European Scientific Cooperative on Phytotherapy (ESCOP) was created in 1989. ESCOP is responsible for the elaboration of monographs about product characteristics to serve as basis for phytomedicines registration, to harmonize the regulation of phytomedicines among EC countries, and to stimulate the introduction of phytotherapy among physicians. According to the Hong Kong Trade Development Council (2002), the requirements imposed by EC regulations on phytomedicines have resulted in the exclusion of several products used in traditional Chinese medicine. As a result, many Chinese companies are registering phytomedicines as nutritional supplments in EC countries.

pharmacological tests; and related scientific literature (ten Kate and Laird 1999; WHO 1999; Hong Kong Trade Development Council 2002).

In the United States, on the other hand, a phytomedicine that makes no therapeutic claims can be registered as a dietary supplement —, otherwise it would be subject to the same requirements as pharmaceutical products. According to Food and Drug Administration (FDA) regulations in place before 1994, phytomedicines were considered food additives and the company that produced them had to prove that they were safe. If the phytomedicine made any therapeutic claims, then it was considered as "over the counter" (medicines sold without prescription) and its producer had to present a monograph or apply for the registration of ethical medicine. In 1994, the FDA created a new category, the dietary supplement that is *a priori* assumed to be safe. The burden of proving whether or not dietary supplements are safe now belongs to the FDA. Although the FDA has been systematically supporting assurance of product safety and efficacy,[39] the North American dietary supplements market is loosely regulated,[40] and most products are not effective and may even cause harm due to toxicities or interactions with other medicines (Chase 2003; Milot 2004).

There are also differences regarding the regulation of phytomedicines in developing countries. In Argentina, for example, there is no distinction among medicines in respect to their origin (natural or synthetic). However, since there is a certain level of autonomy in the country's provinces, there have been specific regional regulations, for example in Buenos Aires, regarding medicinal plants since 1993. In Chile, natural products can be registered as

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[39] This trend can been seen through recent FDA determinations to remove several products containing specific substances like ephedrine from the market. Currently, the FDA is discussing new regulations concerning good manufacturing procedures and the possibility of classifying phytomedicines in the non-ethical group of medicines.

[40] Unlike "over the counter" medicines, dietary supplements cannot use phrases like "effectively proven" or "recommended by doctors" on their labels. They can only list the structure and functions of the product and state that it is not intended to cure, prevent, or diagnose any medical condition.

food or medicine depending on the claims they make regarding therapeutic effects. The Chilean government considers any product that makes a medical claim to be a medicine and therefore subject to the same requirements as synthetic medicines. Yet in the vast majority of developing countries, there are no specific regulations for registration regarding the commercialization of phytomedicines (WHO 1999; ten Kate and Laird 1999).

An important aspect of the phytomedicines market is related to the segment of raw materials from which finished phytomedicines are manufactured — that is, crude drugs (whole leaves, roots, and barks) and bulk drugs (alkaloids, glycosides, and derivatives). In these segments of the phytomedicines market, traders based in New York, Hong Kong, and Tokyo play major roles. The crude drugs segment is a low value-added market. According to United Nations Conference on Trade and Development (UNCTAD) records, international crude drugs exports totaled US$1.03 billion in 2002, 70 percent of which were concentrated in ten countries (49 percent in developing countries and 21 percent in developed countries). Imports totaled US$1.23 billion, 63 percent of which were concentrated in ten countries (38 percent in developing countries and 25 percent in developed countries). In the world trade of bulk drugs exports in 2002 were estimated to be US$2.67 billion with ten developed countries accounting for US$2.30 billion of that total. Imports were estimated to be US$3.12 billion, with ten developed countries representing US$2.23 billion of that total.

Taking into account the differences in national regulations, that phytomedicines may not patentable, and the increasing competition among the world's leading phytomedicines companies (which are based in developed countries),[41] these companies have concentrated their efforts in existing products, since there is already a learning curve effect in place and

their use is less controversial, especially from the point-of-view of regulatory agencies. Thus, developing countries may be able to stimulate new product development, since a small share of all plants has been identified and an even smaller share of them has been studied for their therapeutic effects. In this sense, developing countries should stimulate the introduction of better cultivation practices, but also search for high-yielding medicinal plants that would increase the value of crude extracts and stimulate GMP in the production of finished phytomedicines. These countries should also take into account the competition dynamics at the international level and the incentives and disincentives for new product development.

[41] Here, it is important to mention the entry of some big pharmaceutical companies **into the phytomedicine market** through acquisition of major European phytomedicine companies (Ferreira et al. 1998).

2. Discussion

It is possible to identify other windows of opportunity over the course of the pharmaceutical industry's evolution that offer interesting contrasts to this study about natural resources' potential. Similar windows of opportunity were seen during the development of organic synthesis and pharmacology in the turn of the nineteenth century and the development of antibiotics with penicillin in the first half of the twentieth century.

Organic synthesis emerged in 1828 after the synthesis of urea by Friederich Wohler. Pharmacology essentially began in 1847 after Rudolf Buchheim was named the pharmacology chair at the University of Dopat, although there had been pharmacological studies on certain plants and their alkaloids since the beginning of the nineteenth century.

The development of the chemical industry in Germany is an especially illustrative example. An organic chemistry industry (particularly dyestuffs) emerged in some German states before economic unification in 1871, which allowed Germany after unification to displace France as the locus of new product development in the emerging pharmaceutical industry. This development, along with other innovations, gave Germany the leading position in the chemical industry until the Second World War. Among the factors that contributed to Germany's success were government policies directed toward the development of a chemical industry that could compete with Great Britain and France, investments in science and technology infrastructure (particularly the establishment of technology institutes), and the fact that until 1940s, German patent law offered protection only for pharmaceutical processes, so companies looked for alternative routes to manufacture a given product (Liebenau 1985; Weatherall 1990; Achilladelis and Antonakis 2001).

In antibiotics, it is significant that the United States and many other countries were dependent upon pharmaceutical products developed by German companies until World War II. During the first half of the twentieth century, the U.S. government expressed consistent concerns regarding the dependence of the emerging North American chemical industry on products developed by German companies, especially in pharmaceuticals. The U.S. case deserves a careful analysis. The role of regulation is generally considered to be the main force behind the development of a research-based pharmaceutical industry in the United States. However, the establishment of subsidiaries of German companies in the United States — dating back to the end of the nineteenth century — also contributed to the development of this industry. This mainly happened during the interwar period through the expropriation of German patents and industrial facilities that were sold to U.S. companies that had managed to establish dominant positions in the U.S. domestic market by driving out smaller companies and had become large manufacturers (in this case, the role of government purchasing power and regulation did play an important role).

The expropriation of German patents during World War II also played an important role, as the U.S. pharmaceutical industry had become able to exploit the knowledge disclosure in patents, something that was relatively difficult to do during World War I due to deficiencies U.S. chemistry education and the lack of knowledge about the patenting process. These difficulties in the United States were gradually overcome with large investments in science and technology — especially in the university system, government institutes, and the institutionalization of R&D in some U.S. pharmaceutical companies in the inter-war period. All of these factors allowed U.S. pharmaceutical companies to produce penicillin on a large scale in order to respond to war efforts. After the 1940s, but mainly after the 1950s, the United

States had not only caught up with Germany, but displaced it by consolidating a position of industrial leadership in the pharmaceutical sector. The United States' preeminent position in the pharmaceutical sector was based not only in R&D efforts by companies, but also by investments in health research through the National Institutes of Health (NIH) beginning in the 1930s (United States 1919, 1929; Young 1961; Liebnau 1985; Temin 1980; Steen 1998; Swann 1995; Achilladelis and Antonakis 2001).

Thus, the development of organic chemistry in Germany and antibiotics in the United States shows that an analysis of windows of opportunity in the pharmaceutical sector must take into account the following elements:

- The structure and dynamics of pharmaceutical industry evolution and competition at national and international levels
- Market potential
- Regulations regarding prices and registration of products
- Science and technology infrastructure
- Intellectual property rights
- R&D incentives
- Industrial and technology policies
- Dynamics of competition among nation-states

2.1 The Brazilian Case

The emergence of a pharmaceutical industry in Brazil followed the same pattern observed with the pharmaceutical industry in the United States: the manipulation and marketing of plant

and animal extracts and imported medicines. However, it is also possible to observe a few ways in which the emergence of pharmaceutical laboratories in Brazil in the late nineteenth century seems to have followed a pattern closer to the specialized German pharmaceutical firms (through the initiatives of academic pharmacists). Yet it is important to observe that in Germany, the pharmaceutical industry emerged mainly from the diversification of chemical firms involved in the production of organic chemistry products — mainly dyestuffs that were also found to have therapeutic effects. In Brazil however, most pharmaceutical laboratories with state-of-the-art technological capabilities in the late nineteenth century (i.e., that could isolate alkaloids for the manufacturing of medicines) did not survive into the twentieth century. In addition, the pharmaceutical industry emerged in Brazil in the nineteenth century when the country's economy was based on exportation of primary products based on a slavery system.

Thus, there was a mismatch between the political, economic, and institutional requirements of industrial entrepreneurship and Brazil's integration into the international economy through a primary-exporting model. In the United States, on the other hand, the industrial structure was more consolidated, a scientific infrastructure was being deliberately developed in order to narrow the technological gap in relation to Europe, and public policies were designed to promote national industry. In Brazil, foreign companies or traders used to offer more favorable credit terms to Brazilian retailers and druggists compared to what local producers with the same quality could offer, especially during the interwar period.[42] Brazilian physicians also began to prefer to prescribe foreign medicines. In addition, while the

[42] According to reports from the U.S. Department of Commerce, European companies offered special credit terms for some Brazilian retailers and druggists as a marketing strategy in the early 20th century. The Department of Commerce also observed that North American manufacturer, like their European competitiors, could have offered the same conditions in order to enter the Brazilian pharmaceutical market (United States 1914, 1932).

pharmaceutical industry emerged in Brazil between the end of the nineteenth and twentieth centuries, the first initiatives in the chemical sector seem to have happened only after the mid 1950s and mostly after the 1970s (Fontoura 1938; Scheinkmann 1965; Bertero 1972).

At the turn of the XIX century the situation of the emerging Brazilian pharmaceutical industry was not very different from the U.S. pharmaceutical industry in terms of products and technological capabilities. Yet while some North American companies seemed to have made the transition from artisan or semi-industrialized production of medicines based upon plant extracts to chemical synthesis on industrial scale – especially after the expropriation of German patents in the I World War, Brazilian firms seem not to have been able to make this transition. Brazilian laboratories were not been able to make the required investments or have access to the necessary human resources. There was no public policy oriented to the development of the pharmaceutical or chemical sectors, and a very incipient scientific infrastructure to help domestic companies, as the United States managed to do in the first half of the twentieth century (Bertero 1972; Frenkel et al. 1978).

Another relevant issue is that patent protection for pharmaceutical products in Brazil was abolished in 1945 through the Decreto-Lei nº 7.903. This prohibition did not apply to "new processes aiming at manufacturing of substances, products, or any related material; new products when due to intrinsic properties, analysis or other appropriate technical examination reveal the process upon which they are based." However, most Brazilian pharmaceutical companies with greater technological capabilities had been or were acquired by foreign companies during the first half of the twentieth century. The entry of foreign pharmaceutical firms into the Brazilian market — first German and French, but then also North American — was initially based upon importation and then upon local production, especially after the

1950s. These foreign companies promoted local production by acquiring local producers — basically those firms that were more technologically dynamic, but that were not able to make the transition to chemical synthesis. Also, the Brazilian government did not systematically address industrial and technological development of the chemical industry until the 1970s. While most of the demand for finished medicines had been supplied by local production after the 1950s, Brazil was still dependent on the importation of compounds and knowledge produced outside the country in order to advance technological change (Scheinkmann 1965; Frenkel 1978).

Between the 1950s and the 1970s, different factors were cited as the most likely explanations for the dependent character of the Brazilian pharmaceutical industry in the dynamics of the world pharmaceutical sector (Scheinkman 1965; Bertero 1972; Frenkel et al. 1978):

- The lack of human resources
- The negative effects of socioeconomic conditions
- The incipient stage of chemical sciences' development
- The lack of correlative industries
- The lack of government policies, like those put forward by Germany and United States, that allowed those countries to establish industrial leadership positions
- Weak linkages between companies and universities
- The emergence of large integrated firms competing at international level, which resulted in an international division of productive and innovative labor between developed and developing countries

During the 1970s, the Brazilian pharmaceutical industry acquired one of its main features: industry concentration at the hand of foreign laboratories. More than 75 percent of Brazil's domestic market has been dominated by multinational firms that accomplish only the final phases of pharmaceutical manufacturing in Brazil (Bermudez 1995). But the Brazilian government implemented some policies in the 1970s that were intended to foster the development of the pharmaceutical sector and narrow the technological gap between Brazilian companies and international leaders. These policies included:

- The exclusion of pharmaceutical processes and products from the Patent Law of 1971
- The creation of the "Central de Medicamentos," which was initially intended to act as a public procurement agency and an agency to support technological development in pharmaceuticals
- The creation of programs intended to promote industrial and technological development, including in chemicals and pharmaceuticals
- Programs for the development of science and technology infrastructure in the 1970s and in the 1980s

Although these programs were successful in some areas, the Brazilian pharmaceutical industry remained dependent upon the importation of raw materials (especially active substances) and upon knowledge produced elsewhere — confirming the country's marginal role in the international division of productive and innovative labor in the pharmaceutical sector.

After the 1990s, the Brazilian pharmaceutical industry experienced significant structural changes due to the opening of the Brazilian economy; the end of price controls in

1990; a new Patent Law n.9279 in 1996 reintroducing patent protection for pharmaceutical processes and products; the effects of subsequent mergers and acquisitions in the international pharmaceutical industry and their location strategies in developing countries; and the introduction of a specific law regulating the market for generic medicines.

Market liberalization in Brazil had major effects — such as a sharp increase of importation of active ingredients after 1990, the dismantling of the existing Brazilian fine chemical industry, and an increase in importation of finished medicines and (more recently) finished generic medicines (Hasenclever 2002). Brazil was different from the other developing countries in terms of intellectual property rights because it introduced changes in its intellectual property regime prior to the 2005 TRIPS deadline and also allowed for *pipeline* protection for patent applications filed between January 1995 and May 1997. Since Law 9.279 was passed, most of the pharmaceutical patents issued by the Brazilian National Patent Office (Instituto Nacional de Propriedade Intellectual, INPI) have been granted to non-residents (Bermudez et al. 2000).

As a result of the mergers and acquisitions of leading international pharmaceutical companies, some new companies decided to transform their domestic operations in Brazil (production or packaging of finished medicines) into an export platform for other Latin American countries. Other companies decided to sustain only their marketing activities or to license products to Brazilian companies. Another important change in the 1990s was the introduction of generic medicines to the Brazilian market. Until 1999, there had been two kinds of medicines in the Brazilian market: brand name products, which were patented in other countries, and products that were legal copies of those same medicines and marketed as "similar" medicines through brand names. In 1999, the government passed the Law 9.787

introducing specific regulations for generic medicines registration. According to this law, companies intending to commercialize non patented medicines under generic denomination must prove bioequivalence and bioavailability compared to the original product. Brazil's main objective in passing this law was to lower the price of medicines that were not protected by patents by introducing greater competition (since generics are not marketed under brand names and are sold at lower prices). In these first years following the passage of this law, however, there has been a substitution effect with generic drugs among the higher income classes in Brazil, but there has not necessarily been an expansion of access to medicines for the country's lower income classes (Hasenclever 2002).

Despite these changes, the situation of the Brazilian pharmaceutical industry over the last several years has not been much different from that observed in previous decades. Seventy-five percent of the nation's pharmaceutical market, which registered US$4.2 billion in 2003 in retail sales, is dominated by twenty large foreign companies, while the remaining 25 percent of the market is shared among approximately 380 medium- and small-size domestic companies. Neither Brazilian nor foreign companies invest very much in R&D efforts, and most of these expenditures accrue to Phase III clinical trials for product registration. Only a small number of companies invest in R&D, but the amount spent is considerably lower compared to leading research-based pharmaceutical companies (Hasenclever 2002).

Facing an economic crisis during the 1980s, the Brazilian government saw a considerable reduction in its ability to invest in the pharmaceutical programs mentioned above. In the 1990s, the neoliberal economic policy of Brazil's first elected government after the dictatorship period (1964-1989) resulted in the termination of these particular industrial

and technology policies. At the end of the 1990s, the government that had been elected in 1994 created new mechanisms, such as specific funds based on grant applications, to stimulate science and technology in some sectors of the economy, including biotechnology and public health. However, the law implementing the biotechnology and the health sector research fund only passed at the end of 2001 and the first call for applications only occurred in 2003. In addition, most of the resources approved for these purposes have not been disbursed by the government. It is important to note, though, that at the beginning of 2004, the government reintroduced industrial and technological development to the country's public policy agenda, including an emphasis on the fine-chemical and pharmaceutical industries.

2.1.2 The Brazilian Pharmaceutical Market and Natural Products Research

Regarding the Brazilian market for phytomedicines, Ferreira et al. (1998) observed that in 1994, out of the US$3.831 million registered in total retail sales of pharmaceutical products, only 3.19 percent were sales of phytomedicines medicines (i.e., based exclusively on medicinal plants of natural origin). In addition, 5.08 percent corresponded to medicines containing active substances of plant origin associated with active substances of a different origin. The remaining 89.38 percent corresponded to fully synthetic medicines.

Twenty-five companies, mostly multinationals (there was only one national company and a joint venture between a national and multinational company), held 76.36 percent of the whole Brazilian pharmaceutical market, and most of their products (94 percent of sales, on average) were synthetic medicines. As for the companies selling medicines with active substances of plant origin associated with other active substances, twenty-five laboratories held 78.44 percent of this segment, and eleven (nine foreign companies, one national company, and a joint venture between a national and a multinational company) were among

the leading twenty-five companies. In the phytomedicines market, twenty-five laboratories controlled 84.56 percent of this segment, and eleven companies (nine foreign companies, one national company, and a joint venture between a national and a multinational company) were among the leaders.

According to Ferreira et al. (1998), there are two kinds of companies in the Brazilian phytomedicines market. First, there are large companies whose product line comprises basically pharmaceuticals. For these companies, natural medicines represent a small share of their sales compared to synthetic medicines. These companies, irrespective of their origin, considered the medicinal plant segment to be marginal in relation to their product portfolio, but they showed a greater concern about complying with sanitary surveillance regulation and GMP. Second, there are the smaller laboratories (mainly domestic companies) that concentrate sales in phytomedicines. These smaller companies also invest very little in R&D and rarely make partnerships. In 1999, the National Health Surveillance Authority (Agência Nacional de Vigilância Sanitária, ANVISA) introduced stringent regulations for the registration and commercialization of phytomedicines through Resolution RDC 17/00 regarding chemical and pharmacological characterization of products. Nevertheless, according to Yunes et al. (2001), most of the phytomedicines manufactured in Brazil are based on traditional uses and are not the results of pre-clinical or clinical research.

The most recent data indicate that in 1998, the Brazilian phytomedicines market was around 5.5 percent of the total Brazilian pharmaceutical market (US$10.29 million). It is estimated that in 2003, phytomedicines represented 6.7 percent of Brazil's total pharmaceutical sales, and that there are 293 companies operating in this field (ABIFITO 2003). According to Almeida (2003), this segment may account for around 10 percent of the

total domestic pharmaceutical market by 2010. This estimate is based on a survey of physicians conducted by the Brazilian Association of Pharmaceutical Manufacturers (FEBRAFARMA) in 2002. According to this survey, 10 percent of the physicians interviewed used to prescribe phytomedicines, but 22.5 percent affirmed that they intend to prescribe phytomedicines by 2010. Although Brazil holds more than 22 percent of all existing plant species in the planet, almost 89 percent of the 206 phytomedicines registered in Brazil in 2002 were based on plants of European origin (ABIFITO 2003).

There are several obstacles for the development of a phytomedicines market in Brazil, including:

- The effects of the leading multinational pharmaceutical companies' focus on synthetic medicines, which may slower the growth of phytomedicines market in Brazil
- The low level of R&D investments by Brazilian companies, mainly due to the smaller size of those companies willing to invest in R&D, which also hinder the potential for interaction between companies and universities
- The insufficient number of qualified human resources and limited resources for training within existing companies
- Obstacles related to the wild harvesting and quality of local crude extracts, as well as the storage, standardization, and delivery of these extracts
- Although the government has included the use of medicinal plants in the public health system since 1988, most of the population still associates medicinal plants with quackery

According to recent analyses, if these obstacles are not overcome in the medium and long term, Brazil's plant medicines may follow the same trajectory observed in the evolution of the country's synthetic medicines segment: foreign firms dominating the domestic market and national companies operating only in restricted niches (Gottlieb and Kaplan 1993; Ferreira et al. 1998; Yunes et al. 2001; Montanari and Bolzani 2001; Pinto et al. 2002).

Despite these obstacles, some medicinal plants research initiatives involving interaction between national companies and universities in Brazil are worth mentioning. The pharmaceutical company Biosintética, in collaboration with Universidade de Sao Paulo, is engaged in a three-year study of a Brazilian medicinal plant known as "nó-de-cachorro" with an investment of around R$18.5 million. This plant acts upon the central nervous system and could become a new medicine for Alzheimer's disease. The company is also studying coffee investing around R$300,000 (Panorama Brasil). The other company is Natura, whose main business is cosmetics and which entered the phytomedicines market through its 1998 acquisition of the company Flora Medicinal. Natura recently introduced the phytomedicine Viriliflora, which is used to treat sexual dysfunction (Exame 2001). Finally, it is important to highlight the partnership between the Federal University of São Paulo (UNIFESP) and Ache (the largest Brazilian pharmaceutical company) to study the medicinal plant known as "espinheira santa." These efforts resulted in a patent application filed by UNIFESP and Ache at the INPI and the partnership between UNIFESP and the Brazilian company Pronatus to study the plant known as "mulateiro da várzea."

With respect to natural products research, scientists located in Brazil have been responsible for 5.75 percent of the 9,312 articles published in leading international scientific journals from 1997 to 2001 indexed by the Institute for Scientific Information (ISI). Most of

the articles were related to medicinal plants research. Just for comparison, Brazil in terms of overall scientific output Brazil accounted for 1.21 percent of the world's scientific publication between 1997-2001 indexed by the ISI. (King 2004)

Table 1. Share of Brazilian Articles in the Leading International Indexed Journals in Natural Products, 1997-2001

	1997		1998		1999		2000		2001		Total	
Journal	World	Brazil	World	Brazil	World	Brazil	World	Brazil	World	Brazil	World	Brazil
Biochem. Syst. Ecol.	96	3	98	7	96	9	117	8	118	11	525	38
J. Ethnopharmacology	107	5	137	12	215	21	288	25	196	9	943	72
J. Nat. Prod.	339	4	338	11	452	12	441	5	404	9	1974	41
Phytochemistry	850	42	1118	67	710	37	564	56	447	45	3689	247
Phytochem. Anal.	52	7	47	2	54	4	59	7	66	7	278	27
Phytoter. Res.	156	12	195	13	160	16	146	12	135	11	792	64
Plana Med.	188	10	240	11	241	10	211	10	231	6	1111	47
Total	1788	83	2173	123	1928	109	1826	123	1597	98	9312	536

Source: Pinto et al. (2002).

According to Brito and Brito (1993), **Brazil had** fifty-three research groups at the beginning of the 1990s — including eleven in phytochemistry, twenty-three in pharmacology, and five in ethnopharmacology.

In terms of scientific production, Brito and Brito indicated that of the 969 abstracts published from 1949 to 1989 in the most important national scientific events in medicinal plants, 402 different plant species (of 286 genera) were studied. Of these 402 species, only 106 were studied in terms of pharmacological activity—11.1 percent of which were reported to have toxicity effects. Less than 10 percent of these species were studied with respect to their chemical composition or had their active substances isolated. From the abstracts reporting the isolation of substances, 93 compounds were found. According to Brito and Brito, these results show that there is little interaction between chemists and pharmacologists in Brazil, and that most studies have focused on confirming the traditional use of medicinal plants. There have been very few efforts in Brazil directed toward the isolation of active compounds that may lead to new medicines.

According to Elizabetsky and Wannmacher (1993), most of the medicinal plant research groups in Brazil focus on chemotaxonomy and phytochemistry, but very few of them collaborate with pharmacology research groups. Besides, most research groups that have been involved in natural products research did not consider pharmacology to be their main research area. In the area of pharmacology research, most groups focus on ethnopharmacology, which embraces different disciplines (botany, pharmacology, and chemistry). Despite the relationship between pharmacology research and medicinal plants observed in the early days of natural products research in Brazil, the interest in pharmacological evaluation of medicinal plants is a recent phenomenon, basically occurring only over the last thirty years. But the low level of interaction between pharmacologists with other disciplines is an obstacle for the further development of this research. With respect to phytochemical research, there has been little change since the seminal work of Gottlieb and Mors at the end of the 1970s, according to which in the last "80 years of chemical research on Amazonian plants…barely encompassed more than a hundred plant species" (Elizabetsky and Wannmacher 1993, 138)

According to Elizabetsky and Costa-Campos (1996), there has been little interaction among medicinal plant research groups in Brazil. Of the 422 abstracts published in the "Simpósio de Plantas Medicinais do Brasil" between 1978 and 1992, interaction within the same university was observed in 145 abstracts, interaction between different universities was observed in 154 abstracts, and interaction between universities and research institutes was observed in 58 abstracts. However, only 65 abstracts involved international collaborations. The most likely explanation for the low level of interaction between Brazilian medicinal plant researchers and international researchers is the difficulty involved in these partnerships. This is a very sensitive area of research due to "biopiracy" concerns—not because of the

researchers involved in a project, but because of the fear that knowledge may be appropriated inadequately by foreign companies.

Thus, despite some difficulties, it is possible to affirm that there is a reasonable and qualified research base in natural products in Brazil, especially in medicinal plants. But there is still a need for R&D activities in Brazil in order to facilitate progress in the search for bioactive compounds. This need is due to several factors:

- There are still few medicinal plant research groups in Brazil
- Most of the phytochemical research in Brazil is not related to compounds' therapeutic effects
- There is little concern about intellectual property issues in Brazil, especially regarding the potential for drug discovery, since this is not the goal of most studies
- Phytochemistry has been suffering from a decline in graduate programs due to the higher importance placed on synthetic chemistry, and most phytochemical analyses are not oriented to the isolation of active compounds
- The scarcity of financial resources to support R&D activities
- Companies' behavior regarding R&D and interaction with universities and research institutes, despite recent initiatives in natural products research (mainly involving medicinal plants)
- The lack of public policies to address plant medicines' potential

According to several authors (Brito and Brito 1993; Elizabetsky and Wannmacher 1993; Elizabetsky and Costa-Campos 1996; Ferreira 1998; Pinto et al. 2002), these challenges

do not yet constitute an insurmountable barrier. However, overcoming these obstacles requires the mobilization of existing competencies and the creation of technology institutes oriented toward applied research. An integrated effort to study the chemical diversity of the Brazilian fauna and flora will also be necessary—an effort that will involve the scientific community, the private sector, and the government. Given that almost 20 percent of the world's genetic resources are located in Brazil, and that many species are native to Brazil, this raises an important concern due to cattle ranching and deforestation in the Cerrado and Mata Atlantica, and more recently in the Amazon forest. (MMA 2003; Kaimowitz et al. 2004)

2.1.3 Biodiversity and the Brazilian Government

With respect to the Brazilian government's actions related to biodiversity issues, four issues are worth considering in analyzing biological resources' potential to stimulate technological and industrial development: (1) Investments in science and technology; (2) Regulation of the pharmaceutical market; (3) Intellectual property rights; and (4) Access to genetic resources.

In science and technology, most research efforts in natural products, although sparse and restricted by financial limitations, have been directed toward medicinal plants. The following actions deserve particular attention: the role played by the Central de Medicamentos (CEME) between the 1970s and the 1990s; the role of the Ministry of Science and Technology (Ministério da Ciência e Tecnologia – MCT); the role of the Ministry of Environment (MInistério do Meio Ambiente – MMA); and the recent changes in the regulation of phytomedicines marketed by ANVISA.

In the case of the MCT, it is worth mentioning the investments made by its funding agencies Conselho Nacional de Desencolvimento Científico e Tecnológico (CNPq) and

Financiadora de Estudos e Projetos (FINEP). Until the end of the 1990s, FINEP provided supported related to medicinal plant research through. CNPq promoted programs devoted the improvement of Brazil's science-oriented human resources through the funding of graduate programs. Besides CNPq, the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) from the Ministry of Education also funds the development of human resources (Ferreira et al. 1998). The MCT and the Brazilian Armed Forces announced the elaboration of a project related to biodiversity (JCE-SBPC 2003b). Recently, FINEP and CNPq have jointly managed newly created research funds, and began approving projects related to biotechnology and health sector research. Another important MCT program is the Genome Project, which began in 2000. The Genome Project aims to strengthen the scientific and technology base in biotechnology and related areas. Despite positive results, however, the contingency of government resources and delay in allocation of resources resulted in serious problems for the progress of the projects.

When Brazil ratified the CBD in 1994, the government created the "Programa Nacional da Diversidade Biológica (PRONABIO)" within the Ministry of Environment (MMA) to implement sustainable development policies. Among the programs supported by the PRONABIO, it is worth mentioning the "Programa Brasileiro de Ecologia Molecular para o Uso Sustentável da Amazônia (Probem) to promote the sustainable use of biological resources of the Amazon region[43]. The building of the "Centro de Biotecnologia da Amazonia

[43] The "Associaçao Brasileira para o Uso Sustentável da Amazônia (Bioamazônia)", formed by the Brazilian government, civil society, and scientific community, is responsible for the implementation of Probem. Due to contingency of resource allocation and inexperience of state institutions involved, the performance of the Probem did not fulfill expectations, as could be seen in the case of the delays in the building of the CBA, which was completed in 2002 and opened in 2003.

(CBA)" oriented to phytomedicines, and other natural products (juices, concentrates, and cosmetics) are one the Probem's main project.[44]

Another important MMA institution is the Embrapa, a research institution whose mission is to "develop solutions for the sustainable development of the Brazilian agribusiness through generation, adaptation, and transfer of knowledge and technologies." Embrapa has been involved in research in genetic resources through the creation a germ plasm bank. It has also conducted research on endangered medicinal plants, focusing on their potential uses, and the creation of high-yielding varieties, plant multiplication, and plant regeneration.

In addition to these Brazilian federal government programs, some state and municipal governments have recently begun to address biodiversity's potential for pharmaceutical development. Notable examples include:

- The "Programa Biota" in Fapesp, which is designed to stimulate research in biodiversity and its potential to leverage pharmaceutical development
- The "Projeto de Biotecnologia Vegetal da Melhoria da Qualidade de Fitoterápicos" in Faperj, through which a national company (Laboratório Simões) has obtained support to improve quality and standardization of phytomedicines in partnership with a the Federal University of Rio de Janeiro (UFRJ)
- Some municipal health secretaries have also created specific programs in order to introduce the use of medicinal plants into Brazil's health system

[44] The other Probem's projects are: "Projeto de Conservação e Utilização Sustentável da Diversidade Biológica Brasileira (PROBIO)," and the "FUNBIO"— both of which receive financial support from the GEF [full spelling] and the Brazilian government; and the "Programa Biodiversidade em Recursos Genéticos (Biovida)" to promote knowledge, conservation, and sustainable use of biodiversity and benefit sharing.

It is important to observe that although Brazil ratified the CBD in 1994, there was no specific law regulating access to biological resources and compliance with CBD provisions until Provisional Measure 2.052 (MP 2.052) passed in 2000.[45] MP 2.052 involved several policy discussions, especially because it stipulated that all projects that were already in place were not subject to the new provisions. In 2001, a new Provisional Measure 2.186 passed, replacing the MP 2.052. This new MP was regulated by the Decree n.3495, according to which research on biological resources must be registered through the "Conselho de Gestão do Patrimônio Genético," which is administered by the MMA. The MP 2.186 requires researchers to inform the MMA about the material they intend to collect, the place and date of collection, and whether the material involves traditional knowledge. It also requires the researchers to show evidence of prior informed consent, ABS agreement, and MTA. Any violation of Decree n.3495 can be punished by a fine of up to R$50 million or imprisonment. However, this law placed an enormous burden on the scientific community and disrupted ongoing research. Meanwhile, "tourists" smuggling biological resources without respecting CBD provisions, and who were supposed to be the main target of the law, are generally released after paying the bail (Silveira 2003). There has been an intense debate about the impact of MP 2.052, and in 2003 the federal government passed the Decree 4946 in order to address some of these problems that emerged from this MP. However, some issues still remain. For instance, Decree 4.946 attempts to distinguish between scientific and commercial research, but such division is difficult to establish (Geraque 2003).

According to IBAMA, the international black market for animal and plant species is around US$60 billion each year, of which US$12 billion corresponds to the smuggling of wild

[45] Before 2000, there were only a few regulations regarding foreign researchers' activities in Brazil.

animals. According to a recent Brazilian Congress report, the country loses around US$1 billion per year due to biopiracy. IBAMA indicates that the people who come to Brazil looking for plants, seeds, or animals are highly sophisticated individuals (even though they are supposedly "tourists") with very specific demands. They are aware of the flaws in the Brazilian law and try to establish relationships with indigenous communities. In 2003, two German "tourists" were arrested when, after visiting the Amazon, they tried to return to Germany carrying native seeds and bird-eating spiders.

Since there is no working definition of biopiracy within the WTO, it is difficult to challenge patents based on traditional knowledge or biological resources without being able to exert the idea of intellectual property rights (Escobar 2003). For some researchers, there is "biopiracy" in Brazil due to the lack of a national project to exploit the potential of the Brazilian biodiversity. For example, the building of the CBA, mentioned above, began in 1999 and was completed in 2002, but it only officially opened on December 2003 and has not yet been occupied. Another important issue is Brazil's population has not acknowledged the therapeutic value of natural products the same way that the populations in India and China have (JCE-SBPC 2003).

Despite the uncertainties regarding access to biological resources, there were some bioprospection agreements in the beginning of the 1990s that are worth mentioning:

- An agreement between the North American Aveda Corporation and the Guarani-Kaiowá community in 1994, as well as the Yawaná-Katukina community in 1993, for commercial cultivation of "urucum," "pupunha," and "castanhá-do-pará"
- An agreement between the North American company The Body Shop and the Aukrem Kayapós community

- An agreement between the Universidade Federal do Ceára and the North American company Tom's of Maine in 1994
- An agreement between the North American Merck & Co. and the Uru-Eu-Wau-Wau community for the extraction of a substance from a plant known as "tike-úba"
- An agreement between the Merck AG and the Guajajara community for the commercial cultivation of *Pilocarpus Jaborandi* used in the manufacturing of pilocarpine
- An agreement between the Cognis Corporation and the Centro Nacional de Desenvolvimento Sustentado das Populaçoes Tradicionais (MMA/IBAMA) for the development of perfumes and cosmetics
- An agreement between the Raintree Nutrition Inc. and different indigenous communities and NGOs in the Amazon

Even though there is no publicly available information about the terms of these agreements and their current status, most of them did not involve sharing of intellectual property rights if a patent application was filed resulting from access to genetic resources or traditional knowledge. In addition, most benefits, when materialized, were non-monetary benefits (Fernandes 2002).

Recently the National Cancer Institute established partnerships with the following Brazilian institutions: Fundação Oswaldo Cruz (1999); South American Organization for Anticancer Drug Development (1995); Universidade Paulista (1997); Universidade Federal do Parana (1998); and Universdade Federal do Ceara (2001).

The most publicized agreements involving exploitation of Brazilian biological resources have been the agreements between the pharmaceutical company Glaxo Wellcome and the small Brazilian biotech company Extracta in 1999, between Extracta and Genzyme in 2001, and between the pharmaceutical company Novartis and Bioamazônia in 2000.

In 1999, Extracta and Glaxo signed a three-year bioprospection agreement for the screening of Brazilian plants in order to identify their potential use in the drug discovery process. Glaxo paid Extracta US$3.2 million to build technological infrastructure for improving access to biological diversity. If any compound extracted by Extracta were used for drug development, 3 percent of its world sales would accrue to Extracta, which would be holder of the patent. Currently, Extracta has a collection of more than 10,000 plant extracts. In 2001, Extracta signed a US$1.6 million agreement with Genzyme for the screening of compounds against rare disease. However, the agreement has not yet been approved by the Brazilian government (Radler 2000; Bellinghini 2003).

The agreement between Novartis and the Bioamazônia began to be discussed in 1998 and was signed in 2000. However, it was suspended for a couple of weeks after some members of the Secretaria de Coordenaçao da Amazônia challenged the right of Bioamazônia to make the agreement without the consent of its board of directors and due to the lack regulations regarding access to biological resources. The agreement was supposed to involve around US$ 4 million in resources and an annual supply of up to 10 thousand chromatographic profiles of fungi and bacteria by Bioamazônia to Novartis for three years. Novartis would then have exclusive rights to the information for two years with the possibility of extending these rights. The agreement also involved transfer of technology from Novartis in microbiology, isolation of compounds from natural products, and high-throughput screening.

In addition, if any industrial use for these natural products was identified, Novartis would conduct the initial research outside of Brazil, followed by research conducted by Brazilian scientists. If any product were developed based on access to those biological resources, Novartis would pay 1 percent of the royalties of the net world sales, and patents would be filled by Novartis and Bioamazônia. Due to the intense discussion about the legal aspects of the agreement, Novartis decided not to pursue further discussions and the agreement was terminated. It is also important to observe that one of the elements of the agreement involved the construction of the CBA, which only opened in 2003 (Scharf 2000; Vasconcelos and Komatsu 2000; Vasconcelos 2000).

Following the recommendations of the WHO regarding the use of medicinal plants in the Brazilian health system, the Brazilian government established Portaria 08/CIPLAN in 1988, which recommended the use of phytomedicines by the Sistema Único de Saúde (SUS). In the beginning of the 1990s, Gottlieb and Kaplan (1993, 54) observed that this directive (based on the WHO program) and the CEME_initiatives were nothing but "good intentions with few hopes of success." Such foresight became a reality, since, as mentioned above, there are just a few isolated initiatives by Brazilian states and municipalities. At the end of 2003, the Ministry of Health — as part of the preparations for the Conferência Nacional de Medicamentos e Assistência Farmacêutica — organized a seminar in order to discuss the use of medicinal plants and phytomedicines in the government pharmaceutical assistance programs. As a result of this seminar, the following recommendations were made (Brasil 2003):

- To stimulate the use of medicinal plants within the SUS in a consistent manner, based on efforts by the Ministry of Health, the scientific community, and health workers
- To integrate existing actions regarding medicinal plants within the SUS
- To collect information about the use of medicinal plants and phytomedicines regarding production, marketing, science and technology, and cost effectiveness analyses among different therapeutic alternatives
- To promote R&D in medicinal plants, with emphasis on public health needs
- To establish technical guides for cultivation and quality control of crude extracts and phytomedicines
- To review the Brazilian Pharmacopoeia[46] and to elaborate a separate Pharmacopoeia of medicinal plants
- To establish training programs to incorporate this recommendations among health professionals

Until 1995, there was no specific law regarding phytomedicines in Brazil. In January 1995, the Portaria SVS/MS n.6 established rules for toxicity studies of phytomedicines. According to the Brazilian Association of Phytomedicines Manufacturers (ABIFITO), this measure was not adequate and made it impossible to register of phytomedicines in Brazil. A new regulation, the RDC 17/00, came into force in 2000. This measure established rules for the registration of phytomedicines, and the processes that were waiting for approval by

ANVISA had a period of time to adapt their applications to the new rules. Because of this, most of the companies with phytomedicines that were approved in Brazil between January 1995 and April 2000 have obtained their licenses based on lawsuits (Rates 2001; ABIFITO 2003).

After the RDC 17/00, several applications for phytomedicine registration were not approved by ANVISA in the beginning of 2002. As a result, sales of most phytomedicines companies were considerably affected, jobs were reduced, and most companies were operating 30% idle capacity. In turn, many companies began to adapt their procedures to the new regulations, and the number of applications for product registration denied and products taken out of the market by ANVISA was greatly reduced. ABFITO sent a proposal for a Projeto de Lei to promote the development of the phytomedicines segment. This proposal also has the support of the Ministry of Health (ABIFITO 2003).

With respect to specific public policies regarding the exploitation of biological resources for pharmaceutical development, the Brazilian government only recently recognized the need to reestablish industrial and technology policies that have been abandoned by previous governments. Although pharmaceuticals, fine chemicals, and phytomedicines are three of the industries being emphasized by the government at the time of this writing, there is still no coordinated effort on this front among the Ministries of Environment (MMA), the Ministry of Health (MS), the Ministry of Science and Technology (MCT) and Ministry of Industry and Trade (MDIC).

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[46] The first Brazilian Pharmacopoeia was published in 1929 and had 300 monographs of medicinal plants; the second edition of 1959 had 94. Both presented mainly botanical descriptions. The third edition of 1977 had only 26 monographs though with phytochemical studies, and the fourth edition (1988) just 10 mnographs (Rates 2001).

Conclusions

This study addresses the potential for developing countries to benefit from their biodiversity by channeling these resources into pharmaceutical development. One possible strategy is for countries to stimulate technological and industrial development or to stimulate R&D activities, especially for neglected diseases. In this sense, it is important to characterize this natural resources "window of opportunity" with an eye toward economic, technological, and institutional considerations.

With respect to technology, the window of opportunity has been characterized by the development of modern biotechnology in the late 1970s and the 1980s, as well as by the advances in chemical technology in the 1990s. All of these developments have changed the nature of the drug discovery and development processes. With respect to the international institutional environment, after the mid-1980s a greater concern was placed on sustainable use, intellectual property rights, and the appropriation of benefits resulting from research in biodiversity — all of which resulted in international treaties that promoted significant changes in the institutional environment.

From an economic standpoint, the pharmaceutical industry continued to rely on natural products, including exclusively natural products such as phytomedicines after the 1990s. These elements have specificities that must be analyzed separately. However, an assessment of a developing country's ability to benefit from biodiversity is only possible if these elements are taken into account interdependently at international and national levels, since countries differ in terms of their science and technology infrastructures, industrial capabilities, and trajectory of evolution within the capitalist system.

In the case of pharmaceuticals, the introduction of new technologies in the 1980s and 1990s represented new pathways in the development of medicines and led most pharmaceutical companies to abandon natural products research in their search for new compounds. This movement was also a reaction to the uncertainties in the institutional environment regarding access to natural products and intellectual property rights issues during the mid 1990s. Despite massive investments in new technologies intended to increase the potential of chemical libraries in the search for new compounds, a great percentage of the new chemical entities introduced since the 1980s were still derived (at least partially) from natural products research. Besides, at the same time that new chemical technologies enhanced the potential of synthetic compounds libraries, new technologies have been developed that have allowed scientists to overcome important technological bottlenecks in natural products research. Consequently, natural products research is still an important area in drug development and can represent a window of opportunity for developing countries, where most of the world's biological resources are concentrated. If adequately implemented, these changes in the international institutional environment promoting benefit sharing and technology transfer may enhance developing countries' potential in this regard.

However, developing countries face several challenges. First, ownership over biological resources offers only comparative advantage (and not competitive advantage), especially for those developing countries that either lack a local pharmaceutical industry or that are not systematically engaged in R&D efforts. It is also important to observe that technological change is a cumulative process that demands continuous investment in science and technology. Thus, developing countries must be able to protect and conserve biological resources, while also stimulating endogenous technological development and technology

transfer in order to lessen technological dependency. However, these countries face problems regarding public investment (not only in science and technology) due to several factors, ranging from vulnerability to turbulence in world economy, "structural adjustment" policies, internal macroeconomic conditions undermining local investment initiatives, and other social, economic, political and cultural factors. Thus, developing countries encounter enormous challenges concerning investment in science and technology. Besides, the mechanisms that today's developed countries utilized in their development are not nearly as available to current developing countries.

Introducing new chemical entities to the world market may offer a developing country's pharmaceutical industry strong incentives if a medicine reaches the market and reaps great economic returns. But this trajectory also involves higher risks and higher barriers to entry, especially regarding the costs of approval processes and marketing. This is not to say that developing countries should not focus on new product development, but that new product development should be seen as a long-term strategy — one that is highly dependent upon the evolution of the local industry, industrial and technology policies, and the interrelation of those dynamics to the international pharmaceutical industry.

The other window of opportunity that natural medicines provide is something that involves lower costs and less technological complexity: phytomedicines. There are great incentives for developing countries not only because of the lower costs involved, but also because most biological resources are located in developing countries and most of these resources have not been studied in terms of their therapeutic effects. However, even with phytomedicines, developing countries face important challenges, mainly in relation to international competition due to stringent regulations that have been put in place by some

developed countries (especially in the European Union, which is the world largest phytomedicines market), and the need to invest in commercialization channels and technological modernization (either in crude drugs cultivation, processed bulk, or finished phytomedicines). Yet developing countries also face important problems regarding access to medicines, so encouraging the development of phytomedicines may not only serve industrial and technological development purposes, but public health goals as well.

Another relevant area with intrinsic value for stimulating natural products R&D is in those diseases that large research-based pharmaceutical companies have not researched extensively — diseases that are prevalent in developing countries, but that do not promise enough economic profit to entice these pharmaceutical companies to commit to drug development efforts. In this sense, developing countries have another incentive to look for medicines to address public health problems.

The Brazilian case is a good example for the analysis of the opportunities, obstacles, and challenges involved in exploiting biodiversity's potential within the pharmaceutical industry. Brazil is one of the world's largest countries in terms of biological resources; has a local pharmaceutical industry with industrial and technological capabilities for either finished medicines or fine chemicals; and also has a good scientific and technology infrastructure in health sciences, especially in the university system and at some research institutes. However, with the evolution of the pharmaceutical industry (both in finished medicines and fine chemicals), Brazil's pharmaceutical industry features changes in the regulatory environment, the inadequacy of previous public policies, and a lack of access to and transfer of technology. These trends pose several obstacles to the above mentioned windows of opportunity within the pharmaceutical industry.

It is worth noting that the difficulties faced by Brazil's pharmaceutical industry (especially the fine chemical industry) have increased since the 1990s. Such difficulties create obstacles to Brazil's attempt to benefit from the window of opportunity related to the development of new medicines and to policies for endogenous development. Local pharmaceutical companies are of a smaller size compared to leading multinationals (which dominate the domestic market); and most companies are not integrated. Brazilian companies have also been facing several problems due to intense competition from Indian and Chinese companies. Yet Brazil's local research capabilities in natural products in universities, institutes, and some small biotech companies (most of them in incubators) may open opportunities for technological development through partnerships with large research-based pharmaceutical companies interested in having access to Brazil's biological resources. Here, the stakes are higher and policies should be carefully designed so that they do not run counter to each other.

In the case of phytomedicines, a few factors are particularly significant, including the lower costs, the lower technological complexity involved, the fact that Brazil holds 22 percent the whole plant species in the planet, and that recent efforts to improve quality of products through new regulations may represent an important opportunity. In this case, it is important to devote efforts to improving cultivation practices, to invest in technological capabilities to accomplish toxicity tests and product validation, and to support the entry of locally developed medicines into foreign markets. Taking into account the local capabilities in natural products research and life sciences in general, existing capabilities in partnerships with the private sector may also be directed to R&D efforts in neglected diseases. But these opportunities cannot be considered separately from all the other public policies that have a significant

impact upon the pharmaceutical sector, including price regulation, intellectual property rights, and regulation of production, registration and marketing of medicines, macroeconomic policies, and pharmaceutical assistance.

In terms of this paper's contribution to theory development, there are four main conclusions. First, benefiting from a window of opportunity depends upon local and non-local factors, which are highly interdependent and both have an important impact upon technological development. Second, technological development must be seen from a long-term perspective, since the international environment and competition dynamics among pharmaceutical firms and nations change over time. This means that what may be valid in certain contexts may not be valid in others, because institutions change slowly and "technological borrowing" affects local institutions that are at different stages of evolution in different ways. Third, although technological change can be punctuated by events that alter development trajectories, technological learning is a cumulative process and requires continuous investment in education, research, and development — toward both industrial applications and fundamental knowledge. Finally, it is important to observe that institutions change slowly and that there is a feedback process that has strong influence upon development trajectories.

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