Biodiversity and Technological Development
Opportunities for Developing Countries?

Beatriz de Castro Fialho

STG Working Paper 2004-01

May 2004
Abstract

Despite the emphasis on synthetic medicines, a great part of current prescribed medicines derived somewhat from natural products. It has been also observed a steady increase of the natural medicines market. Such evidences have been pointed out as an opportunity for developing countries with large biological resources to implement industrial and technological development strategies based on those resources. In this regard, the pharmaceutical industry is generally cited for developing countries face not only technological dependency, but also because access to medicines is a huge problem and research-based companies do not direct efforts to diseases prevailing in those countries. But ownership over biological resources offers only comparative advantage. Thus, to analyze these opportunities it is necessary to conduct a careful analysis of the industrial, technological and the regulatory selection environments, both at national and international levels. Although developing countries may share some common characteristics in terms of their insertion in the world economy: higher vulnerability to changes in the world economy, macroeconomic instability, higher socioeconomic disparities, lower bargaining power in international trade negotiations, not all countries have industrial and technological capabilities in the pharmaceutical industry. Brazil is among the five richest Brazil in biodiversity, has an established pharmaceutical industry, is among the top ten world pharmaceutical markets, and has a good science and technological infrastructure in natural products research. But, Brazil is also dependent upon importation of inputs and products originated in leading countries; access to medicine is a public health problem. The aim of this paper is thus to discuss windows of opportunity associated to biodiversity potential in pharmaceuticals for developing countries with special attention to the Brazilian case.

Keywords:

biological resources, economic development, medicinal plants, pharmaceutical industry, Brazil
JEL: O31, L65
# Index

Introduction ........................................................................................................................................... 5
1. Opportunities in Natural Products ................................................................................................. 8
   1.1 Access to Biological Resources: The CBD and the TRIPS .................................................. 8
   1.2 Technology and Industry: Natural Products Research ............................................................. 15
2. Discussion ......................................................................................................................................... 24
   2.1 The Brazilian Case ...................................................................................................................... 25
   2.1.2 The Brazilian Pharmaceutical Market and Medicinal Plants ........................................... 28
Conclusions .......................................................................................................................................... 36
References ............................................................................................................................................ 39
Introduction

The pharmaceutical industry is a highly internationalized industry, with leading companies dominating most domestic markets, except in a few countries (e.g.: India) and concentration of markets in terms of therapeutic classes. Concentration is also observed in terms of innovation, production and international trade in developed countries, where the leading firms are based. This geography of innovation and production reflects the dynamics of knowledge production and its interrelation with other factors such as the industry development and organization at national and international levels. Such characteristics pose several challenges for developing countries. In these countries access to medicines is a problem of difficult solution and most pharmaceutical companies (domestic or foreign) do not invest, or invest very little, in research and development (R&D), especially for diseases that are public health problems like malaria, schistosomiasis, leishmaniasis etc. These countries also have higher levels of socioeconomic inequalities compared to developed countries. Although the majority of the world population lives in developing countries, these represent a small share of world pharmaceutical markets, though a few like Brazil, Mexico and Argentina are among the top ten markets. And though in some of them have developed technological and industrial capabilities for the production of fine chemicals ¹ and finished medicines, in the vast majority of there are no capabilities. Thus, these countries are, in general, dependent upon fine chemicals, process or products developed by leading pharmaceutical companies located in developed countries, through their in house efforts or licensing from other biotechnology companies located in developed countries. Even in those developing countries that managed to establish local production of fine chemicals and finished medicines, efforts directed towards the development of new molecules, when there is any, have been modest compared to what is observed among leading firms from developed countries. Besides, the insertion pattern of developing countries in the world economy has been characterized by higher vulnerability and lower bargaining power in international trade negotiations (Fialho et al., 2003).

It has been argued that biodiversity rich countries could use this potential to implement development strategies, such as technological and industrial development policies to stimulate the pharmaceutical industry, and reduce technological dependency; stimulate the development of natural medicines and take advantage of the market potential of the phytomedicines in developed countries, and to stimulate the development of medicines for neglected diseases. The mainstay for such possibilities has been the fact that from the 250,000-500,000 estimated plant species in the planet, less than 15% have been studied in terms of phytochemical properties and less than 6% in terms of therapeutic properties; in the case of microorganisms, less than 1% was studied (Harvey, 2000; Fabricant and Farnsworth, 2001). In respect to other natural products, like marine organisms and insects, for example, researches are quite recent (mid 1970s), and although no product had been introduced into the market this is a promising field. Besides, despite the substitution of natural medicines by synthetic or semi-synthetic medicines since the first quarter of the XX century, several of current prescribed medicines were developed based on natural products research (Farnsworth et al., 1985; Nisbet e Moore; 1997; Cragg et al., 1997 and 1999; Shu, 1998; Young, 1999; Harvey, 2000).

¹ That is active substances, responsible for therapeutic action, and intermediates used in formulation of medicines.
In the late 1970s several initiatives have been put in place by countries and multilateral organizations in medicinal plant. In 1978 the World Health Organization (WHO) created the Traditional Medicines Programme (TRM) to support the use of traditional medicine in the health system\(^2\), especially in developing countries. There has been also an increasing interest, especially in developed countries, in alternative medicines and natural medicines, due to: rising concerns about efficiency of conventional therapies; problems related to irrational use of synthetic medicines and 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. It has also been observed improvement in cultivation techniques and production methods of phytomedicines, which has allowed improving quality, safety and efficacy of natural medicines. In the beginning of the 1990s it was recognized the sovereignty of nations over biological resources in their territories, and the importance that the access to those resources assured equitable benefit sharing, that access to and transfer of relevant technology should be facilitated. Also at the same time changes in intellectual property rights regimes have allowed patenting of living organisms (Duttifield, 1995; Silva, 1995; Hoareau and Silva, 1999; ten Kate and Laird, 1999; Michael, 2000; Rates, 2001).

From the theoretical standpoint, according to Abramovitz (1979, 1986, 1989) and Abramovitz and David (1996) the greater the technological gap the higher the possibility of a backward country to catch-up and reduce this gap. In this process, the ‘social capability’ in relation the institutional scheme and the relation among resources needed for technological progress in a given period is the most important elements. However, it has been observed that such assumptions, within certain limits, may hold true only for the trajectory followed by some of current developed countries. But one could not observe the same dynamics in current developing countries, given that the technology gap has been widening and among developed and developing countries, not the opposite, despite considerable improvements observed in some newly industrialized countries (Lau, 1996).

In the mid 1980s, in the light of changes in the techno-economic paradigm and institutional restructurating at national and international levels, Soete (1985) and Perez (1985) noted that this period would indicate a more favorable environment for technological backward countries to stimulate industrial, economic and technological development. This is due to the fact that those periods would open ‘windows of opportunity’ for those countries not committed with the previous paradigms, and hence they stimulate the industrial and technological development within the new paradigm. Such opportunity would exist because when there are such kinds of changes there would be a period of learning relatively homogenous for all countries. But benefiting from such opportunity depends upon several factors, among which the country’s capability to actively absorb technology generated outside, endowment of qualified human resources, especially in the new technologies, and a certain level of involvement in research and development efforts, existence of a reasonable productive capability, besides location

\(^2\) In the 1980s, Farnsworth et al. (1985) collected information from the WHO collaborating centers for the TRM program about the role of ethnomedical knowledge in drug development. The study identified 122 compounds derived from 94 plant species (Fabricant & Farnsworth, 2001).

\(^3\) It is important to observed that some natural products can be highly toxic, although toxicity is not a matter of a compound being natural or synthetic (Topliss et al., 2002).
advantages (Soete, 1985; Perez, 1985; Freeman and Perez, 1988; Perez and Soete, 1988). However, one cannot forget that technological change is a cumulative process. In general, according to this approach, the capability of benefiting from a ‘window of opportunity’ is related to local factors at national level, as one can observe from the studies that followed based on the concept of national innovation systems (Freeman, 1987; Lundvall, 1992, Nelson, 1993). However, in all these studies non-local factors, such as the geopolitics of competition among national estates are poorly addressed. Recently, it has been observed an effort of some authors working under this approach to incorporate the role of non-local factors in the analysis of development trajectories (Freeman, 1997; Cimmoli, 1998). But, as it was observed by Lundvall (2002), these aspects have not been sufficiently addressed yet.

In the case of the pharmaceutical industry, as observed in another occasion (Fialho et al., 2003), the possibility of benefiting from a ‘window of opportunity’ during technological change periods, depend upon local factors like: industry structure and behavior of companies; science and technology infrastructure; domestic market dynamics; industrial and technology policies and regulatory environment; technological learning and absorption capacity. But they as well depend on the country pattern of insertion in the world economy and dynamics of industrial competition at world level; and on international regulatory environment.

Thus, this work discusses the possibility of developing countries of benefiting from a window of opportunity related to biodiversity in the area of natural products in the pharmaceutical industry. Section 1 presents the elements that allow characterizing these windows of opportunity regarding the international institutional environment; and the dynamics of technology, industry and regulation. Section 2 discusses this issue in light of the Brazilian case. Brazil is among the five richest Brazil in biodiversity, has an established pharmaceutical industry, is among the top ten world pharmaceutical markets, and has a good science and technological infrastructure in natural products research. But Brazil is dependent upon importation of inputs and products developed in leading countries; access to medicine is a problem. Thus, as a laggard country and with large biological resources Brazil may be an interesting case for the analysis of windows of opportunity associated to biodiversity potential in pharmaceuticals. The last section is devoted to conclusions.
1. Opportunities in Natural Products

The central argument of this study is that it would be possible to point out some windows of opportunity for developing countries related to biodiversity in the pharmaceutical industry: involvement in the search for active biological compounds for the development of medicines; the potential of natural medicines, in particular, phytomedicines; and the potential for the development of medicines for neglected diseases. The emergence of such opportunities are related to changes in the international institutional environment regarding access and use of biological resources; technological changes in the dynamics of drug discovery processes and its consequences for the search of new medicines; the growth of the natural medicines market competing with synthetic medicines. A careful analysis of such opportunities must, therefore, consider the selection environments from institutional, economic and technological standpoint.

1.1 Access to Biological Resources: The CBD and the TRIPS

Historically, developing countries have received no returns resulting from the marketing, by pharmaceutical companies, of medicines developed based on research on biological resources found in those countries (Juma, 1989; Reid et al., 1993). Besides factors associated to the technological dependency of these countries, until the end of the 1980s, those resources, for being considered common heritage of mankind, were seen as freely accessible. But, after the Convention on Biological Diversity (CBD) signed during the United Nations Conference on Environment and Development (UNCED) in Rio de Janeiro, it was recognized the sovereignty of estates over those resources (Reid et al., 1993; Blum, 1993; ten Kate and Laird, 1999; Srividhya, 2000; Strauss, 2000; Dalton, 2004).

The CBD is an international treaty resulting from discussions in different international forums along the 1970s – influenced by previous environmentalist movements – concerned with the extinction of species; conservation, protection and access to biodiversity resources; intellectual property; benefit sharing; sustainable development; and transfer of technology. From the 188 countries, plus the European Community (EC), present at the UNCED, 160 countries and the EC signed the Convention in 1992, which entered into force in 1993 after 39 had ratified it in their national legislations. In 1993 five other countries, including the United States (US), signed the CBD. Currently from the 188 present at the UNCED, 37 have not ratified the Convention through their national laws, among which the United States, Japan and Netherlands. Although the EC signed the CBD in 1992 and most countries forming it have individually ratified the CBD, the EC as an entity have not ratified the CBD. The deadline for those countries that have not ratified the Convention is 2010.

The refusal of the US to sign the CBD in 1992 indicates the main issues that have been debated since the Convention: access to resources; intellectual property; access to and transfer of relevant technology; and benefit sharing. In the case of access to resources it has been discussed that the CBD could result in national laws that may turn difficult access to

---

4 The other four countries are: Czech Republic, Slovakia, Siria and Vietnam.
5 The following countries signatários of the CBD had not ratified it yeat: Armenia; Azerbaijan; Democratic People's Republic of Korea; Finland; Japan; Netherlands; Togo; Czech Republic; Slovakia; United States of America. The following countries present at the UNCED but that did not signed the CBD also did not ratified it: Albania; Andorra; Bosnia and Herzegovina; Brunei Darussalam; Cambodia; Equatorial Guinea; Eritrea; Georgia; 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; Uzbekistan. Only the Dominican Republic and South Africa that did not singed the CBD in 1992, have ratified it in 1994 and 1995, respectively.
biological resources, creating obstacles to technological development based on them. In the case of intellectual property over the results based on access to those resources, and benefit sharing, the main problems are related valuation of resources, its role on the development of products and process, and the future monitoring and proprietorship of future developments based on access to a given resource. In the case of access to and transfer of technology, the main concern has been with the extents of the CBD provisions in respect to the compulsory nature of establishing preferred conditions to developing countries. Another important aspect is that the CBD objectives are to facilitate access to biological resources, to promote protection, conservation and sustainable development with fair and equitable benefit sharing. Since it is a framework treaty, CBD provisions are basically recommendations, and there are no sanctions for those countries bypassing the Convention provisions, such as the so-called problematic issue of ‘biopiracy’ that, as a matter of fact, is not mentioned by the CDB (Burgiel, 2004).

Since 1992, the implementation of CBD recommendations, especially regarding intellectual property and transfer of technology have been in the center of debates and no consensus have been reached among developing and developed countries. In the light of these problems, in 2002 during the World Conference on Sustainable Development (WSSD) in Johannesburg, after intense debate, the CBD Secretariat put forward the Bonn Guidelines. These Guidelines were intended to address demands from developing countries regarding the disclosure of the origin of resources, including traditional knowledge, PIC (prior informed consent), MAT (mutually agreed terms) and ABS (access and benefit sharing) evidences in patent applications. Since then, the associations representing the pharmaceutical (IFPMA, 2003) and biotechnology (Bio, 2004) have reiteratively claimed that such recommendations if widely implemented by countries in their national laws would run counter to CBD objectives since companies wouldn’t be willing to undertake R&D efforts dependent upon such requirements. Another issue that has been raised is related to the difficulties of national patent offices to verify these requirements, demanding a collective effort of collecting and sharing information. An option would be the support for the creation of databases about biological resources, such as the Global Biodiversity Information Facility. But some developing countries have shown some reluctance about such initiatives. They fear that turning this information available would allow companies to develop products without necessarily sharing benefits or would facilitate the smuggling of species, especially the endangered ones with higher value; another concern is expressed in respect to ex-situ collections in developed countries prior to the CBD (Strauss, 2000; Sharma, 2004; Sterckx, 2004; Masood, 2004).

In 2003, during the Fifth Ministerial Conference of the WTO in Cancún, a group of 15 developing countries created the Group of Like-minded Megadiverse Countries intending to coordinated efforts of these countries concerning CBD recommendations and technological capability efforts and transfer of technology involving the exploitation of biological resources.

---

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

7 Defining biopiracy is itself problematic. Here it means the appropriation of biological resources for commercial purposes without the authorization of entitled owners and without any compensation to them.

8 This was the second UNCED follow-up meeting. The first was the Earth Summit+5 in 1997.

9 This is an intergovernmental organization sharing information through the Internet about biological resources such as botanical descriptions.

10 Bolivia, Brazil, China, Costa Rica, Colombia, Ecuador, India, Indonesia, Kenya, Mexico, Malaysia, Peru, Philippines, South Africa and Venezuela.
At the same time 21 developing countries\textsuperscript{11}, some of them also belonging to the newly Megadiverse group, formed a coalition creating the G21 in order to negotiate agriculture and biopiracy issues at the WTO. During the conference developed countries supported the idea that this coalition was ‘a marriage of convenience’ since these countries have many different interests. 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 involving the CBD is related, besides agriculture, to the pharmaceutical and biotechnology sectors, since as already mentioned, prior to the CBD, commercialization of medicines based on natural products found in developing countries had not result in benefits for these countries. It is also important to note that the technology gap existing among developed and developing countries, especially in biotechnology, and the enforcement of intellectual property rights based on 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 the appropriation of benefits accruing from the marketing of results of R&D efforts in pharmaceutical and biotechnology sectors, this discussion concerns also the changes in intellectual property rights regimes.

First it has to be observed that patent protection grants temporary monopoly rights, allowing the holder to also establish prices, generally high to recoup costs related to efforts that resulted in the invention and costs associated with its commercialization. Thus patent protection would create economic incentives for the introduction of the patented invention into the market, since it allows the patentee to forbid third parties to use or commercialize the invention and in consequence to. But, the role of patents as a mechanism to protect inventions and as an appropriability mechanism of economic returns is different among sectors, being particularly important in the case of pharmaceuticals. This is due to the fact that, for pharmaceuticals it would be relatively easy to design around a patent for those skilled in the art. But being skilled in the art is not easy. Therefore, along the evolution of the pharmaceutical industry, countries have taken different positions regarding patent protection for pharmaceuticals processes and products. In general, countries introduce product patents after reaching a certain level of technological capability allowing them to reduce technological dependency. The extent of this discretion was highly reduced after 1995 at international level.

Although there have been international treaties regarding intellectual property since the end of the XIX, countries have had certain freedom to establish in national laws what wasn’t subject to patent protection, such as pharmaceutical products or processes. Until the 1970s not only developing countries but also some developed ones did not protect pharmaceutical products and processes. Such policy was intended to reduce technological dependency and stimulate local industry development. However, at the end of the 1970s it was already possible to find intellectual property rights protection for pharmaceutical process and products in most developed countries\textsuperscript{12}. On the other hand, in most developing countries, despite some

\textsuperscript{11} Argentina, Bolivia, Brasil, Chile, China, Colombiia, Costa Rica, Cuba, Equador, Egito, Guatemala, India, Indonesia, Mexico, Nigeria, Paquistao, Paraguai, Peru, Filipinas, Africa do Sul, Tailândia and Venezuela.

\textsuperscript{12} England 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; Western Germany introduced product patents in 1968; and Sweden and Italy introduced product patents only in 1978.
differences, weak intellectual property rights regime for pharmaceuticals still prevailed. In the beginning of the 1980, the United States\textsuperscript{13} managed to introduce services, intellectual property rights, and investment, into the agenda of the General Agreement on Tariffs and Trade (GATT), during the Uruguay Round initiated in 1986, despite initial reluctance of other developed countries (like the countries from the EC and Japan) as well as from developing countries. Therefore, at the same time it was being discussed access and sustainable use to biological resources resulting in the CBD, it was being discussed the enforcement of intellectual property rights within international trade negotiations. The argument of developed countries was that this harmonization was fundamental so that technology transfer efforts could successful. On the other hand, developing countries expected that developed countries lowered tariff and non-tariff barriers and export subsidies in agriculture and textiles (Pereira, 1993). Although there have been slow advances in reduction of international trade barriers in agriculture and textiles since the end of the Uruguay Round, intellectual property has been enforced at international level. This enforcement is expressed in the Trade Related Aspects of Intellectual Property Rights (TRIPS), signed by 123 countries in April 1994 during the Uruguay Round, entering into force in 1995, under the aegis of the World Trade Organization (WTO) created in 1995 after the end of the Uruguay Round in 1994. Developing countries members of WTO or those countries that intended to ascend the WTO had to adequate their intellectual property laws to the TRIPS until 2005, such as not restricting patent protection to technology fields (Art.65).

Despite the lower bargaining power of developing countries in international trade negotiations, these countries also expected that the TRIPS could stimulate technology transfer agreements, since according to Art.7 one of the objectives of protection and enforcement of intellectual property 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, close to 2005, the opening of international trade, especially regarding agriculture is still in the WTO agenda, and although most developing countries have implemented or are about to implement strong intellectual property rights regimes, they are still technologically dependent and north-south technology transfer is still very low (CIPR, 2003).

One fundamental aspect in discussing intellectual property is the patentability criteria, since there is no consensus whether results of researches using living organisms are inventions, therefore patentable, or discoveries and therefore not patentable. According to TRIPS Art. 27.3(b), member countries have to grant patent protection to microorganisms, non biological and microbiological processes, plant varieties\textsuperscript{14} and objects resulting from genetic engineering, except in cases in which it is necessary to “protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment,  

\textsuperscript{13} According to Tachinardi (1991), between 1970s-1980s, defesa of intellectual property became the main issue in the agenda of the Pharmaceutical Manufacturers Association of US pharmaceutical companies (PhRMA). It als worthy to mention that in 1974 the US introduced the Section 301 among the USTR responsibilities. According to this section USTR is responsible to monitor intellectual property rights around the world and those countries whose intellectual property regimes were considered by the US as insatisfatórios would enter to a “Priority Watch List” and would be passíveis of economic sanctions by the US.

\textsuperscript{14} In 1961 was created the International Convention for the Protection of New Varieties of Plants (UPOV), that is an independent intergovernmental organization. The UPOV secretary is the WIPO Director General, and the WIPO presta administrative and financial services to the UPOV. Currently 64 countries are parties of the UPOV (UPOV, 2004).
provided that such exclusion is not made merely because the exploitation is prohibited by their law”. 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 natural product (Strauss, 2000; Bermudez et al., 2000, Sterckx, 2004). One should observe 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 issues, TRIPS Art.71 established 2000 as an initial date to begin reviewing and discussing amendments to the Agreement. However, there has been no consensus, and changes are still being discussed (Sterckx, 2004).

Another important aspect is that the TRIPS does not mention or define ‘biopiracy’. In March 2004, the World Intellectual Property Organization (WIPO) organized a meeting to discuss ‘biopiracy’, and protection to genetic resources and traditional knowledge. But there was no consensus between developed and developing countries. Both the US and the EC countries are against the discussion of biopiracy in international forums (Vidal, 1999). However, developing countries, in general, has proposed that patent applications should specify the country of origin of genetic resources and traditional knowledge, and eventually evidences of PIC, as recommended by recent CBD provisions put forward by the Bonn Guidelines (Chade, 2004).

Besides the discussions involving the compliance between the TRIPS and the CBD, and that the TRIPS does not allow to discriminate inventions in respect to technology fields, increasing attention has been directed towards the implication of the TRIPS to public health, especially in the relation to the impacts of intellectual property to access to medicines. In the case of pharmaceuticals, strong intellectual property rights regime may result in problems of access to medicines, especially in countries in which the population has a low purchasing power. However, it has to be highlighted that the absence of patent protection does not necessarily mean higher access since other factors must also be taken into account: the model of acquisition/financing of medicines, and public and private resources available; the existence of local capabilities for production and the dynamics of local industry and its insertion in the world pharmaceutical industry dynamics; problems related to geographical access; level of income distribution and price regulation. Nevertheless, this does not mean that the existence of patent protection has no influence upon access to medicines, for in many countries, especially developing ones, medicines are supplied through importation, and hence the existence of intellectual property rights in other countries may influence the level of access to medicines in other countries (CIPR, 2002).

Great part of recent debates about TRIPS and access to medicines have as background the impact of strong intellectual property rights to fight against the HIV/AIDS epidemics, especially in developing countries where access to medicines is a problem. In particular, attention has been placed upon the panel opened at the WTO by the US against Brazil in respect to the Brazilian intellectual property law (Law 9.279 of 1996) especially the compulsory licensing issue¹⁵. The Brazilian case is an example of absence of intellectual property rights for pharmaceuticals associated with a pharmaceutical assistance program that allowed Brazil to provide and guarantee access to antiretroviral medicines at lower costs. This

---

¹⁵ It is important to observe that the TRIPS does not mention compulsory license. In the TRIPS, Art.31 refers to “other use without the authorization of the right holder”, and compulsory license – a government permit to third parties to produce a patented product or process without the consent of the right holder – is one of those uses (WTO, 2003a).
was possible not only because public procurement by Brazilian public administration organs (like the Ministry of Health) – of products not subject to exclusivity (such as medicines not protected by patents) – is based on tendering process according to the lowest price offered, but also because since antiretroviral medicines have been guaranteed by law (Law 9.313 of 1996) domestic companies foresaw a potential that allowed them to invest in technological learning in antiretrovirals, despite competition based on low prices. In addition, Brazilian public laboratories that are committed with public health policies entered this segment supplying finished medicines at low costs based mainly on imported inputs from India and China. But the enforcement of intellectual property rights after the Law 9.279 has pointed to limitations for the program sustainability, since the public procurement law obliges the government to purchase products that are exclusive, like patented medicines, from the original manufacturers 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 negotiating price reductions with pharmaceutical companies systematically. In those negotiations, the Brazilian government, taking into account the capabilities of local companies in antiretrovirals, has signaled the possibility of applying compulsory license, based on Art.71 of the Law 9.279 according with TRIPS Art.31(b). However, given the recent changes in the Brazilian procurement policy regarding antiretrovirals, it has been discussed the extent to which this ‘compulsory license’ is actually a credible threat, especially due to the reliance upon importation of active substances from China and India that will be subject to TRIPS after 2005 (Hasenclever, 2003).

In the light of the discussion about the impact of TRIPS over access to medicines, WTO members signed at the IV Ministerial Conference in Doha (Qatar) in November 2001, the “Declaration on the TRIPS Agreement and Public Health” (WTO, 2001), generally referred as Doha Declaration. The main objective of that declaration (Paragraph 6) is to assure that countries can adopt any measure in order to protect public health. According to TRIPS Art.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). Two important issues have been discussed after the Doha Declaration agreement on TRIPS and Public Health involving the attempt of developed countries to limit the type of diseases that would fall under the Declaration, and the countries to which provisions would apply. Such limitations were rejected by developing countries, mainly concerned with those countries – especially least developed ones – without manufacturing capabilities in pharmaceuticals to apply compulsory license (CIPR, 2002). In 2003, at the end of the V Ministerial Conference in Cancún, WTO members agreed to facilitate importation of “cheaper

---

16 For a discussion about the implications of this, as well as the current brazilian institutional environment regarding regulation of pharmaceuticals in Brazil, to technological and industrial development see Hasenclever (2003).

17 In the case of India, patent applications filed between 1st January 1995 and 31st December 2004 will be examined under the new law, according to the TRIPS provisions in 2005. A very simple example would be the case of the GlaxoSmithKline antiretroviral Combivir™, if a patent application had been filed, it is still uncertain if it will be issued (MSF, 2004).

18 Recently the government passed a decree allowing the importation by the government of medicines produced elsewhere through compulsory license based on Art.71 of the Brazilian Patent Law.

19 The Doha Declaration, however, contains declarations and decisions concerning other issues besides public health.

20 A major concern was related to the avoidance of parallel imports by rich countries. Parallel imports refer to the exportation of products protected by patents without the patent holder permission. The rationale behind this 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 in the TRIPS the principle of exhaustion can be subject to dispute only if “fundamental principles of non discrimination are involved” (WTO, 2003).
generics made under compulsory license if they are unable to manufacture medicines themselves 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 could import generic medicines from other countries producing them under compulsory license, and hence the limitations of the TRIPS art.31(f) were waived for exporting countries. This Decision does limit which countries could use the system. However, a group of 23 countries voluntarily announced that they won’t use the system to import, while 10 other countries about to enter the European Community said they would use the system in cases of national emergency only and before entering the EC; and another 11 countries said they would use the system only in cases of national emergency. A priori, least developed countries don’t have manufacturing capabilities in pharmaceuticals and thus eligibility to use the system, but other countries are also eligible, except those 23 countries that indicated they won’t use the system. To become eligible a country must communicate the WTO affirming the non existence of local capability, or that despite local capabilities, not taking into account the original manufacturer’s capability, these are insufficient to supply the demand. But according to the Decision, as soon as this capability is in place the system could no longer be used. In general countries agreed that this mechanism must be used only to protect public health, wouldn’t be used for commercial and industrial policy goals; there will be packaging systems in order to avoid re-exportation to rich countries at lower prices; and the adequate use of the system will be monitored by the TRIPS Council. Some NGOs have criticized this decision considering it a retrocession in relation to Doha, since it states that the provisions apply to problems recognized in Paragraph 1 of the Doha Declaration that emphasized “HIV/AIDS, tuberculosis, malaria and other epidemics”. But it is worthy to remember that Doha Declaration does not limit the type of diseases (CIPR, 2002).

Summing up, while it was being discussed the implications of the TRIPS to public health, that has important implications for developing countries in respect to capacity building in the pharmaceutical sectors, it was also being discussed the compliance of the TRIPS and the CBD. Thus the Doha Declaration established also that the TRIPS Council would have to examine the compliance of the TRIPS provisions and CBD recommendations. This is supposed to be discussed in the next WTO Ministerial Conference. According to specialists, while the CBD objectives are to promote conservation and sustainable use as well as promote access to technology transfer, the rationale of strong intellectual property rights, assuming a more rigid form in the TRIPS is to limit access to technology. Besides, the CBD interprets genetic resources as phenotypes while the TRIPS interprets them as genotypes. Another important issue is related to the protection of traditional knowledge. This kind of knowledge cannot be protected by patents because it is not possible to attribute novelty and non-obviousness

---

21 The 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”.

22 Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Island, Ireland, Italy, Japan, Luxemburg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United States, United Kingdom.

23 Czech Republic, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia.

24 Hong Kong, China, Israel, Korea, Kuwait, Macao China, Mexico, Qatar, Singapore, Chines Taipei, Turkey, United Arab Emirates.

25 In 2000 the WIPO created the Intergovernamental 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 until the writing of this work there has been little advance in this regard.
criteria, and it is also not recognized as pre-existing art unless it has been published elsewhere\(^{26}\) (Strauss, 2000).

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

Another important question related to access to biological resources and intellectual property is the issue about neglected diseases. In the decision taking process in drug development by pharmaceutical firms substantial attention is paid to the market potential, from the point of view of purchasing power of potential consumers (either individuals or governments) and, second, from the point of view of the disease’s prevalence. These aspects have led to the identification of a group of diseases considered “neglected” or “orphans” due to the underinvestment in R&D efforts directed towards them, given the lower purchasing power of the affected population\(^{27}\) and lower level of prevalence\(^{28}\). According to the International Federation of Pharmaceutical Manufacturers, representing 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 supporting the hypothesis that the enforcement of intellectual property in developing countries has any effect upon research-based pharmaceutical companies in respect to R&D for diseases prevailing in developing countries, except for those diseases that 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 billions, concentrated in developed countries; leading pharmaceutical companies have been responsible for the largest part of sales.

In the early days of the pharmaceutical industry in the XIX century, the development of medicines was based mainly on plants and animals extracts for the preparation of fluid extracts (tinctures and syrups) powder and solid extracts (pills or tablets), and was founded upon knowledge about 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 in place, most products had no proven efficacy and many of them were simply not effective. In the first half of the XIX, with the development of pharmacology and organic chemistry it

\(^{26}\) It has been discussed the possibility that traditional knowledge may be protected by a sui generis intellectual property regime. But even here there is no consensus yet.

\(^{27}\) This is the case of most diseases prevailing in developing countries (e.g.: malaria, leishmaniasis), except those also prevailing in developed countries and with great market potential (e.g.: cardiovascular diseases, diabetes).

\(^{28}\) Developed countries have established comprehensive lists of diseases that are considered neglected and provided mechanisms to stimulate R&D (Meyers, 1997).
became possible to isolate the active substances of plant extracts, identify the mechanism of action of some compounds, and develop medicines based on those active substances (mostly alkaloids). In this same period, advances in chemical synthesis allowed obtaining synthetic dyes; the development of bacteriology changing the base of knowledge about certain diseases; and the founding of the chemotherapy paved the way for the development of synthetic medicines stemming from synthetic dyes in the early XX century. At the end of the 1920s, the discovery of penicillin, manufactured at 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 at world level. Since the 1930s, but mainly since the Second World War, efforts by pharmaceutical companies, which became the locus for product development, were directed towards the search for synthetic compounds and/or full or partial synthesis of actives 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 compounds design process, based on chemical libraries developed along time by pharmaceutical firms during the search for synthetic drugs or drugs based on natural sources (Drews, 1998).

Despite the general trend of pharmaceutical companies to look for synthetic compounds, according to Cragg et al. (1997) from 520 new drugs approved either in the United States and other countries between 1983-1994 reported by the “Annual Reports of Medicinal Chemistry”, 28 were biological products, that is large molecules (vaccines, monoclonals, etc. derived from mammalian sources); and 492 were small molecules, of which 30 derived from a unmodified natural product source; 127 derived from a natural product (e.g. semi-synthetics); 46 derived from a synthetic source but originally modeled on a natural product parent and 289 were exclusively from a synthetic source. This means that from the 492 small molecules drugs, 41.26% derived from natural products. In respect to the therapeutic classes addressed, 64 were antibacterials and 31 were anticancer medicines; of which 78% of antibacterials and 61% of anticancer medicines either derived from natural product (modified or not). Newman et al. (2003), updating these data including records from the “Drug News and Perspectives” observed that between 1981-2002, from 1.031 new chemical entities only 33% were fully synthetic medicines; 23% derived from a natural product (usually a semi-synthetic medicine); 10% 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% derived from a unmodified natural product source; the remaining 15% biological products. In respect to the therapeutic classes, there were 159 anti-infective medicines (90 antibacterial, 23 antifungal, 13 parasitic and 33 viral), of which only 30.2% were fully synthetic medicines; and 65 anticancer drugs, of which only 26% were fully synthetic.

It also important to note that according to Young (1999) modern biotechnology have allowed obtaining medicines based on natural products with lower adverse effects, as illustrated by the case of ergotamine. Between the XVIII and XIX centuries, ergot extracts (obtained from the mold that grows in rye, *Claviceps purpurea*) were used for pain relief after child labor and for headaches. In 1918, Arthur Stoll synthesized the ergotamine tartar, marketed by Sandoz as Gynergen®, and indicated for bleeding control after child labor. Between the 1920s and 1930s ergotamine began to be used also for migraine. In 1943 Stoll synthesized another drug derived
from ergot$^{29}$, the dihydroergotamine, marketed by Sandoz as Dihydergot® or Orstanorm® for migraine. Along 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®. Therefore, in general, in the search of active substances, pharmaceutical companies involved in R&D activities have 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’ method of screening molecules against therapeutic targets) to rational drug design, aiming at overcoming an important obstacle in drug development since most compounds don’t reach the market either because they were tested against “wrong” therapeutic targets or because of unexpected adverse effects. With rational drug design, the challenge became to identify the relevant drug targets in the diseases mechanisms that would make R&D investments worthwhile. The development of combinatorial chemistry in the 1990s, opened the possibility to design molecular structures more rapidly, based on existing chemical libraries; and 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 increased considerably the number of potential therapeutic targets, opening new possibilities for the search of active compounds, although the discovery of therapeutic targets does not necessarily means new drug targets (Rates, 2001; Montanari and Bolzani, 2001; Moore, 2003). Thus since the 1990s, many pharmaceutical companies withdraw from natural products research, directing efforts to combinatorial chemistry and partnerships with biotechnology companies (Cragg et al., 1997). After identifying the drug target, the drug discovery process is followed by the ‘design’ of the appropriate molecule structure, and after this with the help of computational techniques; real chemical structures are looked for in the chemical databases (Rates, 2001; Montanari and Bolzani, 2001).

In the case of the search of fully synthetic compounds it has been observed that the promise of combinatorial chemistry to increase the number of new chemical entities introduced by pharmaceutical firms have not realized yet. This is based on the fact that there has been an innovative deficit in the pharmaceutical industry since the end of the 1990s (Drews e Ryser, 1996; Drews, 1998b; Class, 2002). Different reasons have been pointed out for this shortcoming such as: 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 would be a relatively new technology (Rouhi, 2003a). Another reason for the lower productivity levels in terms of new chemical entities introduced has been related to the exit of pharmaceutical of natural products research, since high-throughput screening techniques needs greater molecular diversity, found mainly in natural sources (Cragg et al., 1997; Newmann, 2003; Rouhi, 2003a).

---

$^{29}$ Between the late 1930s and the 1970s, Sandoz developed other two medicines based on ergot: metisergide (Deseril®), and bromocriptine (Parlodel®) (Tepper, 1997)
In respect to natural products research, it is necessary to distinguish between the potential for the development of pharmaceuticals, and the potential for the development of exclusively natural medicines. In the case of research in plant extracts, one might distinguish the research aimed at obtaining unmodified isolated active compounds or obtaining active compounds with unknown structures according to the state of art as leads to obtain new chemical entities by synthetic or semi-synthetic routes; from 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 for the search of medicinal properties. This can be done through different, but not mutually excluding, strategies: ethnomedical knowledge, such as traditional knowledge or knowledge about uses of medicinal plants by organized systems of traditional medicine; data bases such as the NAPRALERT; random collection followed by one or more bioassays or chemical screening; and or ethnobotanic knowledge (Fabricant and Farnsworth, 2001). After this, it is necessary to assure an appropriate botanical characterization and register time and place where the sample was collected, and then followed by stabilization procedures. Then, the material must be transformed into powder and subject 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 active plant extract, which is then submitted to bioassays (using microorganisms, mollusks, insect, 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 the isolation in large scale (sometimes it is necessary to collect samples again) in order to begin pharmacological evaluation in pre-clinical, toxicological and clinical trials. Despite the complexity involving screening of medicinal plants and that secondary metabolites, the focus of research of pharmaceutical companies, are not produced by plants in sufficient amounts from the 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 would be re-directing companies still involved in natural products research to the search for drug leads in other biological resources (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 through exposing the crude extracts to therapeutic targets, and in the case of evidence of biological activity, then fractioning and isolation of the active compound was pursued. This was a relatively lengthy process, labor intensive and more expensive in relation

---

30 According to Harvey (2000), it has been observed that natural products that are biologically active are generally small molecules with drug-like properties. This would mean lower costs in drug development for biotechnology products or natural products making use of combinatorial chemistry techniques.

31 The most known example is that of the US company Shaman Pharmaceuticals, created 1989, whose strategy for the search of biologically active substances was based on traditional knowledge of healers or shamans from indigenous communities in South America (basically Brazil and Argentina). In the beginning of the 1990s, Shaman had two medicines undergoing clinical trials (Blum, 1993). However Shaman encerrou as operações in 1999. According to analysts one of the reasons was that the company was not able to introduce any medicine into the market after failures at 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 yet well skilled in the drug approval process like large pharmaceutical companies (Moore, 2003).

32 Such as the Ayurveda in India and the Traditional Chinese Medicine.

33 Generally the industry tends to focus in chemical screening, and universities and research institutes in biological assays (Fabricant and Farnsworth, 2001).
to the possibilities opened by combinatorial chemistry. Besides it was not possible to assure whether the lead drug would be chemically workable or patentable, especially after the 1990s due to the discussions involving the TRIPS and the CBD. This has also been pointed as a reason for the withdrawal of some pharmaceutical companies 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 above methods), is followed by drug development that involves changes in the chemical structure of the lead molecules (in order to obtain analogues more potent, less toxic, with small structures, and if possible a new mechanism of action), pharmacological tests in animals and safety studies. Pre-clinical tests (biological and pharmacological) use laboratory animals, cell culture or cell tissue culture, enzymes etc., in order to evaluate toxicity, bioavailability, and pharmacokinetics. Along pre-clinical trials it is necessary to decide which compounds are most likely to become drug candidates in order to pursue Phase I, II, III IV clinical trials\(^{34}\) in human beings; these trials involve higher costs and complex structures, and take around seven years (Hilleman, 2002). This may seem a linear process, however pharmaceutical R&D is not a linear process.

In respect to R&D costs of a new medicine\(^{35}\), in early 1990s estimates varied between US$ 65 millions and US$ 231 millions for each new chemical entity (OTA, 1993). Since the mid 1990s estimates have varied between US$ 500 millions and, more recently, US$ 800 millions as claimed by the industry (PhRMA, 2004). Historically, most of these phases have been realized 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, mainly in the US (Gambardella et al., 2000). Some pharmaceutical companies do also contract out the manufacturing of intermediates (McCoy, 2002).

Going back to the issue related to the attractiveness of natural products research, as observed previously while some pharmaceutical firms have shutdown their respective research centers in natural products (e.g.: Abbott, Pfizer and Bristol-Meyers Squibb), others are still investing in this area (Merck & Co., Novartis, Bayer, and Wyeth) either through in house facilities or in partnerships with botanical gardens, universities and research institutes, small biotechnology companies located mainly in developed countries, and in less degree with institutions located in developing countries. Some companies, like Eli Lilly, have licensed their natural compounds libraries to small specialized biotech companies and making joint R&D agreements. As a matter of fact, R&D agreements between pharmaceutical and biotechnology companies have been a characteristic of the sector since the emergence of modern biotechnology. This has been a two-way relationship, since the greater obstacles in drug

\(^{34}\) In general, it is considered the FDA standards. According these standards 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 along approximately 18 months. Phase II clinical trials are intended to determine the medicine effectiveness in around 100-500 volunteer patients along approximately two years. In Phase III trials the medicines is administered to around 1.000-5.000 volunteer patients along almost three years and half. After Phase III companies can fill a New Drug Application (NDA) for commercialization approval by the FDA. After the medicine is introduced in the market, companies generally submitt approved medicines to Phase IV in which they explore new uses, and long term effects for a given medicine (Hilleman, 2002).

\(^{35}\) Estimates of R&D costs is a controverse issue. In general, companies claim that patent protection is fundamental so that they can recoup high R&D investments that tend to increase each year, and given that the number of new chemical compounds screened are higher than the number of new chemical entitities introduced into the market. But is important to observe that according to Drews (1998a) marketing costs (around 38% of sales) are higher than R&D costs (14%-20% of sales).
development have been the drug approval processes for new chemical or biological entity and marketing. This has been a major obstacle for small biotech companies working on scientific edge. On the other hand, large research based pharmaceutical companies have been pressured by stockholders and increasing competition to increase productivity levels and the number of new products introduced. Since combinatorial chemistry hasn’t led to the expected increase in productivity yet and neither the subsequent mergers and acquisitions, and that a great part of the newer drugs are biotechnology drugs, pharmaceutical companies are also willing to establish partnerships with biotech companies (Moore, 2003).

In the case of the biopharmaceutical companies, several companies specialized in natural products research have been created such as: Phytobiotech; Microbotanica; PharmuMar; Ecopharm; Ecopia Biosciences; Diversa; Microgenomics; Ambergene; Terragen Diveristy; Ariad; Oceanix; Aquaculture Technology; and Kozan to name a few. It also important to not the foundation of bioinformatic firms specialized in databases and screening techniques such as AnalytiCon Discovery (Shu, 1998; Young, 1999; ten Kate e Laird, 1999; Newmann, 2003; Rouhi, 2003c).

Despite the trend of withdrawing from natural products research by pharmaceutical companies due to technological and economic factors, and higher uncertainties regarding the international institutional environment, the difficulties in increasing the number of new chemical entities through combinatorial chemistry, the complexity involving the scaling up biotechnology drugs may change this scenario. The most likely explanations for the revival of natural products research among pharmaceutical companies would be: the intrinsic utility of natural products; the greater diversity they offer and hence can fulfill the needs of expensive high-throughput screening technologies; advances in separation technology, speed and sensitivity in structure elucidation that have allowed overcoming several bottlenecks in natural products research as sources of new drug leads, such identifying biologically active molecules in small samples at low levels (Borris, 1996; Giddins et al., 2000; Montanari and Bolzani, 2001; Pinto et al., 2002; Rajasekharan, 2002; Rouhi, 2003a). Companies and research groups still involved in natural products research have pursued three main strategies: combining the diversity of natural products and the potential of combinatorial chemistry: building around natural products scaffolds using combinatorial chemistry, assembling natural-product-like compounds through synthesis and creating new natural products derivatives (Newmann et al., 2003; Rouhi, 2003d). And, as already observed above, despite the complexity involving natural products research, new medicines based on them have been introduced into the market (Nisbet e Moore, 1997; Cragg et al, 1997; Shu, 1998; ten Kate and Laird, 1999; Young, 1999; Newmann et al., 2003).

In respect to engagement in natural products research for the development of new chemical entities, developing countries face great obstacles. Most of them don’t have industrial and technological capabilities neither in finished medicines nor fine chemical (active compounds or intermediates). Only a small group of countries have manufacturing capabilities of inputs and finished medicines by domestic integrated companies and several small, specialized fine-chemical companies (like India, Korea and China). In other countries like Brazil, Mexico and

---

36 Eisner (2004) observed that the exit of pharmaceutical companies of natural products research (consequently reducing hiring natural products chemists), combined with the fact that for many chemists, natural products chemistry is no longer seen as priority in the chemical field and considered by many others as routine, and that the teaching of natural chemistry may disappear in some universities because of this, create several challenges in the near future for drug discovery (Eisner, 2004).
Argentina, fine-chemical companies are struggling to survive due to several reasons, and imports of finished medicines have been rising recently. Despite those differences, developing countries, as a whole, are highly dependent on products developed by leading multinational companies, and only a small number of firms have begun recently to invest in R&D for new product development. This does not mean that those countries should not devote efforts to enhance and strengthen technological capabilities in pharmaceuticals, on the contrary. These countries must take these issues seriously, especially those regarding partnerships with research-intensive companies interested in access biological resources. It is fundamental to ensure that access to those resources result in technology transfer, and create incentives for future technological development, and not only economic returns per se. These countries must also observe that most pharmaceutical and biotechnology companies are not directly involved in collecting samples (some of them have natural compounds libraries prior to the CBD), 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 foreseen in anti-infectives, since as observed above, most of the anti-infectives (especially antibacterials) introduced since the 1980s have been based on natural products. However, anti-infectious diseases, which are one of the leading causes of death in the world, cover a wide spectrum of diseases like HIV/AIDS and other diseases with lower market potential like malaria. In the anti-infectives segment, antibacterials may be an opportunity for developing countries since pharmaceutical companies are exiting the segment, and 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 e 2003; Schuster 2001; Newmann et al., 2003). Besides, as pointed out above, most antibacterials have been based on medicinal plants, and only a small percentage of plant species have been studied for therapeutic effects. Hence developing countries, like Brazil (holding 22% of all plant species in the planet) may benefit from this window of opportunity. But it has to be considered that regulatory agencies, like the FDA, have imposed several requirements for the approval of new antibacterials, especially efficacy in relation to current medicines (Projan, 2000 and 2003).

However, the potential of medicinal plants is not restricted to 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 years, especially in developed countries that are the world largest pharmaceutical markets. Gruenwald (1995) estimated that in 1994 the world market for phytomedicines were around US$ 12.4 billions, and European Community countries accounted for almost 50% of this, Asia 35% and United States 11%. It was estimated that in the year 2000 the world phytomedicines market were around US$ 22.3 billions (almost 13% annual growth rate), Europe was still the largest market (35%), Asia accounted for 28%, and the United States increased it share accounting for 18% of the total (Hong Kong Trade Development Council, 2002).

It is important to observe that it takes from 2 to 5 years to develop a new phytomedicine and around US$ 2 millions to US$ 5 millions, that may lead to products with synergic effects 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 since 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 they are not inventions. Nevertheless, to enter the phytomedicines segment with competing products of already marketed medicinal plants, costs are basically those involved in product registration and commercialization. But countries differ widely in this respect; some have considered phytomedicines as medicines, others as dietary supplements or nutraceuticals; depending on the medical claims made (Iwu, 1998; ten Kate and Laird, 1999; Rajasekharan, 2000; Yunes et al., 2001; ABIFITO, 2003).

Thus, depending on the country and how it regulate product commercialization, the “newness” of the phytomedicine and the claims made, registration may begin with clinical tests, toxicity, safety, pharmacological and biochemistry tests. Following the recommendations of the WHO some countries have used traditional knowledge as an element for product registration, while others developed specific and stringent regulations like the European Union and Canada. In EC countries\textsuperscript{37}, phytomedicines are considered medicines, but each country differs in respect to the requirements. Recently the European Community established guidelines for the phytomedicines, and in general it is necessary to comply with Good Manufacturing Practices; clinical, toxicological and pharmacological tests and present related scientific literature (ten Kate e Laird, 1999; WHO, 1999; Hong Kong Trade Development Council, 2002). On the other hand in the United States, a phytomedicine making no therapeutic claims can be registered as a dietary supplement, otherwise it is subject to the same requirements for pharmaceutical products. According to the Food and Drug Administration (FDA) regulation until 1994 phytomedicines were considered food additives and the company had to prove they were safe. If there was any therapeutic claim then it was considered non-ethical medicines and companies had to present a monograph or to apply for a registration of ethical medicine. In 1994, the FDA created a new category, the dietary supplement, that are \textit{a priori} assumed to be safe and the burden of proof now belongs to the FDA. Although the FDA have been systematically supporting assurance of product safety and efficacy\textsuperscript{38}, the North-American dietary supplements market is loosely regulated\textsuperscript{39}, and most products sold are not effective and may even cause harm due to toxicity or interaction with other medicines (Chase, 2003; Milot, 2004).

In developing countries there are also differences regarding regulation of phytomedicines. In Argentina, for example, there is no distinction among medicines in respect to their origin (natural or synthetic) but since there is a certain autonomy level at provinces, in Buenos Aires there is a specific regulation for medicinal plants since 1993. In Chile, natural products can be registered as “food” or as medicines depending on the claims of therapeutic effect. In the case

\textsuperscript{37} After the creation of the European Community in 1989 it was created the European Scientific Co-operation on Phytotherapy (ESCORP) responsible for the elaboration of monographies about products characteristics to serve as basis for phytomedicines registration, and as way to harmonize regulation of those products among EC countries, and to estimate the introduction of phytotherapy among physicians. For the Hong Kong Trade Development Council (2002), the requirements imposed by the EC regulation have resulted in the excluído of several products used in the Traditional Chinese Medicine. So that most Chinese companies are registering products as nutritional supplements in EC countries..

\textsuperscript{38} This can been seen through the recent determinations of the FDA taking out of the market several products containing specific substances like ephedrine. Currently, the FDA is discussing new regulations concerning GMP and the possibility to enquadrar phytomedicines in the non ethical group.

\textsuperscript{39} Differently from non ethical medicines, dietary supplments cannot use phrases like “effectively proven” or “recommended by doctors” in labels, but only the structure and functions and state the product is not intended to cure, prevent or diagnose.
of any medical claim the product is considered as a medicine and therefore subject to the same requirements of synthetic medicines. But, in the vast majority of developing countries there is no specific regulation for registration 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 plant) and bulk (alkaloids, glycosides and derivatives). In these segments, traders play the major role and they are based in New York, Hong Kong and Tokyo. The crude drugs segment is a low added value, according to the UNCTAD records exports in 2002 totaled US$1.03 billions, 70% of which concentrated in 10 countries (49% in developing countries and 21% in developed countries), and imports totaled US$ 1.23 billions, 63% of which concentrated in 10 countries (38% in developing countries and 25% in developed countries). In the bulk world trade, with higher added value, exports in 2002 were estimated in US$ 2.67 billions with 10 developed countries responding to US$230 millions; and imports were estimated in US$ 3.12 billions with 10 developed countries responding to US$ 2.23 billions.

Taking into account the differences in regulation, that phytomedicines are not patentable and the increasing competition among world leading companies based in developed countries, these companies have concentrated efforts in existing products, since there is already a learning curve effect and their use are less controversial, especially from the point of view of regulatory agencies. Thus, developing countries could stimulate new product development since a small share of all plants have been described and an even smaller share of them has been studied for therapeutic effects. In this sense, they should stimulate the introduction of better cultivation practices, but also improvement and search of high yielding medicinal plants increasing the value of crude extracts; stimulate GMP in the production of finished phytomedicines. These countries should also take into account the competition dynamics at world level and the incentives and disincentives in new product development.

---

40 Here it is important to mention the entry of some big pharma through acquisition of major European phytomedicine companies (Ferreira et al., 1998).
2. Discussion

Along the evolution of the pharmaceutical industry it is possible to identify other windows of opportunity that offer an interesting contrast to this study, such as the development of organic synthesis and pharmacology in the turn of the XIX century and the development of antibiotics with penicillin.

Organic synthesis emerged in 1828 after the synthesis of urea by Friederich Wohler, and pharmacology in 1847 when Rudolf Buchheim was designated for this chair at the University of Dopat (Estonia), although there were pharmacological studies on certain plants and their alkaloids since the beginning of the XIX century. In this case it is illustrative the development of a chemical industry, basically organic chemistry (particularly dyestuffs) in some German states (before economic unification in 1872), which allowed Germany after unification to displace France as the locus of new product development in the emerging pharmaceutical industry, combined with other elements placed Germany as the leading country in the industry until the II World War. Among the factors that contributed for this there were: government policies directed towards the development of a chemical industry as one of the basis to compete with England and France, investments in science and technology infrastructure, particularly the establishment of technology institutes, which beside a locus for knowledge production were supposed to support industrial and technological development efforts through close interaction with companies; and the fact that until 1940s the German patent law offered protection only for pharmaceutical processes (Liebenau, 1985; Weatherall, 1990; Achilladelis and Antonakis, 2001).

In antibiotics, it is illustrative the case of the United States that as many other countries were dependent upon pharmaceutical products developed by German companies until the II WW. Along the first half of the twentieth century, one can observe permanent concerns of the US government regarding the dependence of the emerging North-American chemical industry upon products developed by German companies, especially in the case of pharmaceuticals. The US case deserves a careful analysis. In general, the role of regulation is pointed out as the main driver for the development of a research based pharmaceutical industry in the United States. However, the establishment of subsidiaries of German companies – since the end of the XIX century – also contributed to this development, mainly during the interwar period through the expropriation of German patents and industrial facilities that were sold to US companies that managed to create dominating positions in the domestic market driving out smaller companies and becoming large manufacturers (in this case the role of government purchasing power and regulation did play an important role). It did also played an important role the expropriation of German patents during the WW II, when the US pharmaceutical industry had become able to exploit the knowledge disclosure in patents, something that was relatively difficult in the I WW, due to deficiencies in the teaching of chemistry in the US, and lack of knowledge in the patenting process. These difficulties were progressively overcome with large investments in science and technology especially in the university system and government institutes, and the institutionalization of R&D in some US pharmaceutical companies, initially in order to address changes in the regulatory environment but also after the experience with patent expropriation in I WW. All these allowed the mobilization of US pharmaceutical companies to produce penicillin in large scale to respond to war efforts. So that after the 1940s, but mainly after the 1950s, the US not only caught-up with Germany but displaced her consolidating an industrial leadership position in the pharmaceutical sector, based not only in
R&D efforts by companies but also by investments in health research through the National Institutes of Health since 1930s. (United States, 1919 and 1929; Young, 1961; Liebnau, 1985; Temin, 1980; Steen, 1998; Swann, 1995; Achilladelis and Antonakis, 2001).

Thus, the cases of Germany and the United States show that the analysis of the possibility of benefiting from windows of opportunity in the pharmaceutical sector must take into account the following elements: the structure and dynamics of industry evolution and competition at national and international levels; market potential; regulation policies regarding prices and registration of products; science and technology infrastructure; and the interrelation of these factors and system of intellectual property rights, incentives to R&D; as well as industrial and technology policies, and dynamics of competition among nation states.

2.1 The Brazilian Case

The emergence of a pharmaceutical industry in Brazil seems to have followed the same pattern observed in the United States: the manipulation and marketing of plant and animal extracts and imported medicines. However, it is also possible to observe few cases in which the emergence 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. But 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 found to have also therapeutic effects. In Brazil however, most pharmaceutical laboratories with technological capabilities according to the state of art of the late XIX century (that is isolation of alkaloids for manufacturing of medicines) did not survived the turn of the century, for different reasons. But the pharmaceutical industry emerged in Brazil in the XIX century when the country’s economy was based on exportation of primary products based on slavery system. Thus there was a mismatching between the political, economic and institutional requirements of industrial entrepreneurship and the Brazilian primary-exporting periphery economy insertion pattern. In the US, on the other hand, the industrial structure was more consolidated, the development of a scientific infrastructure was devoted to narrow the technological gap in relation to Europe and public policies intended to promote national industry. Also, foreign companies or traders used to offer more favorable credit terms to retailers and druggist compared to local producers with the same quality, especially in the interwar period; physicians also began to prefer to prescribe foreign medicines. Besides, while the pharmaceutical industry emerged in Brazil between the end of the nineteenth and twentieth centuries, the first initiatives in the chemical sector seems to have happened only after the mid 1950s and mostly after the 1970s (Fontoura, 1938; Scheinkmann, 1965; Bertero, 1972).

At the end of the century, the situation of the emerging Brazilian pharmaceutical industry was not very different from that observed, for example, in the United States in terms of products and technological capabilities. But, while some North-American companies seemed to have been able to make the transition from artisan or semi-industrialized production of medicines based upon plant extracts to chemical synthesis and industrial scale, Brazilian firms seems to have not been able of making the required investments and also of disposing of qualified

41 According to reports from the US Department of Commerce, European companies offered special credit terms for some retailers and druggist as a marketing strategy. This same report observed that North-American manufacturers could offer the same conditions in order to entry the Brazilian pharmaceutical Market (United States, 1914 and 1932).
human resources, a scientific infrastructure and specific government policies like did US companies in the first half of the XX as already mentioned (Bertero, 1972; Frenkel et al., 1978).

Another relevant aspect is that patent protection for pharmaceutical products was abolished in 1945 through the Decreto-Lei nº 7.903 (27/8/1945). But this prohibition did not apply to “to new process 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 of the Brazilian pharmaceutical companies with greater technological capabilities had already been acquired by foreign companies in the first half of the twentieth. The entry of foreign pharmaceutical firms into the Brazilian market – first German and French but also North-American – was initially based upon importation but then some companies began to produce locally, especially in the 1930s and after the 1950s, through the acquisition of local producers, basically those that were more technologically dynamic but that could not make the transition to chemical synthesis. Also, the industrial and technological development of the chemical industry was not systematically addressed by the Brazilian government public policy agenda until the 1970s. While after the 1950s most of the demand for finished medicines had been supplied by local production, the country was dependent upon importation of compounds and knowledge produced outside the country necessary to follow, or even lead, technological change (Scheinkmann, 1965; Frenkel, 1978).

Between 1950s-1970s different factors were pointed out as the most likely explanations, either for its absence or inadequacy, for the dependent character of the Brazilian pharmaceutical industry in the dynamics of the world pharmaceutical sector: lack of human resources; effects of socioeconomic conditions; incipient development of chemical sciences; non existence of correlated industries; lack of government policies, like those put forward by Germany and US that allowed them to establish industrial leadership positions; weak linkages between companies and universities; and the emergence of large integrated firms competing at world level that resulted into an international division of productive and innovative labor between developed and developing countries (Scheinkman, 1965; Bertero, 1972; Frenkel et al., 1978).

In the Brazilian case, in the 1970s the structure of the pharmaceutical industry acquired one of its current main features: more than 75% of the domestic market dominated by multinational firms accomplishing only formulation that is the last phase of production of pharmaceuticals (Bermudez, 1995).

But in the 1970s the Brazilian government implemented some policies intended to foster the development and to narrow the technological gap in the pharmaceutical sector, among which: the exclusion of pharmaceutical process and products of the Patent Law of 1971 (12/21/1971); the creation of the “Central de Medicamentos” intended initially 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, also in chemicals and pharmaceuticals; and programs for the development of science and technology infrastructure in the 1970s and in the 1980s. However, although successful in some areas, the Brazilian pharmaceutical industry remained dependent upon importation of raw materials, specially active substances, and also dependent upon knowledge produced elsewhere confirming the country’s marginal role in the international division of productive and innovative labor of the sector.
After the 1990s the Brazilian pharmaceutical industry experienced significant changes in its structure: opening of the Brazilian economy; the end of price control in 1990; a new Patent Law n.9279 in 1996 reintroducing pharmaceutical process and products patent protection; the effects of subsequent mergers and acquisition at world level in their location strategies in developing countries; and the introduction of a specific law regulating the market for generic medicines. The market liberalization had major effects like a sharp increase of importation of active principles after 1990, the dismantling of the existing Brazilian fine chemical industry, and recently also an increase in importation of finished medicines, and more recently of finished generic medicines (Hasenclever, 2002). In relation to intellectual property rights, differently from the other developing countries, Brazil introduced changes in its intellectual property regime prior to the 2005 deadline, and also allowed for pipeline protection for patent applications filed between January 1995 and May 1997. Since the Law 9.279 most of the pharmaceutical patents issued by the Brazilian National Patent Office (Instituto Nacional de Propriedade Intelectual, INPI) has been granted to non residents (Bermudez et al., 2000). In the case of the effects of merger and acquisitions of leading companies, some of them decided to transform their domestic operations — production or packaging of finished medicines — into an exportation platform for other Latin American countries; and others decided to keep only the marketing activities or to license products to Brazilian companies. In the case of the generic medicines, before 1999 there were 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. But in 1999, the government passed the Law 9.787 introducing the generic medicines and specific norms regarding product registration. The main objective of the Brazilian government was to lower price of medicines that were not protected by patents introducing greater competition since generics are not marketed under brand names and are sold at lower prices. However, in these first years it has been seen is a substitution effect within the higher income classes and not necessarily an expansion of access to medicines by lower income classes (Hasenclever, 2002).

So that at the end of the 1990s the situation of the Brazilian pharmaceutical industry was not much different from that observed in the previous decades: 75% of the national market, which registered US$ 4.2 billions in 2003 in retail sales, is dominated by a small number of large foreign companies (around 20) and 25% shared among around 380 medium and small size domestic companies. Regarding R&D efforts, either Brazilian or foreign companies invest very little in those activities, mostly in Phase III clinical trials; and 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 since the 1980s, the Brazilian government saw its investments capability to be reduced considerably affecting the programs mentioned above. In the 1990s the neoliberal economic policy of the first elected government after the dictatorship period (1964-1989), resulted in the end of industrial and technology policies. At the end of the 1990s, the government elected in 1994 created new mechanisms to stimulate science and technology in some sectors, among which biotechnology and the health sector, through specific funds based on grant applications. However, the Law implementing the biotechnology and the health sector research fund passed only at the end of 2001 and were regulated in 2002, but the first call for applications occurred only in 2003. But according resources have not been disbursed by the government. In the beginning of 2004 the government reintroduced industrial and
technological development in the government public policy agenda, and among the sector emphasized there were the fine-chemical and pharmaceutical industries.

2.1.2 The Brazilian Pharmaceutical Market and Medicinal Plants

In respect to the Brazilian market for medicines based on medicinal plants, Ferreira et al. (1998) observed that in 1994, from the US$ 3.831 millions registered in retail sales, 5.08% corresponded to medicines containing active substances of plant origin associated with active substances of a different origin; and only 3.19% were sales of medicines based exclusively on medicinal plants, i.e., they were phytomedicines; and the remaining 89.38% corresponded to synthetic medicines. From the total market, 25 companies mostly multinationals (there was only one national company and a joint venture between a national and multinational company) concentrated 76.36% of the whole market, and most of their product lines (94% of sales, in average) were comprised by synthetic medicines. In respect to the companies selling medicines with active substances of plant origin associated with other active substances, 25 laboratories concentrated 78.44% of this segment, and 11 (9 foreign companies, one national company, and a joint venture between a national and a multinational company) were among the leading 25 companies. In respect to the phytomedicines market, 25 laboratories concentrated 84.56% of this segment, 11 companies (9 foreign companies, one national company, and a joint venture between a national and a multinational company) were among the leading companies.

According to Ferreira et al. (1998) there are two kinds of companies in the Brazilian plant medicines market. The large companies whose medicines were basically pharmaceuticals that derived from medicinal plants that represented a small share of their sales, compared to synthetic medicines. These companies, irrespectively to their origin, considered this segment as marginal in relation to their product portfolio, but they showed a greater concern about complying with sanitary surveillance regulation and GMP. On the other side, there were the smaller laboratories, mainly domestic companies that concentrated sales in phytomedicines. These companies also invest very little in R&D, and partnerships with universities are exceptions. Recently, the Brazilian sanitary surveillance authority (Agencia Nacional de Vigilância Sanitária, ANVISA) introduced stringent regulations for the registration and commercialization of phytomedicines through the resolution RDC MS/SVS n.17 (11/19/1999) regarding chemical and pharmacological characterization of products. Nevertheless, according to Yunes et al. (2001), most of the phytomedicines manufactured in Brasil are based in the traditional use and not in results of pre-clinical or clinical researches.

Most recent data indicate that the Brazilian phytomedicines market in 1998 was around 5.5% of the total Brazilian pharmaceutical market (US$ 10.290 millions). It is estimated that in 2003 this market represented 6.7% of total sales, and that there are 293 companies operating in this segment (ABIFITO, 2003). According to Almeida (2003), it is estimated that this segment may account for around 10% of the total domestic pharmaceutical market in 2010. Such growth estimates are based on a survey among physicians by the Brazilian Association of Pharmaceutical Manufacturers (FEBRAFARMA) in 2002: 10% of the physicians interviewed used to prescribe phytomedicines, but 22.5% affirmed they intend to prescribe phytomedicines by 2010. Although Brazil holds more than 22% of whole existing plant species in the planet, from the 206 phytomedicines registered almost 89% were based on plants of European origin (ABIFITO, 2003).
Among the main obstacles for the development of a phytomedicines market in Brazil there are: i) the effects of the leading multinational companies focus on synthetic medicines, so that the growth observed in the world phytomedicines market will take longer to be observed in Brazil, including the greater interest of some multinationals (that recently acquired some of the world leading phytomedicines companies); ii) the low level of R&D investments, mainly due to the smaller size of those companies willing to invest in those activities in the country; iii) consequently, the potential for interaction between companies and universities is hindered, and that, in general, interaction between companies and universities is low; iv) low number of qualified human resources, and limited resources for training in existing companies; v) obstacles related to wild harvesting, quality of local crude extracts, storage, standardization and delays in the delivery of extracts; vi) and although the government have included the use of medicinal plants in the public health system since 1988, this is observed only in some Municipalities, and most of the population still associate medicinal plants to quackery. According to recent analyses, if those obstacles are not carefully addressed and overcome, in the medium and long term, the country may follow the same trajectory observed in the evolution of the synthetic medicines segment: foreign firms dominating the domestic market and the national companies operating 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 initiatives regarding interaction between national companies and universities are worthy to mention. 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 investments of around R$ 18.5 millions. This plant acts upon the central nervous system and could become a new medicine for Alzheimer. The other plant is coffee involving investments of around R$ 300 thousand (Panorama Brasil). The other company is Natura, whose main business is cosmetics and entered the phytomedicines market through the acquisition in 1998 of the company Flora Medicinal (founded in 1912). Natura introduced recently a phytomedicine Viriliflora™, for sexual malfunctions (Exame, 2001). Last, it is important to highlight the partnership between UNIFESP and the largest Brazilian pharmaceutical company (Ache) to study the medicinal plant known as ‘espinheira santa’ and that resulted in a patent filled by the 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’.

In respect to natural products research in Brazil, researchers located in Brazil have been responsible for 5.75% of all 9,312 articles published in leading indexed scientific journals from 1997-2001. Most of the articles were related to medicinal plants research

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochem. Syst. Ecol.</td>
<td>96</td>
<td>3</td>
<td>98</td>
<td>7</td>
<td>96</td>
<td>9</td>
<td>117</td>
<td>8</td>
<td>118</td>
<td>11</td>
<td>525</td>
<td>38</td>
</tr>
<tr>
<td>J. Ethnopharmacology</td>
<td>107</td>
<td>5</td>
<td>137</td>
<td>12</td>
<td>215</td>
<td>21</td>
<td>288</td>
<td>25</td>
<td>196</td>
<td>9</td>
<td>943</td>
<td>72</td>
</tr>
<tr>
<td>J. Nat. Prod.</td>
<td>339</td>
<td>4</td>
<td>338</td>
<td>11</td>
<td>452</td>
<td>12</td>
<td>441</td>
<td>5</td>
<td>404</td>
<td>9</td>
<td>1974</td>
<td>41</td>
</tr>
<tr>
<td>Phytochemistry</td>
<td>850</td>
<td>42</td>
<td>1118</td>
<td>67</td>
<td>710</td>
<td>37</td>
<td>564</td>
<td>56</td>
<td>447</td>
<td>45</td>
<td>3689</td>
<td>247</td>
</tr>
<tr>
<td>Phytochem. Anal.</td>
<td>52</td>
<td>7</td>
<td>47</td>
<td>2</td>
<td>54</td>
<td>4</td>
<td>59</td>
<td>7</td>
<td>66</td>
<td>7</td>
<td>278</td>
<td>27</td>
</tr>
<tr>
<td>Phytother. Res.</td>
<td>156</td>
<td>12</td>
<td>195</td>
<td>13</td>
<td>160</td>
<td>16</td>
<td>146</td>
<td>12</td>
<td>135</td>
<td>11</td>
<td>792</td>
<td>64</td>
</tr>
<tr>
<td>Plana Med.</td>
<td>188</td>
<td>10</td>
<td>240</td>
<td>11</td>
<td>241</td>
<td>10</td>
<td>211</td>
<td>10</td>
<td>231</td>
<td>6</td>
<td>1111</td>
<td>47</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1788</strong></td>
<td><strong>83</strong></td>
<td><strong>2173</strong></td>
<td><strong>123</strong></td>
<td><strong>1928</strong></td>
<td><strong>109</strong></td>
<td><strong>1626</strong></td>
<td><strong>123</strong></td>
<td><strong>1597</strong></td>
<td><strong>98</strong></td>
<td><strong>9312</strong></td>
<td><strong>536</strong></td>
</tr>
</tbody>
</table>

Source: Pinto et al. (2002).
In this regard, Brito and Brito (1993) identified in the beginning of the 1990, 53 research groups, and 11 in phytochemistry, 23 in pharmacology, and 5 in ethnopharmacology. In terms of scientific production, these authors analyzing 969 abstracts published from 1949-1989 in the most important national events observed that 402 different plant species (of 286 genera) were studied. Form the 402 species, only 106 were studied in terms of pharmacological activity, of which 11.1% were reported by authors to have toxicity effects; and less than 10% were studied in respect to chemical composition or involved isolation of active substances. From the abstracts reporting isolation of active compounds, it was reported the identification of 93 compounds. According to the authors, this results show that there is little interaction between chemists and pharmacologists, and that most studies have focused on confirming the traditional use of medicinal plants, but very few directed efforts to isolation of active compounds that may lead to new medicines.

According to Elizabetsky and Wannmacher (1993), most of the research groups in medicinal plants in Brazil focus on chemotaxonommy 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 considered this as their main research area. In respect to pharmacology research, most groups focus on ethnopharmacology that 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 renewed interest in pharmacological evaluation of medicinal plants is recent, basically since the last 30 years. But the low level of interaction with other disciplines is an obstacle for the further development of this research. In respect to phytochemical research, there has been little change since the seminal work of Gottlieb e Mors at the end of the 1970, according to which in the last “80 years of chemical research on Amazonian plants (...)these decades of study barely encompassed more than a hundred plant species (Elizabetsky and Wannmacher, 1993, p.138)

In respect to interaction among research groups in medicinal plants, according to Elizabetzky and Costa-Campos (1996), from 422 abstracts published between 1978-1992 in the “Simpósio de Plantas Medicinais do Brasil”, it was observed interaction within the same university in 145 abstracts, between different universities in 154 abstracts; between universities and research institutes in 58 abstracts; but only 65 abstracts demonstrated international collaborations. The most likely explanation for the low interaction with international researchers is related mainly to the difficulties involved in these partnerships, since this is a very sensitive area of research due to the concerns related to ‘biopiracy’ not because of researchers involved but because of 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 based in natural products, especially medicinal plants. But there is a relative distance required for R&D activities necessary to accomplish the search of bioactive compounds. This distance is due to several factors: i) there are yet few research groups in medicinal plants; ii) most of the phytochemical research are not related to therapeutic effects of compounds; iii) there is little concern about intellectual property issues, especially regarding potential for drug discovery, since this is no the goal of most studies; iv) phytochemistry has been suffering from an “emptying” in graduate programs in detriment of a higher importance given to synthetic chemistry, and most phytochemical analyses are not oriented to isolation of active compounds; v) scarce of financial resources to support R&D activities; vi) companies behavior regarding
R&D and interaction with universities and research institutes, despite recent initiatives in natural products research, mainly medicinal plants; and vii) the lack of public policies.

According to some authors, this distance does not constitute an insurmountable barrier yet. But, to overcome these obstacles it is necessary the mobilization of existing competencies and the creation of technology institutes oriented to applied research. It is also necessary an integrated effort to study the chemical diversity of the Brazilian fauna and flora, involving the scientific community, the private sector and the government. Given that almost 20% of the world genetic resources is located in Brazil, and many species are endemic, this raises an important concern with the extensive exploitation of biological resources as observed in the case of the Cerrado and Mata Atlantica, and recently in the Amazon forest (Brito and Brito, 1993; Elizabetzky and Wannmacher, 1993; Elizabetzky and Costa-Campos, 1996; Ferreira, 1998; Pinto et al., 2002).

In respect to government actions related to biodiversity issues, four aspects are worthy to mention in order to analyze the potential of biological resources as a window of opportunity to stimulate technological and industrial development: investments in science and technology; regulation of the pharmaceutical market; intellectual property; and access to genetic resources.

In science and technology, most efforts in natural products, although sparse and characterized by financial limitations, have been directed towards medicinal plants. The following actions deserve particular attention: the role played by the CEME between 1970s-1990s; the role of the Ministry of Science and Technology (MCT); the role of the Ministry of Environment (MMA); and the recent changes in the regulation of phytomedicines market by ANVISA.

In the case of the MCT, it is worthy to mention the investments through the CNPq, CAPES, and FINEP. In case of FINEP until the end of the 1990, the projects supported related to medicinal plants were distributed by three programs. In the case of CNPq and CAPES actions are devoted mainly to qualification of human resources through the funding of graduate programs (Ferreira et al., 1998). The MCT and the Army Forces announced the elaboration of a project related to biodiversity (JCE-SBP C, 2003b). Recently, FINEP and CNPq that have become co-responsible for the implementation of the newly created research funds, approved the first projects related to the biotechnology and health sector research funds. Another important program within the MCT since 2000 is the Genome Project aiming at strengthening the scientific and technology base in biotechnology and related areas. But despite positive results, the contigenciamento de recursos and delay in repasse resulted in serious problems for the andamento of the projects.

In 1994 the CBD was ratified in Brazil, the government created the “Programa Nacional da Diversidade Biológica (PRONABIO)” within the Ministry of Environment (MMA). Among the PRONABIO programs the following are worthy to mention: “Projeto de Conservação e Utilização Sustentável da Diversidade Biológica Brasileira (PROBIO)”, and the “FUNBIO” both with financial support form the GEF and the Brazilian government; “Programa Biodiversidade em Recursos Genéticos (Biovida)” to promote of knowledge, conservation and sustainable use of biodiversity and benefit sharing; “Programa Brasileiro de Ecologia Molecular para o Uso Sustentável da Amazônia (Prothem)”, where especial focus is placed upon the creation of the “Associação Brasileira para o Uso Sustentável da Amazônia (Bioamazonia)”, an organization formed by the government, civil society and scientific
community, to support the implementation of Probem\textsuperscript{42}, such as the building of the “Centro de Biotecnologia da Amazonia (CBA)” oriented to phytomedicines, juices and concentrated, and cosmetics, and partnerships with state institutions in Amapá and Pará. Also within the MMA, another important role is played by the Embrapa that is a research institute of the MMA whose mission is to “develop solutions for the sustainable of the Brazilian agribusiness through generation, adaptation and transfer of knowledge and technologies”. Regarding the opportunities of biodiversity in medicines, in particular in medicinal plants, Embrapa has been involved in researches in genetic resources through a germplasm bank, and researches on endangered medicinal plants, about their potential uses and ways of creating high yielding varieties, plant multiplication and regeneration.

Besides some programs by the Federal Government, some State and Municipal governments have recently begun to address the potential biodiversity for development. Among these initiatives it is worthy to mention: The “Programa Biota” of Fapesp to stimulate research in biodiversity and its potential to leverage development; the “Projeto de Biotecnologia Vegetal da Melhoria da Qualidade de Fitoterápicos” of Faperj, through which a national company has obtained support to improve quality and standardization of phytomedicines; also some Municipal Health Secretaries have created specific programs in order to introduce the use of medicinal plants in the health system.

It is important to observe that although Brazil has ratified the CBD in 1994, until 2000, when the Provisional Measure 2.052 passed, there was no specific law regulating access to biological resources and compliance with CBD provisions\textsuperscript{43}. The MP 2.052 involved several discussions especially because it considered that all projects that were already in place were not subject to the new provisions. So that in 2001, a new Provisional Measure 2.186 passed, substituting the MP 2.052. This new MP was regulated by the Decree n.3495, according to which researches on biological resources must be registered through the “Conselho de Gestão do Patrimônio Genético”, presided by the MMA, and inform the material to be collected, place and date, if it involves access to traditional knowledge, and show evidence of prior informed consent, ABS agreement and MTA. The disrespect to Decree implies in fees up to R$ 50 millions. However, the scientific community, this MP placed an enormous burden on the ongoing researches (most of them had to be interrupted), while the “tourists” carrying biological resources without respecting CBD provisions, and that were the main target of the MP, are generally released after paying the bail (Silveira, 2003). Since then there has been an intense debate about the impacts of this MP, and in 2003 the Federal Government passed the Decreto 4946 (31/12/03) in order to solve some of these problems. However, a polemic has been raised because this Decree distinguishes scientific and commercial research, but such division is difficult to be established a priori (Geraque, 2003).

According to IBAMA, the world black market for animal and plant species is around US$ 60 billions each year, of which US$ 12 millions correspond to the smuggling of wild animals. According to a recent report of the Brazilian Congress the country looses around US$1 billion with biopiracy. According to IBAMA, those who come to Brazil looking for plants, seed or animals are highly specialized individuals (supposed “tourists”) with specific demand. In

\textsuperscript{42} According to the PPA 2000-2003 report, due to contingenciamento no repasse dos recursos and inexperience of state institutions involved, the performance of the Probem did not fulfill expectations, as it could be seen in the case of the delays in the building of the CBA, completed in 2002 and opened in 2003.

\textsuperscript{43} Before 2000 there was only some regules concerning researches conducted by foreign researchers.
general they are aware of the flaws in the Brazilian law and they try to get close to indigenous communities. In 2003 two German “tourists” were arrested after visiting Amazon they tried to return to Germany carrying native seeds and bird-eating spiders. Besides, since there is no definition of biopiracy by the WTO, it is difficult to challenge patents based on traditional knowledge or biological resources without the appropriate in respect to 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 began in 1999 and was completed only in 2002 but officially opened on December 2003 and have not been occupied yet. Another important aspect, already mentioned above, is that the therapeutic value of natural products is not acknowledged by the population compared to what is observed in India and China (JCE-SBPC, 2003).

In the beginning of the 1990 some bioprospection agreements were in place and are worthy to mention: i) an agreement between the North-American Aveda Corp. and the Guarani-Kaiowá community in 1994, and the Yawaná-Katukina community in 1993, for commercial cultivation of “urucum”, “pupunha” and “castanhá-do-pará”; ii) between the North-American “The Body Shop” and the Aukrem Kayapós commnunity; iii) between the Universidade Federal do Ceará and the North-American company “Tom’s of Maine” in 1994; iv) between the North-American Merck & Co. and the Uru-Eu-Wau-Wau community for extraction of a substance from a plant known as “tike-úba”; v) between the Merck Ag and the Guajajara community for commercial cultivation of *Pilocarpus Jaborandi* used in the manufacturing of pilocarpine; vi) between the Cognis Corp and the Centro Nacional de Desenvolvimento Sustentado das Populações Tradicionais (MMA/IBAMA) for the development of perfums and cosmetics; viii) between the Raintree Nutrition Inc. and different indigenous communities and NGOs in the Amazon. Although there is no publicly available information about the terms of these agreements and their current status, most of them didn’t involved sharing of intellectual property rights if a patent application were filled resulting from access to genetic resources or traditional knowledge; most benefits, when materialized, were non monetary benefits (Fernandes, 2002).

Recently the NCI 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). According to the NCI these agreement had already finished and they are begin renewed, and in 2001 the NCI established a partnership with the Universidade Federal do Ceara.

But the most publicized agreements involving exploitation of Brazilian biological resources have been the agreement celebrated between the pharmaceutical company Glaxo Wellcome and the Brazilian small biotech Extracta in 1999, and more recently between Extract and Genzyme; and the agreement between the pharmaceutical company Novartis and Bioamazonia in 2000.

In 1999 Extracta and Glaxo signed a 3-year bioprospection agreement for the screening of Brazilian plants in order to identify their potential use in the drug discovery process. To have access to biological diversity, Glaxo paid Extracta US$ 3.2 millions for the building of technological infrastructure. In the case any compound extracted by Extracta were used for drug development, 3% of its world sales will accrue to Extracta, which will be holder of the patent. Currently, Extracta has a collection of more than 10.000 pant extracts. In 2001, Extracta signed a US$ 1.6 million agreement with Genzyme for the screening of compounds
against rare disease. But the agreement is still under analysis by the Brazilian government (Radler, 2000; Bellinghini, 2003).

The agreement between Novartis and the Bioamazonia began to be discussed in 1998 and first signed in 2000, but was suspended couple of weeks after some members of the Secretaria de Coordenação da Amazônia challenged the right of Bioamazonia to celebrate the agreement without the consent of its Board of Directors, and due to the lack of a law regulating access to biological resources. The foreseen agreement was supposed to involve resources around US$ 4 millions and the annual supply of up to 10 mil chromatographic profiles of fungi and bacteria by Bioamazonia to Novartis for 3 years. Novartis would have exclusivity over the information for two years extendable. The agreement also involved transfer of technology from Novartis in microbiology, isolation of compounds from natural products, and high-throughput screening. And if any industrial use was identified, the researches would carried on by Novartis outside and by followed by Brazilian researchers, and if any product were developed based on access to those biological resources Novartis would pay 1% of royalties of world net sales, and patents would be filled by Novartis and Bioamazonia. Due to the intense discussion about the legal aspects of the agreement, Novartis decided not to pursue further discussions and the agreement was finished. It is also important to observe that one of the elements of the agreement involved the building of the CBA that opened only in 2003 (Scharf, 2000; Vasconcelos and Komatsu, 2000; Vasconcelos, 2000).

In what concerns the use of medicinal plants in the Brazilian health system following the recommendations of the WHO, the Portaria 08/CIPLAN of 1988 recommended the use of phytomedicines by the Sistema Único de Saúde (SUS). In the banging of the 1990s Gottlieb and Kaplan (1993, p.54) observed that this directive – based on the WHO program – as well as 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 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, the following recommendations were made: the need to stimulate the use of medicinal plants within the SUS in a consistent manner, based on efforts by the Ministry of Health, 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 upon public health needs; to establish technical guides for cultivation and quality control of crude extracts and phytomedicines; to review the Brazilian Pharmacopoeia\textsuperscript{44}; and elaborate a separate Pharmacopoeia of medicinal plants; as well as to establish training programs to incorporate this recommendations among health professionals (Brasil, 2003).

In relation to regulation, until 1995 there was no specific law regarding phytomedicines. In 1/31/1995 the Portaria SVS/MS n.6 established rules for toxicity studies of phytomedicines.

\textsuperscript{44} The first Brazilian Pharmacopeia was published in 1929 and had 300 monographies of medicinal plants; the second edition of 1959 had 94. Both presented mainly botanical descriptions. The third edition of 1977 had only 26 monographies though with phytochemical studies, and the fourth edition just 10 monographies (Rates, 2001).
According to the Brazilian Association of Phytomedicines Manufacturers (ABIFITO) this measure was not adequate and made impossible to register of phytomedicines in Brazil. A new regulation came into force only in 2000 with the RDC 17 establishing rules for the registration of phytomedicines, and the processes that were waiting for analysis by ANVISA had a term to adequate applications to the new rules. Because of this, most of the companies with phytomedicines 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 phytomedicines registration were not approved by ANVISA in the beginning of 2002. As a consequence sales of most phytomedicines companies were considerably affect, the number of jobs also reduced, and most companies was operating with 70%. In turn, many companies began to adequate their procedures to the new regulation, and the number of application for product registration denied and products taken out of the market by ANVISA were greatly reduced. ABFITO sent a proposal for a Projeto de Lei, to promote the development of the phytomedicines segment. This proposal does also have the support of the Ministry of Health (ABIFITO, 2003).

In respect to specific public policies regarding the exploitation of biological resources in the pharmaceuticals for industrial and technological development, only recently the government recognized the need to reestablish industrial and technology policies that have been abandoned by the previous governments. Although pharmaceuticals and fine-chemicals are two of the sectors emphasized as well as phytomedicines, at the time of the writing of this work there were no information about a concerted effort among the Ministries of Environment (MMA) Ministry of Health (MS), Ministry of Science and Technology (MCT) and Ministry of Industry and Trade (MDIC).
Conclusions

This study addresses relevant aspects for the analysis of benefiting by biodiversity in the pharmaceutical sector by developing countries, either 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 window of opportunity in respect to economic, technological and institutional drivers.

In respect to technology, the window of opportunity is characterized by the development of modern biotechnology in the late 1970s-1980s; and advances in chemical technology in the 1990s, changing the nature of drug discovery and development processes. In respect to the institutional environment, after the mid 1980s greater concern was placed upon sustainable use, intellectual property and appropriation of benefits resulting from research in biodiversity, resulting in international treaties that promoted significant changes in institutional selection environment. From the economic standpoint, it is observed not only the continuous reliance of industry in natural products, but also a renewal after the 1990s in exclusive natural products such as phytomedicines. These elements have specificities that must be analyzed separately. However, any assessment about a window of opportunity in the pharmaceutical industry associated to biodiversity and the capability of a developing country to benefit from this, is only possible if these elements are taken into account interdependently at international and national levels, since countries differ in terms of science and technology infrastructures, industrial capabilities, trajectory of evolution within the socioeconomic system and pattern of insertion in this 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 exit natural products research in the search of new compounds. This movement was also a reaction to the uncertainties in the institutional environment regarding access to those resources and intellectual property issues since the mid 1990s. But despite massive investments in new technologies intended to increase the potential of chemical libraries in the search of new compounds, a great part of the new chemical entities introduced since the 1980s derived somewhat from biotechnology or natural products research. Besides, at the same time that new chemical technologies enhanced the potential of synthetic compounds libraries, there have been developed new technologies that have allowed overcoming important technological bottlenecks in natural products research. So that, 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 biological resources is concentrated. Besides, changes in the international institutional environment, promoting benefit sharing and technology transfer, if adequately addressed, may enhance this potential.

But for this, developing countries face several challenges. First, ownership over biological resources offers only comparative advantage (and not competitive advantage); especially for those developing countries that lack a local pharmaceutical industry or that although with local industrial and technological capabilities are not systematically engaged in R&D efforts. It is also important to observe that technological change is a cumulative process, and demands continuous investment in science and technology. Thus, developing countries must be able at the same time to protect, to conserve biological resources and to stimulate endogenous technological development and technology transfer, so technological dependency can be
minored as well as its effects. However these countries face several problems regarding public investment not only in science and technology due to several reasons ranging from vulnerability to turbulences in world economy, “structural adjustments” policies, internal macroeconomic conditions undermining local investment initiatives, as well as other local factors. Thus these countries face enormous challenges concerning the support of and investment in science and technology. Besides, the mechanisms that current developed countries have made use of along their development trajectory have been reduced considerably for current developing countries.

In the case of the development of local pharmaceutical industry, following the leader trajectory targeting the development of new chemical entities to be introduced in the world market may offer high incentives if a medicine reach the market and reap of great economic returns. But this trajectory also involves higher risks and higher entry barriers, especially regarding approval process and marketing. This is not to say that developing countries should not focus new product development, but that this might be seen as a long term strategy and highly dependent upon the evolution dynamics of the local industry, industrial and technology policies, and the interrelation of those dynamics to the world industry dynamics and competition dynamics among countries.

The other window of opportunity involves lower costs and less technological complexity: phytomedicines. In this case, there are great incentives for developing countries not only because of lower costs involved, but also because most biological resources are located in those countries and most of these resources have not been studied in terms of view of their therapeutic effects. However, even in this case, 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 Europe that is the world largest market), the need to invest in commercialization channels and technological modernization, either in crude drugs cultivation, processed bulk, and finished phytomedicines. But developing countries do also face important problems regarding access to medicines, so that encouraging the development of this segment may not only serve industrial and technological development purposes but also public health goals.

Another relevant area with intrinsic value for developing to stimulate natural products research and development is in those diseases to which large research based pharmaceutical companies have directed low efforts: diseases prevailing in developing countries and not interesting from the economic point of view for those countries to commit with drug development efforts. So 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 potentials, obstacles and challenges in exploitation of biodiversity as a window of opportunity in the pharmaceutical industry. Brazil is one of the largest countries in terms of biological resources; has a local pharmaceutical industry with industrial and technological capabilities either for finished medicines or fine-chemicals; and also has a good scientific and technology infrastructure in health sciences especially in the university system and some research institutes. However the evolution of the pharmaceutical industry (both in finished medicines and fine chemicals), the current industry features and changes in the regulatory environment, the lack or inadequacy of previous public policies, associated with the recent difficulties regarding promotion of sustainable and
technological development, access to and transfer of technology pose several challenges to the benefiting of the above mentioned windows of opportunity.

In the case of pharmaceuticals, it is worthy to note the difficulties faced especially by the fine chemical industry and that were worsened since the 1990s. Such difficulties create obstacles for the benefiting from a 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 (dominating the domestic market), the vast majority of companies are not integrated as well as most companies with fine chemical capabilities (also of a smaller size); Brazilian companies have also been facing several problems due to intense competition with Indian and Chinese companies. But the local research capabilities in natural products in universities and 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 the Brazilian biological resources. Here stakes are higher and policies should be carefully designed so that they don’t run counter to each other. In the case of phytomedicines, taking into account the lower costs and lower technological complexity involved, and that Brazil holds 22% the whole plant species in the planet and 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 improve cultivation practices, invest in technological capabilities to accomplish toxicity tests and product validation, 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 research and development efforts in neglected diseases. But all these opportunities cannot be taken into account separately from all the other public policies with higher impact upon the pharmaceutical sector such as price regulation; intellectual property rights; regulation of production, registration and marketing of medicines; macroeconomic policies; and pharmaceutical assistance.

In terms of the contribution of this work for theory development, four main conclusions are drawn. First, benefiting from windows of opportunity depends upon local and non-local factors, which are highly interdependent, and both have important impacts upon technological development. Second, technological development must be seen in the long run perspective, since the international environment and competition dynamics among firms and nations change along time so that what may be valid in certain contexts may not be in others, for institutions change slowly and “technological borrowing” interact with local institutions, that differ in terms of evolution. Third, although technological change can be punctuated by events that alter technological trajectories, this is a cumulative process and requires continuous investment in learning, research and development either oriented for industrial applications and fundamental knowledge. Finally, it is important to observe that institutions change slowly and is a feedback process with strong influence upon development trajectories.
References
____. Thinking about Growth, Cambridge: Cambridge University, 1989.

_____. Lei 5.772 de 21 de dezembro de 1971. Institui o Código de Propriedade Industrial e dá outras providências.

_____. Lei n.6.938, de 31 de Agosto de 1981, Dispõe sobre a Política Nacional do Meio Ambiente, seus fins e mecanismos de formulação e aplicação, e dá outras providências.


_____. Lei 9.729 de 14 de maio de 1996. Regula direitos e obrigações relativos à propriedade industrial.

_____. Decreto n.3.181, de 23 de Setembro de 1999, Regulamenta a Lei no 9.787, de 10 de fevereiro de 1999, que dispõe sobre a Vigilância Sanitária, estabelece o medicamento genérico, dispõe sobre a utilização de nomes genéricos em produtos farmacêuticos e dá outras providências.

_____. Medida Provisória n.2.052-2, de 28 de Agosto de 2000, Regulamenta o inciso II do § 1o e o § 4o do art. 225 da Constituição, os arts. 1o, 8o, alínea "j", 10, alínea "c", 15 e 16, alíneas 3 e 4 da Convenção sobre Diversidade Biológica, dispõe sobre o acesso ao patrimônio genético, a proteção e o acesso ao conhecimento tradicional associado, a repartição de benefícios e o acesso à tecnologia e a transferência de tecnologia para sua conservação e utilização, e dá outras providências.

_____. Medida Provisória n.2186 de 23 de Agosto de 2001, Regulamenta o inciso II do § 1o e o § 4o do art. 225 da Constituição, os arts. 1o, 8o, alínea "j", 10, alínea "c", 15 e 16, alíneas 3 e 4 da Convenção sobre Diversidade Biológica, dispõe sobre o acesso ao patrimônio genético, a proteção e o acesso ao conhecimento tradicional associado, a repartição de benefícios e o acesso à tecnologia e transferência de tecnologia para sua conservação e utilização, e dá outras providências.

_____. Decreto n.3.945, de 28 de Setembro de 2001, Define a composição do Conselho de Gestão do Patrimônio Genético e estabelece as normas para o seu funcionamento, mediante a regulamentação dos arts. 10, 11, 12, 14, 15, 16, 18 e 19 da Medida Provisória no 2.186-16, de 23 de agosto de 2001, que dispõe sobre o acesso ao patrimônio genético, a proteção e o acesso ao conhecimento tradicional associado, a repartição de benefícios e o acesso à tecnologia e transferência de tecnologia para sua conservação e utilização, e dá outras providências.


_____. Decreto 4.830 de Setembro de 2003. Dá nova redação aos arts. 1o, 2o, 5o, 9o e 10 do Decreto nº 3.201, de 6 de outubro de 1999, que dispõe sobre a concessão, de ofício, de licença compulsória nos casos de emergência nacional e de interesse público de que trata o art. 71 da Lei nº 9.279, de 14 de maio de 1996.

_____ Decreto n.4.946, de 31 de Dezembro de 2003, Altera, revoga e acrescenta dispositivos ao Decreto no 3.945, de 28 de setembro de 2001, que regulamenta a Medida Provisória no 2.186-16, de 23 de agosto de 2001.


BRASIL. AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA, Portaria n.6, Institui e normatiza o registro de produtos fitoterápicos junto ao Sistema de Vigilância Sanitária, 31 de Janeiro de 1995.

_____ Resolução RDC n.17, Dispoe sobre o registro de medicamentos fitoterápicos,


Drews, 1998


HONG KONG TRADE DEVELOPMENT COUNCIL. Review and Outlook of Hong Kongs’ Chines Medicine Export Markets. Hong Kong: Hong Kong Trade Development Council, april 2002.


LAU, Lawrence J., “ The sources of long-term economic growth: observations from the experience of developing countries” in LANDAU, Ralph, TAYLOR, Timothy and


44


SCHEINKMANN, José, 'A indústria farmacêutica no Brasil', Revista Brasileira de Farmácia, 6, nov-dez, 1965, pp.323-353.


STERCKX, Sigrid., Some reflections on tensions between the regulation of patenting and the conventional on biological diversity”. Conference on Governance of Biodiversity as a global public good: bioprospection, intellectual property rights and traditional knowledge. Louvain-la-Neuve, 5th and 6th, February 2004. Universite Catholique de Louvain, Belgium.


VASCONCELOS, Lia and KOMATSU, Alberto, “Brasil nao sabe explorar potencial de sua biodiversidade”, Sao Paulo, Gazeta Mercantil, 24 de julho de 2000, pp.1,3,4 and 5.


