



# **CMH Working Paper Series**

Paper No. WG2: 11

## **Title**

TRIPS and R&D Incentives in the  
Pharmaceutical Sector (Correa C)

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**TRIPS AND R&D INCENTIVE IN THE PHARMACEUTICAL SECTOR**

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November 2001

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## Introduction

Economists and policy makers face a difficult dilemma in the area of innovation: how to reconcile the aims of intellectual property, which provides innovators with incentives by restricting use of the innovation and thereby guaranteeing extraordinary gains, with the society's interest in allowing maximum use of innovative products, by keeping their price low and ensuring diffusion, imitation and improvement. (OECD, 1992, p. 50)

A fair balance between the private and the social benefits of innovation, requires the development of a policy framework which does not only ensure that new technologies are created, but also that competitors are able to work and improve on them. As taught by the economic theory on technical change, innovation and diffusion are “two faces of the same coin”: innovation leads to diffusion which in turn influences the level of innovate activity (OECD, 1992, p. 51).

Moreover, from a social and ethical perspective, it is essential that policy mechanisms ensure that innovation results reach those who need them. One obvious example is the case of pharmaceuticals, diagnostic kits and other health-related products upon which the health or life of human beings depend<sup>1</sup>.

If the policy framework leads, by exclusion of competition and lack of controls on abuses, to monopolistic market structures, innovators can maintain high price/cost margins, retard further innovation and deny access to innovative products, specially to the poorer segments of the population. In contrast, some degree of competitive threat induces firms to continue to innovate and keep prices low. The monopolistic elements should diminish, in particular, where diffusion (that is, adoption by other users) opens up important technological opportunities and where it is important to satisfy essential societal needs. Innovation policy needs to provide incentives for both the *creation* and the *diffusion* of new technology.

Intellectual property is one of the possible components of an innovation policy<sup>2</sup>, but its impact varies according to the sectors at stake<sup>3</sup> and the level of development of the country where such policy is implemented<sup>4</sup>. The granting of exclusive rights increases

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<sup>1</sup> A resolution approved on April 23, 2001 by the United Nations Commission on Human Rights. calls on governments to ensure the accessibility of pharmaceuticals and medical treatments used to treat pandemics such as HIV/AIDS, as well as "their affordability for all," in accordance with international law and international agreements. The resolution also calls on governments "to safeguard access to such preventive, curative or palliative pharmaceuticals or medical technologies from any limitations by third parties."

<sup>2</sup> The creation of monopolies to exploit innovations is one of the alternative ways for coping with the market failure that affects the creation of knowledge; the other two being subsidies or public involvement in research and development, to be financed by means of general taxation (Sideri, 1994, p.5).

<sup>3</sup> In many industries IPRs are not a crucial incentive for expenditures in innovative activities. In some cases (such as semiconductors) the key factor is the *lead time* in introducing new products onto the market. See e.g., Levin *et al*, 1987.

<sup>4</sup> See UNCTAD, 1996; Correa 2000a.

appropriability and may stimulate investment in innovative activities, but it reduces the availability of knowledge and may retard innovation: benefits may be increased if competitors could imitate and improve on the innovation to ensure its availability on favourable terms (Levin et al, 1987, p. 783). If the power conferred to the rights-holder is too strong, diffusion may be severely limited, further innovation jeopardized and many would-be adopters be deprived of access to needed products. A sound intellectual property policy should, hence, strike a balance between the right to exclude and the right to use innovations.

The achievement of such balance is one of the stated objectives of the TRIPS Agreement (article 7). Though the adoption of the Agreement allowed developed countries to impose on developing countries and economies in transition the core of their own IPRs systems<sup>5</sup>, it aims at balancing the rights of producers and users of technology, and leaves room for establishing pro-competitive measures that may facilitate access to and further innovation on protected goods and technologies. Of particular importance are, in this regard, the provisions relating to parallel imports, exceptions to exclusive rights and compulsory licenses which have been examined elsewhere<sup>6</sup>.

The relationship between the incentives to innovate and a broad and rapid diffusion of the products of innovation is critical in the field of pharmaceuticals, since they are an important component in any health policy. In some cases, the availability of pharmaceuticals at affordable prices makes the difference between life and death.

The research-based pharmaceutical industry has played an important role in the discovery and development of new medicines. The patent system is of particular importance for the pharmaceutical industry, as indicated by many studies (Mansfield, 1986; Levin *et al*, 1987) and by the high profile that the issue of patent protection has had in industry's national and international public actions<sup>7</sup>. US pharmaceutical companies, in particular, had a decisive role in bringing intellectual property into the GATT agenda in 1986, and in the development of the relevant rules, as contained in the TRIPS Agreement<sup>8</sup>. Developing countries were not part of the circles of consensus that set the agendas in GATT. Furthermore, if they resisted the US multilaterally they could have expected to be subjected to the Special Section 301 of the US Trade Act (Drahos, 2001. p. 9)

The TRIPS Agreement represented a major victory for the large pharmaceutical companies. For the first time in history, an international agreement obliged to grant patents on pharmaceutical products, in the framework of an agreement "with teeth", that is, under which trade sanctions may be applied against non-complying countries. The Agreement also strengthened the rights conferred by process patents, and generally the remedies available to enforce patent rights.

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<sup>5</sup> See, e.g., Drahos, 2001; May, 2000, Ryan, 1998.

<sup>6</sup> See an annotated bibliography in Velásquez et al, 2001.

<sup>7</sup> See, e.g., FIM/IFPMA, 1998.

<sup>8</sup> Pfizer's CEO chaired the US Advisory Committee on Trade Policy and Negotiations which emphasized the need to go beyond purely trade policy matters in the Uruguay Round, and was one of the founders of the Intellectual property Committee (IPC) established by thirteen companies (six out of which with interests in pharmaceuticals) to coordinate their policy positions during negotiations (Ryan, 1998, pp. 68-69)

Despite the dramatic change that the adoption of TRIPS entailed for patent law, and the fact that pharmaceutical companies were among the principal beneficiaries of the new rules, the Agreement was approved by them with some reservations, due to the inclusion of certain safeguards and limitations that in industry's views undermined adequate and effective IPRs protection<sup>9</sup>.

"Effective" IPRs protection is seen by the pharmaceutical industry as critical for it to recoup its large R&D expenditures (FIM/IFPMA, 1998, p. 9). This has led the industry and some developed countries' governments to oppose to the adoption of pro-competitive measures, as illustrated by the legal action brought against South Africa (Bond, 1999). The room for maneuver left by the TRIPS Agreement to apply that kind of measures<sup>10</sup> has been *de facto* circumscribed by such actions.

The pharmaceutical industry is among the most R&D intensive industries, measured by the percentage of sales devoted to such activities (OECD, 1992). Thus, the US National Science Foundation estimated that R&D expenditure in the pharmaceutical industry, in the USA was 9.8 billion dollars in 1996, near 7% of total R&D in that country<sup>11</sup>. Though the contribution of the private sector to pharmaceutical R&D is undeniable, the arguments often made about the need for "strong" IPRs are based on a number of assumptions that need to be objectively reviewed, having in mind public health concerns and, in particular, the needs of the poor.

This paper briefly discusses, first, the ways in which the patent system is operating today in the pharmaceutical field. It indicates that the intended objectives of the system are being eroded by the granting of patents on developments of secondary or no technical relevance, which are often effectively used to block legitimate competition. Second, it argues that though the private investments in pharmaceutical R&D are admittedly high, it is unclear to what extent the current arrangements are cost efficient.. Third, the paper argues that, while the role of the public sector in drug research is often underestimated, the privatization of publicly funded research results may not be an optimal option. Fourth, it considers the implications of patent protection for pharmaceuticals in developing countries for global R&D, and the extent to which current R&D addresses the diseases of the poor. Finally, the paper considers the extent to which legitimate measures, such as compulsory licenses and parallel imports, aimed at increasing today's affordability of drugs, imperil the sustainability of private R&D in pharmaceuticals. It concludes that there is little basis to think that this is the case and to justify limitations on the use of such measures by developing countries.

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<sup>9</sup> See the testimony of P. Richardson (General patent Counsel of Pfizer) on behalf of the Intellectual Property Committee to the House of Representatives Hearing before the Subcommittee on Trade of the Committee on ways and Means, January 23, 1992.

<sup>10</sup> The Doha Ministerial Conference Declaration on the TRIPS Agreement and Public Health (WT/MIN(01)/DEC/W/1, 14 November 2001) has confirmed such room for maneuver, particularly in relation to compulsory licensing and the exhaustion of rights.

<sup>11</sup> US National Science foundation, Division of Science Resources Studies, Research & Development in Industry, 1995-96.

## Patents and pharmaceutical innovation<sup>12</sup>

An implicit assumption in many claims for a strong patent protection is that pharmaceutical R&D efforts are concentrated on the development of “new” drugs and that the patent system is working in accordance with its intended objectives as a tool to encourage genuine “inventions”.

The patent system was devised in order to reward inventiveness, encourage technical progress and foster the dissemination of innovations. The restriction on the free movement of ideas that the granting of a patent entails is usually justified by the inventor’s contribution to society and by the need to recover the investment necessary for invention (Gutterman, 1997; Granstrand, 1999; Le Bas, 1999). There is no doubt that the development and exploitation of numerous contributions to technology have been closely linked to, although not necessarily determined by, the possibility of obtaining exclusive rights to exploit inventions (Archibugi and Malaman, 1991).

Nonetheless, it is apparent that the attainment of the main objectives of the patent system, which are in themselves valid, is increasingly offset by serious shortcomings in the system’s design and management. One increasingly widespread view is that the patents system (especially as it operates in the United States of America) is in crisis and that there is a danger of it stifling the very innovation it is supposed to foster.<sup>13</sup> The National Academies of the United States have taken up the criticism leveled by many academics and sectors of industry (Barton 2000) and have expressed their concern about the lax application of the patentability standards, especially as regards non-obviousness and usefulness, in the examination and granting of patents. As a result, many “low quality” patents<sup>14</sup> often with broad coverage are being granted<sup>15</sup>.

Lester Thurow, an economist at MIT, has also expressed serious doubts about the efficacy of the patent system for ensuring a satisfactory rate of innovation at the lowest social cost: “the time has come not for marginal changes but for wide-open thinking about designing a new system from the ground up” (Thurow, 1997, p96)<sup>16</sup>. He wonders why patent rights of equal effect and duration should be granted to inventors who have made different contributions, some of them significant and others less so, and how it is possible

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<sup>12</sup> This section is partially based on Correa, 2000b.

<sup>13</sup> See, Gleick, 2000, p.44; *The Economist*, April 8, p. 17; Abrol and Usha, 1993.

<sup>14</sup> According to a study of patents litigated to judgment in USA, 54% were found to be valid, and 46% were invalid (Lemley and Allison, 1998).

<sup>15</sup> The National Academies, Board on Science, Technology and Economic Policy, “Request for proposals for research on intellectual property in the knowledge-based economy”, March 23, 2000.

<sup>16</sup> Other scholars have also recently suggested substantial reforms in order to address the shortcomings of the patent system. Hart, for instance, has proposed a new patent law regime based on competitive market bidding prior to the inventive process. He argued that current debates surrounding patent law cannot be resolved due to a lack of empirical information created by the current regime itself. The proposed system is designed to individually tailor economically efficient patent rules to each invention by utilizing competitive market forces to obtain the empirical information necessary to do so (Hart, 1994, p.217). Kremer, an economist at the Massachusetts Institute of Technology, has proposed specifically in relation to pharmaceuticals, that governments offer to buy patents from the drug companies that hold them and then make them publicly available so that anyone can produce the drugs in question (Kremer, 1996).

to ensure that patents actually encourage, rather than hold back innovation. He also advocates differential treatment for the developing countries, which are basically dependent on technology from outside (Thurow, 1997).

As noted by Merges and Nelson,

“The classical argument for a patent to reward effort and creativity presumes and invention marked by considerable originality on the part of the inventor, rather than one that mainly represents taking a speedy path down a trail that was obvious to many. In a number of technologies, however, which we will call “science based”, the efforts of “inventors” are strongly guided by the evolution of an underlying science” (Merges and Nelson, 1996, 128)

In fact, thousands of patents are granted each year in the United States for minor, purely trivial developments or for substances (including genes) that already exist in nature and which have merely been *discovered* but not *invented* by their would-be “owner”. In 1999, the United States Patent and Trademark Office granted over 160 000 patents, twice the number granted ten years ago.

This is the fruit of loose criteria for patentability,<sup>17</sup> of the excessive flexibility in assessing the degree of non-obviousness, novelty and usefulness of the applications submitted to it and of shortcomings in the examination procedures<sup>18</sup> (Gleick, 2000, p.44).

Other patent offices throughout the world are following suit, occasionally in the mistaken belief that an examination conducted by the patent office of a highly industrialized country is a sound guarantee. Many of the patents granted are astounding, not so much for their inventiveness as for their triviality.<sup>19</sup>

Nevertheless, patents for large numbers of trivial inventions are no great worry, because their economic value is scant or limited. The problem arises, however, when these same lax criteria and deficient examinations concern areas of greater economic and social importance. Even if the patent granted is weak and questionable, if the firm that owns it is sufficiently wealthy, in many cases it will aggressively assert its rights against potential competitors, and will elbow out of the market small and medium-sized firms without the means to take on costly and lengthy litigation<sup>20</sup>.

Patents are often used as a device by large companies to block innovation in smaller companies. In many cases, “large corporations use the patent system to safeguard their

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<sup>17</sup> The adoption of a notion of *local* innovation for knowledge disseminated by media other than publication outside the United States has led, for example, to the patenting of plants and knowledge widely used by indigenous communities in developing countries (Correa, 1999; The Crucible Group, 2000).

<sup>18</sup> For example, less than 50% of the examinations conducted by the Office refer to relevant background bibliography; the examination is by and large limited to analyzing previous patents. See, Aharonian, 2000.

<sup>19</sup> Examples of some of the patents granted in the United States include an “invention” to inhibit the intake of food and consisting of a pair of elastic bands across the mouth, allowing wearers to breath but preventing the intake of food. (US 4,883,072); a patent for a hunting device consisting of a cape and a hat serving as a decoy for prey (US 5,197,216); a patent for a hat for four-legged animals (US 4,967,317). see, Feinberg, 1994.

<sup>20</sup> Barton has drawn attention to the use of these “strategic litigation” practices. See, Barton, 1995.

research and to intimidate smaller companies with IPR litigation –other large companies may be in a position to ‘deal’ or fight but not small ones” (Macdonald, 2001, p.35). The costs of litigation are not trivial. In (December 27) 1998, the New York Times reported the median cost of US patent litigation was \$1.2 million, per side, and the costs of litigation in complex cases was much higher. In *Polaroid v. Kodak*, each side reportedly spent over \$100 million (Love, 2001, p. 3).

In the pharmaceutical field, only a few “new chemical entities” (i.e. molecules not pre-existing) are developed and patented each year <sup>21</sup>, but many of them do not represent a significant therapeutic progress. There is “a great deal of emulation of successful drugs by rival companies” (Casadio Tarabusi and Graham, 1998, p. 78), leading to the development of “me-too drugs”<sup>22</sup>. In the United States between 1981 and 1991, less than 5% of drugs introduced by the top 25 companies were therapeutic advances (UNDP, 1999, p. 169). Nearly half of the new drugs approved for use in the USA in the 1990s did not offer important clinical improvements (Oxfam, 2000, p.26)<sup>23</sup>. As noted by Mills, the patent system

“creates a strong incentive to do ‘me-too’ research- research which produces drugs which are similar but not identical (since this would violate patent rights)... Me-too drugs are less desirable from a social perspective since they divert scarce expertise into areas already being researched, and reduce incentives to do original research” (Mills, 2001, p. 11).

In addition, a significant part of R&D activities<sup>24</sup> are devoted, by the firms that hold basic patents on chemical entities, to subsequent modifications or changes in the form of administration, including new formulations and dosage forms. As described by the pharmaceutical industry itself, after the development of a new chemical entity

“[T]he innovator may also, in the light of the marketing experience, modify the product in an attempt to produce formulations that have more desirable properties; these formulations may be patentable in their own right. Different dosages may be

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<sup>21</sup> Between 1975 and 1996 only 1.223 new chemical entities were developed (WHO, Globalization, TRIPS and access to pharmaceuticals, WHO/EDM/2001.2, March 2001).

<sup>22</sup> The development of “me-too” drugs is considerably less risky than pioneer drugs; they may also be less lucrative insofar as they commercialization increases competition (see e.g., Ernst & Young LLP, 2001).

<sup>23</sup> In accordance with one study, out of the 2.257 new drugs introduced between 1981 and 2000, only 7 (0,31%) were major therapeutic innovations in an area where previously no treatment was available, 67 (2,96%) were important therapeutic innovations, and 192 (8,51%) were products with therapeutic value but did not fundamentally changed the pre-existing therapeutic practice (Prescribe International, January 2001). See also Froud et al, 1998, p. 574.

<sup>24</sup> The US Pharmaceutical Industry Association estimates that R&D devoted to the development of new chemical entities is 78.5% (<http://www.phrma.org/updates/06252001>). See also Kettler, 1999, p. 49; Ogg *et al*, 2000, which found the figure to be 71%. If this latter figure were correct, and considering that R&D by the “research-based” pharmaceutical companies amounted in 2001 to an estimated \$ 30 billion (PhRMA, 2001), R&D for processes and products other than new chemical entities would represent around \$ 9 billion annually, several times the total investment made for neglected diseases (see, e.g., *Médecins Sans Frontieres*, 2001).

desirable, a variety of product presentations may be required. These will be the subject of the same time-consuming and exhaustive investigation as the original formulation and presentation. The research department will at the same time be attempting to produce another NCE having even more desirable characteristics in treating the same or similar indications” (FIM/IFPMA, 1998. p.19)

In fact, thousands of patents are granted annually in this sector, despite there being very few new chemical entities.<sup>25</sup> This paradox can be explained by the enormous capacity that the sector’s major firms have built up not only for developing authentic inventions, but also to take out patents on secondary, occasionally trivial developments, in order to extend their monopoly over a product or process, beyond that allowed by the original patent.<sup>26</sup>

For example, some five years after having patented cimetidine, SmithKline & French obtained a new patent for a polymorph ( a particular crystalline form of the molecule), which had in fact actually been described in the original patent. The effect of this patent would have been to delay for several years the marketing of generic products. The patent was challenged – with success – before the courts in several countries on grounds of lack of novelty, thereby aborting the attempt to extend the monopoly of the original patent. Had the patent remained in force, the public would have been denied access to the drug at more competitive prices when the original patent expired.

There are various ways in which barriers are frequently raised around products in the public realm, or patents on the point of expiring, with the aim of preventing legitimate competition. The means employed to expand patent protection beyond the scope and the term of basic patents on new drugs include the protection of:

*a)Formulations:* they consist of particular way of preparing a medicine with an active ingredient, which may be unpatented, in combination with certain additives.

Patent claims are often directed to pharmaceutical formulations. For instance, patents have been granted separately with regard to the injectable and oral forms of ofloxacin, a drug of relevance to the treatment of HIV patients. The practical consequences of this type of patents may be significant. For example, in Thailand -where there are serious problems of HIV infection- there is no current patent for didanosine (“ddl”) as such. Nevertheless, the firm Bristol Myers Squibb (which did not discover the product, but purchased it under license from a federal United States laboratory) patented a formulation of “ddl” thereby blocking the Thai Government’s attempts to purchase the drug at a price that was more affordable to its population.

If formulation claims are accepted subsequent to a patent on the relevant active ingredient, the patent owner may be able to artificially extend the term of protection granted under the basic patent<sup>27</sup>. Unless the composition (which often consists of the simple mixture of

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<sup>25</sup> The chemical and pharmaceutical industry accounts for about one third of the around 160.000 patents granted each year in the USA (Aharonian, 2000).

<sup>26</sup> See, Zaveri, 1998; Keayla, 1999; Cook, Doyle and Jabbari, 1991.

<sup>27</sup> See, e.g. Cook, Boyle and Jabbari, 1991, p. 91.

components) includes additives that generate a truly new and inventive product, a pharmaceutical composition should generally be deemed anticipated by the effective ingredient that it contains, and not patentable.

b) “*Selection*” inventions: these occur when a single element or group of elements of an already known large group are selected in order to take out a patent based, for example, on a feature that was not specifically described in an earlier patent for the larger group.

Under a “selection patent” a single element or a small segment within a large known group is “selected” and independently claimed based on a particular feature not mentioned in the large group<sup>28</sup>. If the large group of elements is already patented<sup>29</sup>, the patent owner may use the selection patent to extend the term of protection beyond the expiration of the original patent, at least for the selected subset. While accepted in some jurisdictions when the selected elements possess a surprising advantage, selection patents have been denied when the supposed advantage is a property shared by all or nearly all of the large group. Germany has refused selection patents because disclosure of even a large group of elements is deemed to be fully equivalent for the purposes of inventive step to the disclosure of each compound within the group<sup>30</sup>.

c) “*Analogy processes*”: this relates to processes that are not in themselves innovative, but which allow a product with innovative features to be obtained.

Some countries have permitted the patenting of non-novel processes (sometimes called “*analogy processes*”) if the resulting chemical is novel and displays unexpected properties. In these cases, a novelty fiction is applied: novelty is “transferred” from the resulting product (which is novel) to the process (which is not). This fiction has been used in some cases to grant protection to text book process for the preparation of salts, on the ground that the salt as such was novel.

The United States has held “analogy process” claims to be unpatentable unless they are inventive in themselves<sup>31</sup>, but has carved out an exception for biotechnology. The products and processes of biotechnology have posed hard problems for applying the inventive step standard, since many biotechnology “inventions” repeat previously invented processes in slightly different contexts. This problem led to a statutory amendment of U.S. law in 1995, which lowered the non-obviousness standard by deeming a biotech process claim non-obvious if it involves new and non-obvious starting materials or produces a new and non-obvious result<sup>32</sup>. While this solution, targeted only to biotechnology, may be deemed

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<sup>28</sup> A “selection invention” may take place, for instance, when a range of products characterized as having N carbon atoms has been patented, and later on a patent on a specific range (e.g. C1-C4) is claimed. Substantial differences exist in the treatment of these patents, including between the European Patent Office (EPO) and some national offices in Europe.

<sup>29</sup> Often broad (“generic”) patent claims are admitted, covering a large number (sometimes thousands) of possible compounds.

<sup>30</sup> See, e.g., Grubb, 1999, p. 197-199.

<sup>31</sup> See, e.g., Grubb, 1999, p. 206.

<sup>32</sup> See, e.g., Dratler, §2.03[3].

discriminatory -- and hence inconsistent with article 27.1 of the TRIPs Agreement -- it has been extended by case law to other fields of technology<sup>33</sup>.

d) *Combinations* of known products. For instance, patents on the combination of the following formulations were granted in the USA: Aspirin 325 mg. + Carisoprodol 200 mg. + Codeine Phosphate 16 mg, with the expiry date 13/08/2002.<sup>34</sup>

e) *Optical isomers*: Patents are often applied for compounds which are an optically active enantiomer<sup>35</sup> of a compound previously known only in racemic form. While some patent offices, such as the European patent Office (EPO), have ruled that such enantiomers may be deemed novel, the existence of inventive step has been denied, since it is obvious that in such types of molecules optically active forms can exist and it is routine to test whether one or the other enantiomers in isolation is more active than the mixture of both ("racemic" mixture). Today, it is generally accepted that one optical isomer will typically have much higher activity than the other, so that superior activity for at least one of the isomers as compared to the racemate is to be expected<sup>36</sup>.

f) *Active metabolites*: In some cases, patents may be accumulated on a compound and on the active metabolite that produces the desired effect in the body. For instance, in the case of terfenadine, which had been sold for many years in the United Kingdom as an antihistamine, the patent holder obtained a further patent on the active metabolite and attempted to block competition in the market of terfenadine, after the patent for the latter had expired. This was deemed to be an unacceptable attempt to extend patent protection<sup>37</sup>.

g) *Prodrugs*: When metabolized in the body, inactive compounds can produce a therapeutically active ingredient, called "prodrug". Countries must determine whether the patent on the compound covers the prodrug, and the extent to which claims relating to certain compounds should also be allowed to include their prodrugs<sup>38</sup>.

h) *Polymorphs*: Some therapeutically active ingredients present polymorphic forms, that is, crystallize in diverse forms, which may have different properties that are more or less significant in terms of their therapeutic use. Independent patent applications on such forms<sup>39</sup> have become frequent. Such forms can be deemed within the prior art -- and

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<sup>33</sup> See, e.g., Grubb, 1999, p. 207.

<sup>34</sup> Source: Keayla, 1999, p. 18.

<sup>35</sup> Enantiomers are chemical compounds which behave in relation to one another as an image does to its mirror image. In organic chemistry, enantiomers occur for example in compounds which comprise a carbon atom with four different substituents. See, e.g., Hansen and Hirsch, 1997, p. 113. It is estimated that over a quarter of known pharmaceuticals present that property. See, e.g., Cook, Doyle and Jabbari, 1991, p. 84.

<sup>36</sup> See, e.g., Grubb, 1999, p. 199-200; Hansen and Hirsch, 1997, p. 113-118.

<sup>37</sup> See, e.g., Grubb, 1999, p. 212-213.

<sup>38</sup> In the UK, for instance, it was held that sales of hetacillin, an acetone adduct of ampicillin which was immediately hydrolyzed in the body to ampicillin, infringed the ampicillin patent, because it was "ampicillin in disguise" (Grubb, 1999, p. 211).

<sup>39</sup> For instance, "Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings..." (WO 96/30375).

therefore non-patentable -- if they were inevitably obtained following the process of the basic patent on the active ingredient or were covered by a previous product patent.

Some companies have sought to patent polymorphs as a means to extend the monopoly protection of a known active ingredient. For instance, SmithKline applied for a patent on a polymorph of cimetidine approximately five years after the original patent was granted. That patent, however, was nullified in the UK and other countries on the grounds that the polymorph was inevitably obtained by applying the process already claimed in the original patent<sup>40</sup>. Another example is the case of ranetidine. The patentee obtained in the United States a patent for a polymorph expiring in 2002 as opposed to 1995 for the main patent<sup>41</sup>.

i) Variants of known *manufacturing processes*, including for the production of salts and purification. For instance, Claritin, Schering-Plough's medication for allergies, which earned US\$ 2.7bn in 1999, was "evergreened" by a patent on purification process, extending its US patent from 2004 to 2014. Schering-Plough's first patent on the active ingredient was acquired as far back as 1981. Legally, competitors can copy the older product when its patent expires, but heavy branding makes it harder to enter the market (Oxfam, 2000, p.26).

j) *New uses of known products*: In some jurisdiction, patents are granted on the new pharmaceutical use of a known non-pharmaceutical product ("first indication") as well as on the subsequent pharmaceutical use of a medicine ("second indication")<sup>42</sup>.

For instance, the various Wellcome entities (Burroughs-Wellcome, Glaxo Wellcome, the Wellcome Foundation) are listed as the assignee in approximately 633 U.S. patents which claim as inventive a method for achieving a particular result. In 289 (45.6%) of those, it specifically describes the method using the words therapeutic or therapy. Similarly, Squibb is identified as the assignee of approximately 1,392 method patents of which 412 (29.6%) describe the invention in those terms. For Merck, the figures were 3,250 and 1,094 (33.6%); for SmithKline, 1,076 and 467 (43.4%). In other words, more than a quarter but something less than half the time drug companies themselves describe these patents in terms that characterize them as therapeutic methods<sup>43</sup>.

Some countries have adopted special rules for the protection of the *first indication* of a known product, thereby expanding the scope of protection beyond its ordinary boundaries. In Europe, for example, on the basis of a legal fiction, article 54(5) of the European Patent Convention<sup>44</sup>, permits that the identification of the first medical indication of a known product be sufficient to get a patent on the product<sup>45</sup>. The United

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<sup>40</sup> See, e.g., Cook, Doyle and Jabbari, 1991, p. 89; Hansen and Hirsch, 1997, p. 113.

<sup>41</sup> See, e.g. Cook, Doyle and Jabbari, 1991, p. 90; Grubb, 1999, p. 205.

<sup>42</sup> An example of a patent for the *use* of a known drug is AZT (Retrovir), which was synthesized in 1964 by the Michigan Cancer Foundation as a possible anti-cancer drug. Another more recent example is sildenafil ("Viagra").

<sup>43</sup> Communication by Prof. Davis, 2001.

<sup>44</sup> See, e.g., Stieger, 1982.

<sup>45</sup> The Technical Board of Appeal of the EPO has ruled that such claims should be deemed as covering all

States, patents may be granted in the case of new found uses, but confining them to a particular “method-of-use.” Such method-of-use patents do not encompass protection of the product as such<sup>46</sup>.

In some countries patents are also granted for a “second indication”, i.e., when a new use is discovered for a product that already has pharmaceutical use<sup>47</sup>. Many national laws treat the new use as *process* patent claims of one of two kinds: “use” claims (such as “the use of X as an antihistaminic”) or claims on one or more actual process steps (e.g. “a method of preventing...”) <sup>48</sup>.

The new use of a medicine is equivalent, however, to a therapeutic method<sup>49</sup> which is deemed non-patentable in many countries. In order to avoid this problem, the European Patent Office accepted to protect such uses when the patent claims are framed under the “Swiss formula”, that is, in the form of a process for the manufacture of a medicine<sup>50</sup>.

This solution is based on a novelty fiction and contradicts, in essence, the principles of patent law. The “Swiss formula” suffers from “the logical objection that it lacks novelty, since it claims the use of the compound for preparation of a medicament, and normally the medicament itself will be the same as that already used for the first pharmaceutical indication”<sup>51</sup>. As pointed out by Domeij in relation to the EPO decision on second indications,

“The Enlarged Board of Appeal was aware that the formulation of claims was doubtful from a novelty view point: the manufacturing process and the pharmaceutical resulting from the process did not differ in any way from the pharmaceutical and the manufacturing process used when the pharmaceutical was manufactured for its first indication. On this point, however, the Enlarged Board of Appeal had little say, except that the manufacturing process could be deemed new when the end product (the pharmaceutical) could be used in a new way...“The novelty requirement is met with aid of the disclosure of a new indication, while the technical effect requirement is met,

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therapeutical uses of the product like in the case of claims on a pharmaceutical composition. Infringement of such claims would only take place when the product is commercialized for direct therapeutical use, and not in bulk (Grubb, 1999, p. 218). The approach of granting patents for first medical indication of a known product may be deemed discriminatory vis-à-vis other sectors, although it may be justified as a limitation to the exclusion of the patentability of therapeutical methods. See sub-Section II.4 on “Methods for Treatment and Diagnostics”.

<sup>46</sup> See, e.g., Merges, 1992, p. 489.

<sup>47</sup> This was the case, for instance, of nimodipine, a known cardiovascular agent for which an application to cerebral disorders was found.

<sup>48</sup> See, e.g., Grubb, 1999, p. 208. The patenting of use inventions depends on whether the purpose of the use is novel and non-obvious. Method inventions may be judged independently of the purpose. Even if intended for a novel purpose, the key consideration in determining the patentability of a method invention is whether it could be anticipated by other methods. See, e.g., Hansen and Hirsch, 1997, p. 120.

<sup>49</sup> Patent applications on the second medical indication of a known product are usually written as instructions to the physician on how to employ a certain composition to treat a particular disease.

<sup>50</sup> “Use of X for the manufacture of a medicine to treat Y”.

<sup>51</sup> See, e.g., Grubb, 1999, p. 221.

and the medical procedure ban avoided, by the feature “production of a pharmaceutical”. Only with such a construction of the claims is it possible simultaneously to meet the novelty requirement and avoid the ban on patents for medical procedures. This solution, however, is contrary to an established principle of patent law. The new technical features in the claims are deemed to be those which are to be taken into consideration when assessing whether the invention constitutes a medical method” (Domeij, 2000, p. 183).

The legal outcomes and administrative and judicial practices observed in respect of the protection of pharmaceutical uses vary significantly in different jurisdictions. There is considerable margin for maneuver to allow each country to determine its own policy. Ideally, it should seek to afford protection to developments that are truly innovative, and reject those that are designed to block competition and delay the marketing of alternative products that are cheaper for consumers.

The large number of patents obtained on these secondary developments suggests that a significant part of firms’ R&D budget is not devoted to the discovery and development of *new drugs*, but to the acquisition of patent rights that are used as commercial barriers against generic competition.

### **Efficiency in R&D activities**

An assumption that underlies statements on the need to guarantee high levels of IPRs protection, is that the significant funds devoted to such activities are efficiently used<sup>52</sup>. Some studies have shown that the research productivity of the largest US drug corporations increased in the 1980’s vis-à-vis the 1970’s, as well as the expected profitability (Gambardella, 1995, p. 142), but a decline in the rate of innovation has been observed during the 1990’s (FIM/IFPMA,1998)<sup>53</sup>.

The nature of pharmaceutical research has changed dramatically in the last 20 years with the application of the "rational drug design" method and the use of combinatorial chemistry, high-throughput screening, genomics, bio-informatics and other techniques (Kettler, 1999, p. 36). With discovery by design, scientists use knowledge about the causes of human disorders, the properties of drug compounds, and their action in the human organism, to conceptualize the structure of an “ideal” molecule that is expected to restore the altered equilibrium. The ideal molecule is then given to the laboratory chemists, who search for substances whose molecular structures match as closely as possible the theoretical model . This methodology permits to reduce the cost of the “discovery” stage, but does not eliminate the need for bioassay, animal and other tests of the new drug. Under this new paradigm of drug research, pharmaceutical innovation can be divided among different laboratories and firms, based on their different abilities and experience

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<sup>52</sup> For arguments about the greater efficiency of the private industry vis -a-vis the public sector in undertaking R&D, see Kealey, 1996, pp. 242.

<sup>53</sup> In fact, the innovation rate (measured by the development of “new chemical entities”) has substantially decreased in the 1990s. See, e.g., FIM/IFPMA, 1998, p. 21. It is unclear whether a recent reported increase in the number of NCEs may indicate a change in that trend. See Southgate, 2001, p. 80-81.

(Gambardella, 1995, p.23; 79). There is, in fact, a growing trend to contract drug development work with specialized companies; the scale of laboratories is no longer a critical advantage, as it probably was when drug discovery was substantially based on mass screening (Simpson, 1998).

Despite the opportunities opened by these changes for drug research, the pharmaceutical industry has undergone a process of concentration leading to the emergence of very large firms. Bigness, however, does not guarantee a better performance in R&D. On the contrary, under the new paradigm of research, large firms, including pharmaceutical corporations, show “strategic and organizational inertia” which may retard and discourage innovation rather than foster it (Pavitt, 1992; Gambardella, 1995).

The amount effectively invested by pharmaceutical companies for the development of new drugs is a highly disputed issue, in part because there is little transparency on the real expenditures made<sup>54</sup>. Though this issue is beyond the purpose of this paper, it is worth noting that the lack of adequate information limits any serious effort to assess the likely impact of patent protection on pharmaceutical R&D. The figures on R&D provided by the industry (about \$500 million per drug)<sup>55</sup> does not correspond to actual expenditures, but to expenditures adjusted for cost of capital and to compensate for R&D failures<sup>56</sup>. The assumptions made for these calculations are very controversial. In some cases, estimates were based upon capital costs as high as 15 per cent plus inflation, amounting to up to 69 per cent of the total cost (Love, 2001).

It should also be noted that though R&D is an important element in the dynamics of the pharmaceutical industry, of much greater importance seems to be the marketing effort, which involves spending up to three times higher than on R&D (Foud et al, 1998, p. 573). In addition, available data suggests that pharmaceutical companies spend more on marketing and administration than on research and development. As percentages of sales, research and development expenses account for 10-20%, while marketing and administration range from 30-40% (Médicins Sans Frontieres, 2001a)<sup>57</sup>.

In sum, the debate about the role of IPRs in promoting drug research would benefit from a deeper discussion about the conditions under which such activities are undertaken, particularly about the real magnitude of expenditures involved, and on the cost- efficiency of the dominant organization for drug R&D. To the extent that R&D do not represent the main cost item for pharmaceutical firms and that, under strong IPRs protection, such firms may charge the prices that the market would bear, they will have little incentive to improve cost-efficiency in their R&D activities.

## **Public involvement in pharmaceutical R&D**

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<sup>54</sup> See, e.g., Public Citizen, 2001.

<sup>55</sup> See, e.g., FIM/IFPMA, 1998., p. 9. See also Kettler, 1999.

<sup>56</sup> In order to be accurate and do not mislead on the out of pocket expenses actually incurred, reports on R&D should break the costs out into two main categories: the costs of pre-clinical and clinical research, with the costs of financing reported as a separate item.

<sup>57</sup> See also Families USA, 2001.

Though the pharmaceutical industry undertakes some basic research (Ogg *et al*, 1999; Hicks and Katz, 1997), in most cases, the discovery of important new drugs is made by public institutions, which later license their development and exploitation to private firms. Some 70% of drugs with therapeutic gain were produced with government involvement (UNDP, 1999, p.69). Basic Research that led to the discovery of potential “drug leads” has almost always been publicly funded at universities, in-house government facilities, or research institutes in Europe, North America, and Japan. Since the beginning of the 20<sup>th</sup> century, publicly funded research has led to major drug lead discoveries in, for example, tuberculosis (streptomycin and rifampicin), other infectious diseases (various antibiotics), and cancer (various types of chemotherapy)<sup>58</sup>. More recently, publicly funded research has led to the discovery of antiretrovirals for the treatment of HIV/AIDS. Publicly funded genome research has also produced many drug leads (Médicins Sans Frontières, 2001b, p. 20).

In addition to direct involvement in R&D, many developed countries’ governments grant tax and other incentives for R&D, including or particularly in pharmaceuticals. Subsidies for R&D are available in many OECD countries, and are permissible, under certain conditions, under the WTO agreements. In the USA, for example, tax credits<sup>59</sup> and market exclusivity have been granted for the development of “orphan drugs”<sup>60</sup>. The US government paid for the initial development, pre-clinical research, and clinical research<sup>61</sup> of many important drugs, including many used for cancer and HIV-related diseases.

There are many examples of public funding of drugs important for the treatment of HIV infection and related diseases, such as 3TC, Invirase, Ziagen, Zerit and Viramune. For instance, the drug d4T -one of the components of a dual therapy to slow the progression of the AIDS virus which Bristol-Myers Squibb sells under the brand name Zerit- was synthesized by Michigan Cancer Foundation in 1966 with the utilization of public funds, and its use to treat AIDS was discovered by Yale University, which holds a patent. Despite the public funding for R&D, Zerit is reported to sell at a price considerably higher than the product available from generic producers (Rosenberg, 2001, p.31 and 52).

It seems possible to conclude that, though the private industry invest the largest part of global funds for health research, the public sector has made and continues to make a significant contribution to pharmaceutical research, including the discovery and/or

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<sup>58</sup> In the area of cancer, a study concluded that of the 37 cancer drugs developed since 1955, the US federal government was directly or significantly involved in the pre-clinical development of 18 drugs. In addition, it played some role in the pre-clinical research for 10 other drugs. In only nine of 37 cases was the National Cancer Institute (NCI) not involved at all in the pre-clinical research. When the drugs reached the stage for clinical research, NCI's role was even more pronounced—NCI played an important role in the funding of clinical research for 34 of the 37 drugs (Chabner and Shoemaker, 1989).

<sup>59</sup> According to one study, pharmaceutical companies received \$ 106.9 million between 1983 and 1993 in tax credit in that country. See <http://www.cptech.org>.

<sup>60</sup> Similar “Orphan drugs” incentives have been implemented in Japan, Singapore, Australia and, more recently, in the European Union.

<sup>61</sup> According to PhARMA clinical evaluation (phases I to IV) account for around 35% of total R&D expenditures (FIM/IFPMA, 1998, p. 20).

development of many important drugs currently on the market. The public sector role in the discovery and development of new drugs is not substantially dependent on the availability of IPRs, since its research agenda is not dominated by profit making objectives.

However, in some countries explicit policies have been applied in order to promote the use of patents and licensing by the public sector as a means to foster technology transfer to the private sector. For instance, in the USA, a public-private cooperative model was promoted since the enactment of the Bayh-Dole Act in 1980, which has been extensively used by the pharmaceutical sector to market public research results under exclusive rights within and outside USA.

While this approach may have increased the commercialization of publicly funded research results, serious doubts have been raised with regard to the benefits of privatizing the results of public funded research, particularly early outcomes and research tools that may be broadly used by the industry:

“Bayh-Dole does not make any sense to promote invention, since while patents may be needed to induce inventing, they should not be granted if inventing would go on in any case... On the other hand, a case can certainly be made that, for many university ‘inventions’ that were funded with public monies... the results of research would be published in any case. Firms, in many instances, would have ample incentive to work with and ‘develop’ what comes out of university research. They usually can patent the developments, or gain the advantage of a head start on the market, or both. No ex-ante grant of an exclusive license is needed to motivate this work, and the presence of a patent and the requirement to get a license to do further work on the original idea may restrict the number of parties who will do that work.

We think that the basic argument behind Bayh-Dole – that companies need to have an exclusive license on an embryonic invention in order to try to develop and commercialize it - is for the most part empirically wrong. Much of inventive activity, in fact, involves exactly companies trying to develop something useful and patentable out of ideas in the public domain. Traditionally the award of the patent has come after something useful has been achieved, rather than well before that stage” (Mazzoleni and Nelson, 1998, p. 277-278; 281-281)

In sum, a significant part of pharmaceutical R&D is not directly dependent on the availability of IPRs, since invention undertaken by public laboratories would take place in any case. Further, the assumption that patents and licensing will maximize the social returns of public investment in R&D, underestimates the effectiveness of publication and other means of knowledge diffusion that may enable society to benefit more than under a system of appropriation and restrictive licensing<sup>62</sup>. Of course, these conclusions do not deny that IPRs, particularly patents, are important devices for the pharmaceutical industry. They do point to the fact that relying on IPRs as the main incentive to develop new drugs is one of the possible public policy options which, as discussed below, does not work

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<sup>62</sup> See also on this subject Mowery, Nelson, Sampat and Ziedonis, 1999, p. 269-306.

efficiently when the development of drugs for the poor is at stake (Médicins Sans Frontières, 2001b, p. 19).

### **Patent protection in developing countries**

One of the main arguments for the recognition of IPRs, particularly patents, for pharmaceuticals is that in order to ensure future R&D it is essential that “strong” IPRs protection be conferred universally. The argument is based on the undeniable contributions that the industry’s R&D has made in the identification of products that provided curative or preventive tools<sup>63</sup> for a vast array of human diseases. Such contributions would not be possible if companies could not recover their high investments in R&D and make a profit thereon. Patents and other IPRs provide one of the mechanisms that encourages future R&D on new products, in exchange for the exclusive use of the R&D outcomes for a certain period.

This argument suggests that the failure to grant appropriate IPRs protection, including in developing countries, would reduce the future flows of funds for R&D and lead to a fatal decline in the innovation performance by the industry. Two important questions, in this context, are the extent to which (a) the income generated by patents in the developing world is actually invested to develop the medicines needed by the poor; and (b) the granting of patents in developing countries, under conditions substantially similar to those applicable in developed countries, is essential to provide incentives for industry’s global R&D activities.

### **Medicines for the poor**

Many of the medicines created for the developed countries markets are equally important for developing countries, particularly for their most affluent population. However, developing countries have clearly different drug demands than developed countries (Lanjouw and Cockburn, 2001, p. 266). The diseases of the poor attract very little R&D efforts by the large pharmaceutical industry, since they are not promising income generators. R&D is driven by market considerations. R&D targeting diseases found in developing countries is marginal. Of the annual health-related research and development worldwide, only 0.2% goes for pneumonia, diarrhoeal diseases and tuberculosis – yet these account for 18% of the global disease burden. (UNDP, 1999, p.69)<sup>64</sup>. According to UNDP,

“In defining research agendas, money talks louder than need - cosmetic drugs and slow-ripening tomatoes come higher on the list than a vaccine against malaria or drought-resistant crops for marginal lands. Tighter control of innovation in the hands of multinational corporations ignores the needs of millions. From new drugs

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<sup>63</sup> The industry may choose in many cases whether to follow a preventive or a curative approach. Thus, it has been noted that “Vaccines are the most cost-effective technologies known in health care, preventing illness in a one-time dose. But they generate smaller profits and have higher potential liabilities than treatments used repeatedly. As a result a consortium of US pharmaceutical companies has united to develop antiviral agents against HIV, but not to produce a vaccine against AIDS” (UNDP, 1999, p.69).

<sup>64</sup> Between 1975 and 1997, only 13 of 1223 new chemicals entities, or 1% were for the treatment of tropical diseases (Byström and Einarsson, 2001, p.35).

to better seeds for food crops, the best of the new technologies are designed and priced for those who can pay. For poor people, the technological progress remains far out of reach” (UNDP, 1999, p.68).

The pharmaceutical industry may not be expected, in reality, to allocate substantial resources in areas where the profitability that may be obtained is low, even if “strong” patents were granted<sup>65</sup>. There is no visible increase in R&D for diseases such as malaria, schistosomiasis, trachoma, malaria, chagas, leprosy and leishmaniasis, despite the fact that *most developing countries* already grant product patents for pharmaceuticals, that *all* such countries will be bound to do so in 2005 and that, even those countries that have delayed the introduction of product patents, have been obliged to grant “exclusive marketing rights” which are *de facto* – though not *de jure* - equivalent to patent protection. This strongly indicates that such industry may be a part of the solution to health problems in developing countries, but cannot be deemed the main instrument to bring the new medicines needed for the devastating diseases that affect the poor. In this sense, a strong patent protection may be of little relevance for the solution of the dramatic problems of poor people in the developing world.

### **Impact on R&D of IPRs in developing countries**

Developing countries account for 80% of the world population, but for only 20% of the global pharmaceutical market (Médicins Sans Frontières, 2001b, p., 16). Several authors have studied the possible impact of the introduction of IPRs - particularly patents - in developing countries, and showed that the incremental incentive provided by additional countries granting product patent protection is not likely to stimulate much additional investment in R&D (Chin & Grossman, 1990; Dearthoff, 1992)<sup>66</sup>.

Scherer examined, in particular, the impact of the introduction of pharmaceutical patents in developing countries, which account for only about one-fifth of world gross national product and where multinational drug companies already had substantial operations despite weak patent protection. He found that if such countries change their laws to provide patent protection for new drugs, these companies will increase their income. With greater quasi-rent potential, drug companies will reoptimize and develop more drugs; under certain conditions (described in Scherer’s model) they would develop 18 drugs instead of 15, leading to a new level of net profits. But in order to leave developing countries’ citizens as well off as before the introduction of patents, a three-fold increase in the number of new drug products would be required. “Indeed”, concludes Scherer, assuming diminishing returns in either the production function or the quasi-rent function or both, it is difficult to imagine circumstances under which such a three-fold increase could

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<sup>65</sup> For instance, Eli Lilly has been reported to order its 6.900 researchers not to bother with any drug unlikely to top \$ 500 million in annual sales (“Eli Lilly: Life after Prozac”, Business Week, July 23, 2001, p. 53).

<sup>66</sup> The more general issue of the welfare implications of the introduction of IPRs in developing countries has been extensively addressed by the literature. Since IPRs protection leads to the transfer of income from consumers in the markets in which IPRs is protected to the inventors or producers, mostly in the developed countries, the harmonization of IP regimes would tend to cause a redistribution of welfare away from Third World countries and in favor of the most industrialized ones (Sideri, 1994, p.7). See also Nogués (1993) and Keely (2000).

ensue. The opposition of LDC citizens to strong pharmaceutical patents becomes understandable” (Scherer, 1998a).

It is uncertain what the cost effects of the exploitation of the new research possibilities opened by “genomics” and “proteomics” will be, and the extent to which the application of those disciplines and other new techniques may help to reverse the declining trend in the development of new products. What is certain, however, is that all WTO Member countries are obliged to recognize pharmaceutical patents, and most developing countries already grant them despite the transitional periods provided for by the TRIPS Agreement<sup>67</sup>. Therefore, pharmaceutical firms will be able to generate patent-based income almost universally, since most countries in the world are contributing or will soon contribute to their R&D budgets and profits.

Can the granting of compulsory licenses or the admission of parallel imports by some developing countries threaten the long term viability of drug R&D? This is unlikely because the developed countries’ markets already provide a significant mass of resources for R&D, and the pharmaceutical firms have had large sales in many developing countries, including the largest markets, even in the absence of patent protection<sup>68</sup>. In addition, the contribution to R&D that could be made by some developing countries or regions is negligible in global terms. For instance, Africa – one of the regions where the problems of access to drugs are more severe - only accounts for around 1.3% of world pharmaceutical sales<sup>69</sup>.

### **Conditions of protection**

A more detailed consideration of the conditions for the granting of compulsory licenses and the operation of parallel imports, seem to confirm that the use of such mechanisms is not likely to substantially affect future flows of funds for R&D.

#### *Compulsory licenses*

The granting of a compulsory license may be an important tool to introduce competition and thereby lower the prices and affordability of drugs. The threat to future industry’s income and funding for R&D posed by the granting of compulsory licenses has been grossly exaggerated by some industry’s advocates<sup>70</sup>. When a compulsory license is granted, it only applies to *particular* medicines under particular circumstances. A scenario of use of such licenses by a large number of countries on a large number of items is unrealistic.

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<sup>67</sup> Only thirteen countries notified the application of the “mail box” transitional provision of the TRIPS Agreement (WTO, 2001, p. 6). Many of those countries (e.g. Brazil, Argentina) already grant product patents for pharmaceuticals.

<sup>68</sup> For instance, in Brazil and Mexico the large pharmaceutical firms already controlled the largest part of the markets before the introduction of product patent protection in the 1990’s.

<sup>69</sup> See [www.ims-global.com/insight/report/global/report.htm](http://www.ims-global.com/insight/report/global/report.htm).

<sup>70</sup> According to Rozek (2000) compulsory licensing in pharmaceuticals undermines the incentives of international pharmaceutical firms to engage in innovative activities (Executive Summary).

Despite that patent laws in many developed and developing countries provide for compulsory licenses, this mechanism has been rarely used, with the noticeable exception of the USA, and of Canada between 1969 and 1991 (Correa, 1999).

Although in the United States the patent law does not provide for compulsory licenses, this is probably the country with the richest experience in the granting of compulsory licenses to remedy anti-competitive practices. More than one hundred such licenses have been granted (Scherer, 1998b) involving several thousand of patents . Compulsory licenses have been granted in the United States in relation to present and future patents. In some cases, moreover, the patentee was required to make the results of its research readily available to other industry members<sup>71</sup>, or to transfer the know-how actually used in production<sup>72</sup>.

In Canada, compulsory licensing in respect of medicines was first introduced in 1923. The Patent Act, SC 1923 c 23, allowed for compulsory licenses to be granted for the manufacture, use and sale of patented medicines. In 1969, the Canadian Patent Act was amended. The grant of compulsory licenses became admissible for importation (not only manufacturing ) of a patented medicine. After the 1969 revision a large number of compulsory licenses were granted against a 4% royalty on net sales prices<sup>73</sup>; if the medicine was composed of different active ingredients, the royalty was divided by the number of patents at stake (Gendreau, 1997, pp. 2-3).

The Andean Group countries, Chile and Mexico introduced different types of compulsory licenses in 1991. However, no such license has been granted. The same applies to Argentina, Brazil<sup>74</sup>, India<sup>75</sup> and other developing countries. The fact that compulsory licenses have not been granted does not seem, however, that the system is without value. As noted by Ladas (1975)

“The practical value of the existence of compulsory license provisions in the Patent Law is that the threat of it usually induces the grant of contractual licenses on reasonable terms, and thus the objective of actually working the invention is accomplished” (p.427)<sup>76</sup>.

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<sup>71</sup> Hartford -Empire case (Finnegan, 1977, p. 139).

<sup>72</sup> For instance, in *FTC v. Xerox Corporation* (Goldstein, 1977, p. 124). See also Correa and Bergel, 1996.

<sup>73</sup> In the case of sales of medicines for export, the royalty applied generally was 15% of the net selling price in bulk (Gaikis, 1992, p. 21).

<sup>74</sup> The Ministry of Health, however, has recently indicated the possibility of using compulsory licenses in relation to anti-retrovirals commercialized by Merck Sharp & Dohme and Roche, unless a price reduction was agreed. The license would be granted for production by the State-owned Farmanguinhos (Fundação Oswaldo Cruz) (*O Estado de São Paulo*, May 16, 2001).

<sup>75</sup> Indian drug company CIPLA is reported to be in the process of requesting compulsory licenses in South Africa, probably involving patents on 3TC, AZT and combinations of these drugs, plus nevirapine.

<sup>76</sup> More recently, Beier (1999) has presented a similar view in a comprehensive study on the matter. He argues that compulsory licenses "through their mere existence as well as through the apprehension of compulsory license proceedings are liable to increase the willingness of a patent owner to grant a voluntary license" (p. 260).

There are some objective factors that explain why the compulsory licensing system does not seem to attract many applicants.

First, many national laws require that the compulsory licensee undertake the *production* of the patented invention in the country where the license is to be granted. However, only a few developing countries possess the entrepreneurial and technical capabilities necessary to envisage the local production of drugs, or markets big enough to justify local production.

There is nothing in the TRIPS Agreement that prevents a member to establish that a compulsory license be worked through importation, and not local production. However, once the obligation to protect pharmaceutical products become fully operative (after 2005), it will not be possible to find independent foreign sources for the importation of a protected product other than the patent owner or his licensees; therefore, the compulsory license would be *de facto* impracticable. The only alternative source of supply could be another compulsory licensee for the same patent in a foreign country<sup>77</sup>, but this also has a limitation: a compulsory license should be granted, in accordance with article 31 (f) of the TRIPS Agreement, to supply “predominantly” the domestic market<sup>78</sup>.

Second, a compulsory license may be revoked when the circumstances that led to its granting have ceased to exist and are unlikely to recur (article 31 (g) of the TRIPS Agreement). If, for example, such a license was granted to remedy a situation of abusive prices, it may be revoked when the prices are normalized, a possibility that is under the control of the patent owner. Paradoxically, the most efficient a compulsory licensee is in remedying an anticompetitive situation, the highest the possibility of losing the license he had obtained.

The precarious nature of a compulsory license, in fact, creates a strong risk and discourage the request of any such license by third parties, since they may not have sufficient time to recover their investments. Though the legitimate interests of the compulsory licensee should be considered before the revocation of the license is decided, it is highly uncertain how this safeguard will be applied<sup>79</sup>.

Third, given the stiff opposition by patent holders to the granting of compulsory licenses, many domestic companies may prefer to look for other options rather than to confront with patent holders (often actively backed by their governments). Further, many local companies are growingly dependent on voluntary licenses granted by large

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<sup>77</sup> As discussed below, if imports were made from a compulsory licensee, the importation may be deemed covered under the “exhaustion principle”. Therefore, it would not be necessary the use of a compulsory license in the importing country (since the “parallel” imports would be, in any case, legitimate).

<sup>78</sup> The Council for TRIPS has been mandated by the Doha Ministerial Conference to “find and expeditious solution to this problem and to report to the General Council before the end of 2002” (para. 6 of the Declaration on the TRIPS Agreement and Public Health, WT/MIN(01)/DEC/W/?, 14 November 2001)

<sup>79</sup> Article 31 (g) of the TRIPS Agreement is a good candidate for revision, should the TRIPS Agreement be subject to review in the future, in order to allow a compulsory license to last for the whole life of the patent, provided that the licensee complies with the terms and conditions of its granting.

pharmaceutical companies, and would be reluctant to enter into disputes that may limit their future access to commercially interesting products.

Fourth, compulsory licenses must be *non-exclusive*; this means that the patent owner can continue with the exploitation of the invention and can compete, as aggressively as it wishes, with the compulsory licensee, with the advantages conferred in many cases by the prestige of brand names and abundant resources for marketing. In fact, the market share that compulsory licensees may obtain may be small and even insignificant, on account of the reputation and dominant presence of the patent owner in the market (Watal, 2000). Given the characteristics of competition in the pharmaceutical market, often high priced medicines perform commercially better than their low priced equivalents.

Finally, if a compulsory license is granted, the licensee will be bound to pay a royalty to be determined in accordance with “the economic value” of the license (article 31 of the TRIPS Agreement). In the United States such licenses have been granted against a reasonable royalty, generally determined on the basis of the “willing-buyer, willing-seller” formulation (Finnegan, 1977, p. 140). Though in some cases royalties of up to 6% have been reported (McGrath, 1991), royalty rates have been rather modest in others<sup>80</sup>. For instance, in the case of Ciba-Geigy and Sandoz merger (1997), the FTC specified that the royalties for the non-exclusive Cytokine licenses (which involve gene therapy), and the Anderson gene therapy patent, could be no greater than three per cent off the net sales price.

In the United Kingdom, royalty rates charged for “licenses of right” granted pursuant to the 1977 revision of the UK Patent Act were reportedly higher than those indicated for USA and Canada. The royalties paid varied from about 23 per cent to 31 per cent, while most of the reported royalty rates were between 25 per cent and 28 per cent on the licensee's selling price (Cohen, 1990, p. 28 )

To sum up, recourse to compulsory licenses (as currently regulated under the TRIPS Agreement) by developing countries will not be always easy nor automatically solve the problems of access to drugs. For the same reasons, the system does not pose a serious challenge to the position of patent holders and their capacity to extract benefits from their rights. Moreover, according to some studies<sup>81</sup>, the royalties received from voluntary/compulsory licensees may provide the patentee with a sufficient compensation for the R&D costs<sup>82</sup>. The amount obtained through payments under a generalized compulsory license scheme (i.e. patents without exclusive rights) may, under certain conditions, be equivalent to the sums obtainable under exclusivity, but prices charged to consumers would be substantially lower (Challú, 1992).

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<sup>80</sup> In some cases the compulsory licenses were conferred in the United States royalty free. For instance, in *FTC v. Xerox Corporation* (Goldstein, 1977, p. 124).

<sup>81</sup> See, e.g., Kamien, 1992; Kamien, Oren and Tauman, 1992; McGee, 1966.

<sup>82</sup> Arrow noted that when royalty payments may be requested, an inventor will be able to obtain profits without affecting the competitive nature of the industry (Arrow, 1962). It is common practice for the pharmaceutical companies to license their products under patent to other companies. See, e.g., Cabiedes Miragaya, 1992.

Scherer analyzed the extent to which the granting of compulsory licenses in USA affected R&D expenditures by firms and, particularly, whether such licenses diminished or destroyed the incentives to undertake R&D by patent holders. His statistical findings relating to 70 companies showed no negative effect on R&D in companies subject to compulsory licenses but, on the contrary, a significant rise in such companies' R&D relative to companies of comparable size not subject to such licenses (Scherer, 1998b, pp. 107-108). It has also been found that in view of the significant effort devoted to the development of "me too" drugs, an extensive use of such licenses may allow to reduce the costs of R&D. According to Tandon,

"Firms spend large sums of money on efforts to "invent around" the patents of their competitors. Under generalized compulsory licensing, these expenditures would be unnecessary, which might increase the welfare benefits" (Tandon, 1982, p. 485).

In the light of the above analysis, it seems safe to conclude that it is unlikely that pharmaceutical firms be deprived of any significant portion of their patent-based income through the use of compulsory licenses. Further, when such licenses are granted, the patent owners normally receive a fair contribution to their R&D budgets while, at the same time, the affordability of drugs is improved as a result of increased competition.

#### *Parallel imports*

Parallel imports involve the import and resale in a country, without the consent of the patent holder, of a patented product which was put on the market of the exporting country by the title holder or in another legitimate manner. The underlying concept for allowing parallel imports is that since the inventor has been rewarded through the first sale or distribution of the product, he has no right to control the use or resale of goods put on the market with his consent or in other form that allowed him to obtain a compensation. In other words, the inventor's rights have been "exhausted"<sup>83</sup>.

Parallel imports can only take place in relation to "legitimate" products sold in a foreign country. This means that while selling the patented products in such country, the patent owner is obtaining, as part of the products' price, a compensation for the protected technology. If the product is sold by a licensee (voluntary or compulsory) the patent owner will receive a royalty payment.

Hence, when parallel imports take place, the patent owner has received a remuneration for the invention, as a share of the total sales price charged in the country of origin. Parallel importation does not deprive the patent owner of contributions to future R&D, though the level of such contributions may be lower than what he would have obtained if the segmentation of markets prevailed<sup>84</sup>.

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<sup>83</sup> The doctrine of "exhaustion of rights" may be applied at the national level (rights are deemed exhausted domestically and the commercialization in foreign countries is not deemed to have exhausted the patentee's rights), at the regional level, as in the case of the European Community (exhaustion is deemed to have occurred if commercialization took place in a country member of a regional agreement), or at the international level. The presentation made in the text refers to this latter case.

<sup>84</sup> No economic analysis on this issue has been made. The net impact of parallel importation on contributions

There is no evidence that the parallel importation of medicines is taking place on a broad scale in developing countries. In many developing countries, such imports are not permitted<sup>85</sup>, or they are so under different, in some cases, quite restrictive, conditions. Thus, parallel imports are allowed in the Andean Group countries when the product was sold by the patent owner or by other party with his consent or economically linked to him (article 54, Decision 486). In Brazil, they are permissible only if the products are sold with the consent of the owner and provided that the invention *is not exploited locally* (article 68.4, Law 9.279). In Argentina, the principle is that only a local voluntary licensee is authorized to parallel import (article 36.c), Decree 260/96).

In the case of South Africa, the scope for parallel imports is also quite limited, since it is subject to a Ministerial order (by the Minister of Health) and only applies for medicines put on the market by the owner or with his consent (article 15C, Medicines Act). Despite this narrow scope, the provision of the South African law was strongly questioned by large pharmaceutical companies<sup>86</sup>.

The pharmaceutical industry strong objection to parallel imports<sup>87</sup> does not seem to be supported by the current situation. It has been argued that the exports of drugs sold at low cost in developing countries to higher-priced markets would affect the industry's ability to fund future R&D<sup>88</sup>. This may be true if parallel trade would reach a significant dimension, but there is no indication that this is likely to happen, at least in the short term.

In effect, trade in medicines is subject to quite stringent national regulations that erect effective barriers to market access. Moreover, parallel imports would only take place where significant price differentials exist. Pharmaceutical firms may reduce such differentials or sell the patented products under different trademarks or packaging in major markets, in order to make parallel importation difficult or unattractive (Watal, 2000). Further, any country may adopt measures to prevent parallel imports (provided that such restriction is not found inconsistent with WTO obligations<sup>89</sup>).

The possibility of allowing for parallel imports is, like the availability of compulsory licenses, an important device to discipline markets and induce drug suppliers to commercialize their products on reasonable conditions. Parallel imports from compulsory licenses may provide in some instances (particularly after the TRIPS Agreement becomes fully operative in all countries) the only way to get access to low priced medicines.

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to R&D will depend, among other things, on the price differentials and volumes of sales, as well as on price elasticity in the importing country.

<sup>85</sup> Many laws do not clarify whether parallel imports are admissible or not. In the absence of a specific rule allowing them, they are likely to be subject to the patent owner exclusive rights.

<sup>86</sup> The legal action was withdrawn in April 2001.

<sup>87</sup> See, e.g. Bale, 2000.

<sup>88</sup> Arguments against parallel trade also include that it will increase opportunities for "counterfeit and substandard products to enter the market" (Bale, 2000, p. 18), but this is essentially a problem of law enforcement that can be addressed under normal procedures.

<sup>89</sup> See Correa, 2000a, p. 82.

Some laws stipulate that in order to be admissible under the Agreement, the supply of the parallel imported products should be made with the *consent* of the patent owner. Therefore, the supply by a compulsory licensee, or even by a voluntary licensee who is not authorized to parallel export would not be legitimate<sup>90</sup>. This restrictive approach<sup>91</sup> seems to be grounded on the “consent theory” developed in Europe<sup>92</sup>, which erroneously assumes that the patent owner enjoys a positive right to the first sale of a protected product (Govaere, 1996, p. 80).

However, patent rights only grant negative rights, that is, the legal faculty to exclude infringers, but no positive rights<sup>93</sup>. Therefore, the consent theory does not provide a sound legal ground when applied to patents. According to the “reward theory”<sup>94</sup>, while selling the patented product in a foreign country, the patent owner is obtaining, as part of the product's price, a compensation for the protected technology (Yusuf and Moncayo von Hase, 1992, p. 117). When the patented product is sold by a licensee, either voluntary or compulsory, the patent owner receives a royalty payment. Hence, parallel importation, even if originating from a compulsory licensee does not deprive the patent owner of contributions to future R&D<sup>95</sup>.

It should also be noted that article 31(f) allows a compulsory license to be granted “predominantly” for the domestic market, thereby admitting that at least part of the production under license can be parallel exported. Based on the principle of “effective interpretation”, which requires that a treaty be interpreted to give meaning and effect to *all* the terms of the treaty, it seems necessary to admit that parallel imports originating from a compulsory licensee are to be deemed lawful.

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<sup>90</sup> In the USA, for instance, parallel imports are authorized “in the absence of enforceable contractual restrictions” (Barrett, 2000, p. 984).

<sup>91</sup> A restrictive interpretation has been suggested on the scope of article 6 of the TRIPS Agreement, according to which the patent owner’s consent will be required as a condition for the legality of parallel imports. This interpretation has been grounded on the footnote to article 51 of the TRIPS Agreement and on approach adopted by the Washington Treaty on Integrated Circuits. However, article 51 only applies to trademarks and copyrights and the Treaty specifically deals with semiconductors. There is nothing in the TRIPS Agreement that would sustain the application of such interpretation in the area of patents.

<sup>92</sup> Some decisions by the European Court of Justice have admitted, however, parallel imports originating from a country where no patent protection was granted. See, e.g., the *Merck v. Primacrown* and *Beecham Group v. Europharm* cases, ECJ, 5 December 1996, joined cases C 267/95 and C-268/95.

<sup>93</sup> See the unambiguous wording of article 28 of the TRIPS Agreement, and the coincident interpretation given by the WTO Secretariat in a recent paper (WTO, 2001); see also Govaere, 1996, p. 80-81.

<sup>94</sup> The reward theory was first formulated by the US Supreme Court who held in *Adams vs. Burke* (84US (17 Wall.)453 (1873)) that “[W]hen the patentee, or the person having his rights, sells a machine or instrument whose sole value is in its use, he receives the consideration for its use and he parts with the right to restrict that use. The article... passes without the limit of the monopoly. That is to say, the patentee or his assignee having in the act of sale received all the royalty or consideration which he claims for the use of his invention in that particular machine or instrument, it is open to the use of the purchaser without further restriction on account of the monopoly of the patentee”.

<sup>95</sup> No economic analysis on this issue has been made. The net impact of parallel importation on contributions to R&D will depend, among other things, on the price differentials and volumes of sales, as well as on price elasticity in the importing country.

## Conclusions

It seems undeniable that the pharmaceutical industry has an important role to play in the future development of new drugs. Nothing in this paper aims at denying such role. However, several assumptions generally made with regard to pharmaceutical R&D and the patent system need to be objectively reviewed.

Much of the R&D made by large pharmaceutical companies is not aimed at developing “new” drugs, but is targeted to the development of substitutes to competitor’s drugs with little or no contributions to the pool of available therapies, or to minor changes on existing products and processes, in many cases intended to extend the term of the monopolistic position that patents confer. The granting of such patents, in some cases with very low or inexistent levels of inventive activity, distorts the nature and function of the patent system, and provides a basis for blocking genuine competition, particularly after the expiration of the basic patents on a given drug.

The consideration of the level of IPRs protection in pharmaceuticals needs also to take into account whether the current organization for R&D provides an adequate framework for a cost efficient realization of such activities. It seems clear that commercially driven R&D organizations are unlikely to provide solutions for the diseases that mainly affect the poor.

The debate on the extent of IPRs protection for pharmaceuticals often falls short of recognizing the significant support received by the pharmaceutical industry for R&D activities and the decisive role of the public sector, particularly in the discovery phase. The marginal dollar invested in R&D by the pharmaceutical sector has a lower social return than the same dollar invested by the public sector, which will continue to invest absent a profit. Patenting and licensing practices applied by public R&D institutions should be reviewed, since they may restrict rather than foster innovation.

Given the relatively low weight of developing countries in the pharmaceutical market, the pro-competitive measures that such countries may adopt in the framework of the TRIPS Agreement, will not significantly diminish global incentives for R&D save, perhaps, in the case of products specific for the poor. In this latter case, however, even if developed, the new products may remain unaffordable.

Many developing countries have provided in their national laws for mechanisms (such as compulsory licenses and parallel imports) that mitigate the market power conferred to patent owners. The use of such safeguards (though limited today) may facilitate access to *existing* patented drugs and to generics after the expiration of the relevant patents. It is unlikely that the use of those safeguards affect in any significant manner the funding of future R&D. Statements about the harm that the adoption of such measures in developing countries may cause to global R&D, are not grounded on any conclusive evidence.

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