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*Issues in the Post-2005 TRIPS agenda*

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# *Issues in the Post-2005 TRIPS agenda*

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## **Abstract**

Pharmaceuticals is one of the few industries in which patents are recognized as being key instruments for privately appropriating the economic benefits of innovation. Competition is largely based on innovation, and basic science is becoming increasingly crucial for the discovery and development of new products. Pharmaceuticals also occupy an extremely socially sensitive sector: large parts of the population increasingly perceive health care as a fundamental human right. For developing countries in particular, health has become a major issue, magnified by the tragedies of pandemics like HIV/AIDS. Controversies about the welfare implications of patents have characterized this industry ever since its inception. But in the last thirty years or so, the establishment of a strong tendency towards an extremely tight IP at the global level regime has made this debate even more heated. In this work, we begin by succinctly reviewing the main problems and the available evidence concerning the relationships between IPRs, innovation and welfare in pharmaceuticals. Next, we summarize the main theoretical arguments in favour and against (strong) IPRs in pharmaceuticals and present the little direct available empirical evidence, concerning respectively innovation and drug prices. Finally, we focus on TRIPS and Access to Care in developing countries, with particular reference to the case of HIV (the most emblematic example of the problems generated by enforcement of the TRIPS agreement).

## **1. Introduction**

Pharmaceuticals is one of the industries where the debate on the role and effects of patent protection is more virulent. This sector brings the trade-offs and issues involved in patent theory and practice to their extreme consequences. Pharmaceuticals is one of the few industries in which patents are recognized as being key instruments for privately appropriating the economic benefits of innovation and, therefore, serving as an important incentive for innovation. In this sector, competition is largely based on innovation, and basic science is becoming increasingly crucial for the discovery and development of new products. Pharmaceuticals occupy an extremely socially sensitive sector: large parts of the population increasingly perceive health care as a fundamental human right. The very definition of what a just society should look like increasingly involves references to health care. For developing countries in particular, health has become a major issue, magnified by the tragedies of pandemics like HIV/AIDS. Controversies about the welfare implications of patents have characterized this industry ever since its inception. But in the last thirty years or so, the establishment of a strong tendency towards an extremely tight IP at the global level regime has made this debate even more heated, especially but not exclusively for developing countries.

In this chapter, we begin by succinctly reviewing the main problems and the available evidence concerning the relationships between IPRs, innovation and welfare in pharmaceuticals. Section 2 summarizes the main theoretical arguments in favour and against (strong) IPRs in pharmaceuticals and present the little direct available empirical evidence, concerning respectively innovation and drug prices. Section 3 focuses on TRIPS and Access to Care in developing countries, with particular reference to the case of HIV (the most emblematic example of the problems generated by enforcement of the TRIPS agreement) and the post 2005 issues. A brief conclusion summarizes the main points.

## **2 IPRs, Innovation and Welfare in Pharmaceutical Industry**

### ***2.1 Patents as an incentive to innovation: the background***

Patents are considered to be a key factor sustaining innovativeness and growth in the pharmaceutical industry. At the same time, the very nature of the product of this sector - drugs and health - magnifies the social costs involved by patent protection. Critiques that the monopoly power granted by patents was leading to excessive prices and profits have been recurrently advanced. For example, in the USA, the Kefauver Commission debated this claim in the 1960s, and suggested that patent protection should be considerably shortened (Comanor, 1986). But these suggestions were never transformed in laws and it was felt at the time that the patent system was sufficiently balanced: if anything, its negative implications should be counterveiled by inducing competition after patent expiry or – as in many European countries - by price controls.

The debate has become even more heated in the last decade, following the tendency towards the establishment of a very tight IPR regime, first in the USA and then in other industrialized countries and - through the Trips - at the global level. The main steps of these process have been already discussed in this volume (see Cimoli et al., 2011) and we shall not recall them again.

To organize the discussion of these issues, it might be worthwhile to remind instead the two basic arguments for (strong) patent protection. First, patents provide an incentive for profit motivated agents to engage in innovative activities: absent patents, the outcome of research would have the characteristics of a public good, with consequent under-investment. Public funding of research would then become necessary. Second, patents disclose information and may induce the commercialization of innovation and the development of markets for technology, allowing for an “ordered” path of exploitation of such knowledge and avoiding the wasteful duplication of efforts.(Arora et al. 2001).

The first argument is certainly relevant for pharmaceuticals which has been – especially after World War II - a highly innovative (and profitable) industry: it is one of the most R&D intensive sectors (with the R&D to sales ratio approximating 15% in recent years<sup>1</sup>). The costs of R&D are substantial and they have been soaring in recent years. Moreover, innovation is an extremely uncertain process, which - as Sutton (1998) suggests - can be usefully described as a lottery. In addition, it has to be reminded that innovations tend not to build on preceding work: technological progress is only mildly cumulative and firms find it difficult to use the knowledge accumulated in developing one product for developing a truly different one. Thus, large R&D portfolios allow firms to pool the risk of promising molecules failing at one point in the R&D process. Profits from the sale of products that succeed on the market can cover the costs of unsuccessful R&D undertakings (Fink, 2008). Conversely, imitation is relatively easy and marginal costs of production are comparatively low. Thus, without patents, the product of the pharmaceutical industry - i.e. the knowledge embodied in the drugs - would be a public good.

These features contribute to define the patterns of competition in the industry and market structure. Firms compete first by trying to discover and develop new drugs. If and when a new molecule is discovered, it is patented and then it goes through a lengthy period of development which may take a decade and entails dramatic rates of attrition: the “real” life of a patent is thus much shorter than the statutory duration. After the introduction of a new drug innovators, mainly thanks to patent protection, obtain a dominant position and enjoy high profits. As patent expiry approximates, innovators engage in developing variants of the original product, trying to obtain new patents and/or extensions to further indications. These strategies of patent “evergreening” have become increasingly important (and controversial), as the generics segment of the industry

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<sup>1</sup>. Estimates vary drastically according to different sources and methodologies. For example, the Pharmaceutical Research and Manufacturers of America (PhRMA) provides a figure around 19% in the USA, whereas according to the National Science Foundation R&D intensity is around 8-10%. It is worth reminding though that marketing expenditures have been also increasing rapidly reaching a ratio to sales ranging between 20-25% in the USA according to different sources (Gagnon and Lexchin 2008).

grows and consolidates. Innovators try also to defend their market power through marketing strategies, which often result in even higher prices of the branded drug (Pammolli et al., 2002).

## *2.2 Patents as an incentive to innovation: the evidence*

However, it is not clear how much does patent protection actually stimulate innovation in pharmaceuticals. The empirical evidence on these issues is surprisingly thin. There is extremely robust evidence – mainly obtained by surveys - that in pharmaceuticals patents are deemed by managers to be an important tool for privately appropriating the economics benefits of innovation and that R&D would be substantially reduced in the absence of patent protection (Mansfield et al., 1981; Levin et al., 1987, Cohen et al. 2000). Yet, innovative pharmaceutical companies have historically used instruments other than patents to extract profits from their innovations: for example, advertising, direct foreign investment and licensing.

Moreover, throughout the history of pharmaceuticals, the scope and efficacy of patent protection has varied significantly over time and across countries. Many European countries offered protection only for processes, not products. France introduced product patents in 1960; Germany in 1968; Japan in 1976; Switzerland in 1977; Italy, Netherlands, and Sweden in 1978; and Canada and Denmark in 1983. In many cases, the absence of this protection did not seem to produce negative effects on innovation.

Last, it is worth reminding that the remarkable performance of this sector has been sustained by the combination of different factors, other than patents. Summarizing heroically a complex story (see for instance, Henderson et al., 1999), two fundamental factors have to be emphasized. First, public support to biomedical research. Second, the development of the Welfare State - especially of National Healthcare systems - provided a rich market for drugs in the developed world - even if obviously the features varied drastically across countries – which sustained industry growth on the demand side.

The role of public support to biomedical R&D can hardly be overestimated. It boomed

after World War II and - especially in the USA – it continued to grow steadily thereafter. Nowadays, it is estimated that almost 50% of biomedical R&D is funded in the USA by public sources -- mainly the national Institutes of Health, NIH - (De Francisco and Matlin, 2006) and according to other estimates Federal Government sponsored health-related research was even larger than the whole sum spent by the industry (CBO, 2006). This research is primarily directed towards more basic science, although there are many instances of new drugs being developed almost entirely through NIH support: whilst it is difficult to estimate – both conceptually and statistically - the shares of basic and applied research, an overwhelming share of basic research leading to new molecules is certainly performed in public institutions and financed by public funding.

Public research creates the opportunities for the discovery and development of new drugs and hence for private R&D investment. Indirectly, it raises the productivity of private R&D by supporting the training of researchers working in the private sector. More generally, public funding is essential for developing the fundamental knowledge base and infrastructures that allow the industry to prosper and to attract further funding through the financial markets, venture capital and public equity funds which have sustained the development of biotechnology.

On the demand side, the health of the pharmaceutical industry depends quite obviously on the ability of consumers to pay for the products they are offered, especially when patent protection makes drugs very expensive. In this respect, a crucial role is played again by governments, which to different degrees and in widely different fashions contribute to pay for drugs. To give an example, even in the USA, the share of national health expenditures borne by public funds has been increasing from around 25% in 1960 to almost 40% in 1970 (following the introduction of Medicare and Medicaid in 1965) to reach 46.2% in 2007. And an increasing proportion of national health expenditures is given by prescription drug expenditures, reaching more than 10% in recent years.

Given the basic pre-conditions, only a few studies have tried to measure directly the impact of patent protection on innovation in pharmaceuticals. Indeed, these exercises are made difficult to carry on and to interpret because of both paucity of data and the existence of complex —often non-linear - relations between measures of patent protection, innovation and other crucial variables like technological opportunities and size of the market. Thus, Schankerman (1988) estimated the value of patent rights using data on patent renewal rates and fees for France, and computed the equivalent cash subsidy to R&D, obtaining a value of only 4 percent. However, this result might depend on the fact that, in France, drug prices are very low. Indeed, a similar exercise for Germany yielded a value of 15.2 percent (Lanjouw, 1998b).

These studies focus on the impact of patents on R&D or on innovation as measured by patents themselves. Arora et al. (2008) use survey data to estimate the so-called patent premium — that is, the proportional, incremental increase in the value of an innovation that is realized by patenting it. A value of the premium less than one would, therefore, imply a loss. Results indicate an expected patent premium around 1.3 in biotechnology and 1.05 for drugs. However, these values increase considerably — to 2.45 and 2.3, respectively — if the patent premium is computed conditionally on having actually patented the innovation. These results imply that a 10% increase in the patent premium increases R&D by 10.6 % in biotech and by 8.9 % in drugs, corresponding to an equivalent subsidy rate equal to 22 percent. Moreover, a 10% increase in patent premium increases patent applications by 14.3 percent in biotech and by 12.5 percent in drugs.

These results are broadly in line with the findings by Acemoglu and Linn (2004), who estimate that, in pharmaceuticals, a 1% increase in the size of the market for pharmaceuticals products raises the number of new drugs by 4-to-6 % implying an elasticity of innovations to R&D ranging from .8 to .85.

### ***2.3 Strengthening patent regimes***



A slightly different question concerns the strengthening of patent regimes. First, it has been noted that reforms of patent laws do not appear to have had a significant impact on the innovative capabilities of industries like the Italian or Japanese pharmaceuticals industries. If anything, patent protection to drugs might have had a negative effect, further weakening national industries mainly composed of generic producers (Scherer and Weisburst 1995). Conversely, the cases of India, Israel and partially Brazil are examples where vibrant domestic production of generics has been developed in the absence of patent protection (see, among others: Lanjouw 1998a, Ramani and Maria 2005, Chaudhuri 2006). Here, the little evidence available so far suggests that the introduction of TRIPS might have deleterious effects, without promoting indigenous innovative activities. A few Indian companies are actually trying to enter the club of innovative firms, with mixed results thus far. On the other hand, while evidence does not yet show any dramatic shake-out of local producers of generics, most analysts seem to agree that a substantial restructuring is bound to occur. Similarly, data concerning the Brazilian case show a marked increase in domestic patenting activities, which is however due almost exclusively to foreign multinationals (Laforgia et al., 2008).

These insights are confirmed by other studies, which suggest that the relationship between innovation and the strength of the IPR regime has an “inverted U” shape. With specific reference to pharmaceuticals, Qian (2007) examines the effects of patent protection on pharmaceutical innovations for 26 countries that established pharmaceutical patent laws during 1978–2002. Controlling for country characteristics through matched sampling techniques she finds that national patent protection alone does not stimulate domestic innovation. Domestic innovation accelerates in countries with higher levels of economic development, educational attainment, and economic freedom. But if anything, above a threshold further enhancement of IPRs actually reduces innovative activities.

In sum, there are strong reasons to doubt that strengthening IPRs - especially in developing countries - would have a positive impact on domestic innovative activities. Such effect presumes sufficient scientific and technological capabilities, access to knowledge and active participation in research networks, and large domestic markets and/or the ability to export. Conversely, stronger IPRs might possibly make life more difficult for local brands and generics producers, especially if data-exclusivity agreements and patentability for second-use provisions are enforced. Similarly, there is so far no evidence that stronger IPRs in developing countries have introduced incentives for developing drugs for local diseases — for example, malaria. Decisions concerning the direction of innovative activities are still influenced by considerations of profitability, both by local and foreign innovators (Ramani and Maria, 2005).

Finally, it is important to notice that over the last two decades the productivity of R&D and the innovative performance of the industry have been falling. Despite the enormous opportunities opened by the “molecular biology revolution” since the mid 1970s and in a period when the patent regime was becoming increasingly stronger, R&D expenditures have increased tenfold while patenting output increased only sevenfold since 1978 (Nightingale and Martin 2004). The number of New Chemical Entities (NCE) approved by the FDA in the U.S. has been declining since the early 1990. Similarly, Pisano (2006) shows that the number of compounds developed by commercial organizations that have progressed at least to human clinical testing has not increased significantly since the advent of the biotechnology revolution. Moreover, only a half of NME approvals result from “priority” NMEs— those judged by the FDA to provide “a significant therapeutic or public health advance” over existing drugs— and only about one-third of new-drug applications submitted to the FDA are for new molecular entities. Most of the rest are either for reformulations or incremental modifications of existing drugs or for new “on-label” uses. The issue remains however hotly contested, given that these kind of drugs do sometimes entail significant benefits.

Various explanations have been suggested to explain the “falling productivity” paradox. Some interpretations are relatively optimistic, emphasising that the production of new drugs is characterised by strong cyclical components. The current downswing might therefore be considered as a temporary phenomenon. Other explanations point to either more stringent regulation<sup>2</sup>, or to an intrinsic difficulty in discovering new drugs for increasingly complex pathologies (signalling an incumbent “maturity” of the industry, see Nightingale and Martin, 2004). In a more radical stance, it is suggested that large pharmaceutical companies have moved away from truly innovative research, either developing compounds originating from basic research conducted at universities, hospitals and biotechnology companies (one third of new drugs) or concentrating on the development of me-too-drugs and minor improvements upon existing products. According to this interpretation, now big pharma does little more than serve as a manufacturing and especially marketing organisation, exploiting knowledge generated by public research and biotechnology firms.

The question remains open: while drug discovery and development now rely on a dense web of interactions between universities, biotech companies, hospitals, firms organizing trials, and so forth, large corporations still maintain key positions as integrators of the whole process (Orsenigo et al. 2001). Also, it is not possible to draw from these observations any strong inference about the relationships between the strength of the patent regime and innovative performance. One might suggest that the recent performance of the industry would have been much worse with a milder IPR regime. Yet, if anything, these trends confirm at least that no simple relation exists between patent protection and innovativeness.

## ***2.4 Patents as incentives to commercialize innovations***

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<sup>2</sup> However, in more recent years, regulations have become more relaxed and approval times shortened (due to the Prescription Drug User Fee Act in 1992 and the FDA Modernization Act in 1997).

The second set of arguments supporting (strong) patents conceives IPRs as a mechanism for inducing the development and commercialization of inventions and for creating markets for technologies (Arora et al., 2001). The Bayh-Dole Act is clearly based on these assumptions.

Here again, as discussed in Cimoli et al. in this volume (Cimoli et al 2011) both the theory and the empirical evidence are far from conclusive.

First, the development of the biotechnology industry is customarily considered as one of the best examples of the positive role of patents in this respect. Indeed, there is evidence that markets for technology have grown rapidly in the last two or three decades and that patenting has favoured the creation of new specialized “knowledge-base” companies who sell or licence their patents to larger corporations. The boom in university patenting and in the creation of biotech companies (often founded by university scientists) are typically cited as examples of the positive effects of the “new” IPR regime on the commercial exploitation of basic scientific research.

Yet, according to some analysts the picture is not unambiguously rosy. First it must be simply noted that, as universities and public research institutes have adopted aggressive strategies for patenting and commercializing their research efforts, the taxpayers pay twice for medical R&D: first through government-sponsored scientific research and then through above marginal cost pricing of patented medicines (Fink, 2008). Second, the performance of the biotechnological segment looks disappointing in terms of both operating profits and new drugs and it is argued that the business model which has emerged in this sector - based on strong patents on results of basic research, venture capital and knowledge transactions between specialized biotechnology firms and larger companies developing and marketing the resulting drugs - might not be economically and socially efficient. A more effective organizational architecture should imply free basic research and more integrated and long-term oriented firms (Pisano, 2006, Coriat et al., 2003).

Third, as discussed in other chapters of this book, various studies have shown that the effects of the Bayh-Dole Act on technology transfer from university to industry are largely overestimated. Third, there is contrasting evidence that university scientists have shifted their focus from basic to applied research. Much of the research conducted in universities is located in the so-called Pasteur's quadrant (i.e., it is at the same time basic and use-inspired (Stokes 1997)), and, if anything, the evidence seems to indicate strong correlations between patenting and publishing (Agrawal and Henderson 2002, Azoulay et al. 2004, Geuna and Nesta 2006, Breschi et al. 2005). Walsh et al. (2003), in a survey of biomedical researchers in universities and private companies, find no major delays or abandonment of projects due to transaction costs, but some evidence of increasing obstacles and delays in securing material transfer agreements for research purposes. Other studies, however, find evidence for a quantitatively modest, but statistically significant, anticommons effect (Murray and Stern 2006) and document solid evidence on publication restrictions for sponsored research in the life sciences (Thursby and Thursby, 2006). More generally though costs of litigation have been soaring and industry increasingly complains about the negative effects of very aggressive patenting policies by universities.

In the case of developing countries, stronger IPRs might hinder the development of domestic scientific capabilities if royalties on basic research tools are too expensive. However, for these countries, it has been sometimes argued that well-defined IPRs may attract foreign direct investment (FDI) and, possibly, related R&D. This argument has some empirical support (Maskus et al., 2004), particularly as it concerns clinical trials and market-development activities. Yet, it is widely recognized that IPRs are only one of the motivations leading to FDI. Other considerations — the availability of local skills, research infrastructures and capabilities, and demand characteristics, as well as other institutional and legal preconditions — are usually more important<sup>3</sup>. Moreover the recognition of patent protection in developing countries with

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<sup>3</sup>. A counter-argument is that increased foreign direct investment might produce a crowding-out effect on skilled labour and local researchers for domestic companies.

small domestic markets may push large pharmaceutical companies to concentrate their production facilities in one country – to benefit from economies of scale – and use this country as an export base for the others. In that case the extension of strong IPR regime may hinder FDI.

## **2.6 The Costs of IPRS: distortions on research directions and effects on prices**

Jointly with the potential benefits on innovation, patents entail direct costs to the society.

First, they can distort the directions of innovative activities: research focuses on diseases whose patients are typically rich enough to pay for prescriptions, and, more generally, on patentable cures and treatments (excluding, for example, nutrition, exercise, environment, etc.). Diseases which are rare and/or hit disproportionately poor countries are neglected: for example, patenting related to tropical diseases account for around 0.5% of overall pharmaceutical patents (Lanjouw and Cockburn, 2000).

Second, patents imply higher prices due to monopoly power. In the case of pharmaceuticals, this cost is magnified by the intrinsic properties of the market for drugs. Given the value that users attribute to the product, demand elasticity tends to be low. Moreover, most consumers are insured (privately or publicly) against at least a part of the cost of prescription drugs, so they are only partially interested in drug prices. The prescribing physicians alike are not completely sensitive to prices, both because they will not pay for the prescribed drugs, and because the respect of professional norms makes them more attentive to the safety and therapeutic value of medicines. Patients are not completely informed about the properties of a drug. Also the physicians' prescribing behavior is heavily affected by advertising and brand loyalty, and follows routinary patterns: much of the information available to physicians is provided by the companies themselves. Thus, producers exploit these asymmetries and the low demand elasticity by charging prices much higher than marginal costs.

For these reasons and also for considerations related to the containment of public health expenditures, in many countries (the USA and Germany being notable exceptions), drug prices are subject to various forms of control.

Once again, it is very difficult to evaluate, in general, the effects of stronger IP protection on drug prices. Scarcity of data and the extreme difficulties in computing comparable price indexes (Danzon and Kim 1998) prevent systematic analysis. Clearly, such effect will be different across countries. Some estimates suggest that patents increase prices by an average of 300- 400% above the competitive market price, and in some cases by more than 1000% (Baker, 2004). Price increases after the introduction of patents were estimated by Watal (2000) and Fink (2000) to range from 50 percent to 200 percent in India, while Baker and Chatani (2002) suggest that the average increase in price for pharmaceuticals due to patent protection is probably close to 400 percent (see Maskus, 2001, for a survey).

Three issues deserve specific attention. First, higher prices induced by patent protection stimulate further excessive marketing expenses and political lobbying. Second, price regulations may limit price increases. However, patent holders may choose not to supply the local market at the regulated prices. Conversely, when prices are defined on the basis of reference indexes of prices in other markets, firms have an incentive to bargain for the highest possible prices in the low-price economies in order to gain a higher set of global reference prices (Maskus 2001). Third, price discrimination is often considered as a possible counterbalance to unaffordable drug prices in poor countries. However, this implies banning parallel imports, an important source of low price drugs in many countries (and a source of exports for producers in developing countries). Further, price discrimination is often viewed as anticompetitive because it allows firms to set prices according to market power in each country. Indeed, Maskus (2001) shows that prices are often higher in developing nations than would be expected under a simple price-discrimination equilibrium and, indeed, are at times higher than in the rich nations.

### **3. The signing of the TRIPS and the North/South conflict on Public Health**

#### **Issues**

##### **3.1. The changes introduced by the signing of the TRIPS**

If the effects of strong drug patenting regimes are fiercely debated in industrialized countries, it is hardly surprising that the signing of the TRIPS agreement in 1994, extending to Southern countries the same type of IPR regime that was designed in the North, should renew the controversy.

In substance, TRIPS heralded the enforcement of the new, stricter patent regime introduced in the Northern countries in on a worldwide scale (Reichman and Lange, 1998, Coriat and Orsi, 2002, Cimoli et al 2009). By implementing so-called "minimum standards", this treaty insured a dramatic worldwide upward harmonization and introduced a radical break with some of the foundations and rules which had hitherto shaped international IPR protection. With specific reference to drugs, two main new "minimum standards" were introduced: the patentability of molecules became mandatory in all member countries, and the length of patent protection was extended to 20 years (see Coriat et al. 2006 for a broader discussion).

Two different deadlines were fixed for compliance to the new requirements: 2005 for the majority of DCs, 2011 for LDCs<sup>4</sup>. In practice, however, few countries could resist the pressure exerted by developed countries to anticipate the date of compliance. Thus Brazil modified its IP law to comply with the TRIPS as early as 1996 (Orsi et al 2003) and Thailand even earlier, in 1994-1995. India is a remarkable exception, since it extensively used its right to copy existing molecules right up until the end of the deadline (2005), thus playing a crucial role in the supply of low-cost generic drugs. India thus became until 2005 "the pharmacy of the third world".

It should be recalled that before the signing of the TRIPS agreement, international relations in these matters were governed by *very loose common rules*. International relations in the field of IP

<sup>4</sup> For LDCs this deadline was subsequently extended to 2016.



protection were governed by only two important treaties (Berne and Paris) which imposed few constraints on the signatory countries: before TRIPS, international treaties recognized *the right of different countries to implement different systems of IP protection, according to their level of economic development* and the products concerned. Among these products, essential drugs, considered “basic needs”, were ranked of the highest importance (Scherer and Watal, 2002). Thus, a number of countries dispensed *with any form of IPR for drugs*, while many others dispensed only with patenting therapeutic molecules<sup>5</sup>. As mentioned before, in many cases (Brazil, India, Thailand, just to mention the most important generic drug producers), this made it possible to establish a large local industry for the low-cost production of generic drugs, as a means to ensure access to treatment for the poorer segments of the population (Orsi et al., 2003).

It has to be noticed that in addition to TRIPS, bilateral and regional free trade agreements between the USA, Europe and developing countries are introducing further restrictions:

- a) requirements to extend the patent term for delays in obtaining authorizations to market new drugs and to make patents available for new uses of known products;
- b) provisions that prevent marketing approval of a generic drug during the patent term without the consent of the patent holder
- c) protection of test data submitted to regulatory agencies for marketing approval through exclusive rights lasting at least 5 years, creating in effect a huge barrier to entry for generic suppliers (who should generate their own test data) and conferring market exclusivity even if a patent has not been granted in a particular country.

The developing countries were quick to bring the issue of the impact of the TRIPS on public health care to the forefront. The main preoccupation was the access to drugs in developing countries (Roffe, 2006), particularly in relation to the generic drugs hitherto produced at low cost by certain Southern countries. Since the pandemic was at that time exploding all over the

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<sup>5</sup> According to a recent survey by UNCTAD, before the signing of the TRIPS, no less than 53 countries did not recognize any form of protection for therapeutic molecules in their IP laws and codes (UNCTAD-ICTSD 2005).

world, with a concentration in the poorest countries of the South (and above all in sub-Saharan countries), the debate has been centred on the question of access to HIV/AIDS treatments. Before generic ARVs came into the market in the early 2000s, the price of ART<sup>6</sup> was around 10 to 12 thousand dollars per person per year. Obviously, this prohibited access to care for almost all PLWHIV (people living with HIV) in Southern countries, where no health insurance system, even when there is one, can support such a cost for each patient<sup>7</sup>.

In this context, following the pressures by Southern countries, in November 2001 the fourth Ministerial Conference of the WTO in Doha adopted a Declaration on TRIPS and Public Health<sup>8</sup>. This “Doha Declaration” explicitly acknowledges that IPR can damage public health through their effect on the price of drugs and it affirms the right of countries to interpret and apply the TRIPS in the best way to protect public health. Thus: *“We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all”* (The Doha Declaration, 2001, Article 4). However, the legal status of this declaration is rather weak, since none of its stipulations were ever introduced into the TRIPS agreement itself.

The legal provisions of which Southern countries can make use involve certain exceptions to exclusive patent rights (TRIPS, 1994, Articles 30 and 31), known as “TRIPS Flexibilities” relate mainly to the use of compulsory licenses.

Despite those flexibilities contained in the agreement, the signing of the TRIPS established a new legal “global order”, where the right to “learn by imitating and copying” -

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<sup>6</sup> ART: Antiretroviral Therapy denotes the different combinations of 3 ARVs (tritherapies) used since 1996 in the fight against AIDS.

<sup>7</sup> In fact, it was only in the early 2000<sup>7</sup>, with the arrival of generic copies (proposed by the Indian manufacturers) that this cost fell to around 140 dollars per person per year. For certain drugs this price has continued to fall ever since.

<sup>8</sup> WTO document number: WT/MIN(01)/DEC/2 available at [www.wto.org/english/thewto\\_e/minist\\_e/min01\\_e/mindecl\\_trips\\_e.htm](http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm)

abundantly exploited by today's developed countries as long as they needed it, is now denied to the newcomers (See Maskus 2003 and Maskus et al 2004).

Regarding access to drugs, it has to be noted that until 2005, solutions could be found to cope with the AIDS pandemic. Since many of the active substances used against HIV/AIDS were available on the market before the signing of the TRIPS (or for some countries, notably India, up until the deadline for TRIPS compliance), generic producers could supply Southern countries at very low costs<sup>9</sup>. This fact, combined in certain cases with “preferential pricing” for Southern countries offered by big pharmaceutical firms within the framework of the ACCESS programme<sup>10</sup>, generated competition not only between generic producers and the big pharmas, but also between the generic producers themselves, ultimately leading to substantial reductions in the prices of the most widely used tritherapies: less than 100 dollars per person per year (for a standard 3TC/d4T/NVP combination) today. At the same time, international aid really started to take off in 2003, notably with the setting up of the GFTAM, a multilateral organisation whose annual budget has now reached several billion dollars a year<sup>11</sup>.

All these elements help to explain the significant results that were achieved during the first half of the 2000s.

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<sup>9</sup> From the beginning of the 2000s, Indian generic producers were able to supply tritherapies at the price of 140 dollars per person per year, (compared to 10 to 12 thousand dollars for the same combinations in patented form). More on this issue below

<sup>10</sup> The ACCESS programme (also known as the Accelerated Access Initiative) was launched in the early 2000s. Under the aegis of major international organizations (the United Nations Population Fund, UNICEF, the World Health Organization, the World Bank and UNAIDS) a partnership was set up with large pharmaceutical companies (Boehringer, BMS, Glaxosmithkline, Merck, Roche, later joined by Abbott) with the aim of offering access to treatment to developing countries. Within this framework, and using a classification based on the human development indicator, countries classified as the “developing” or “least developed” are eligible for different but significant reduction in the price of ARVs. However, each pharmaceutical company sets its own restrictions on eligibility, determining on a case-by-case basis the nature and price of the drugs offered. These idiosyncratic distinctions account for the large price discrepancies observed for the same drug in different countries. They also explain the weak final impact of the ACCESS programme on price reductions observed after 2000. For more details on this issue, see (Lucchini *et al.*, 2003).

<sup>11</sup> The setting up of the GFTAM (Global Fund against Tuberculosis, Aids and Malaria) in 2003 is the most emblematic and visible of the initiatives taken by the international community to fund access to health care in Southern countries. The same period (the beginning of the 2000s) also saw the reorganisation of the World Bank AIDS programme, at the level of multilateral aid, and the launching of the PEPFAR initiative in the United States, which was, however, a bilateral aid programme marked by severe restrictions (details in Coriat 2008).

### **3.2 Threats posed by the post-2005 scenario and the new situation wrought by the financial and environmental crisis**

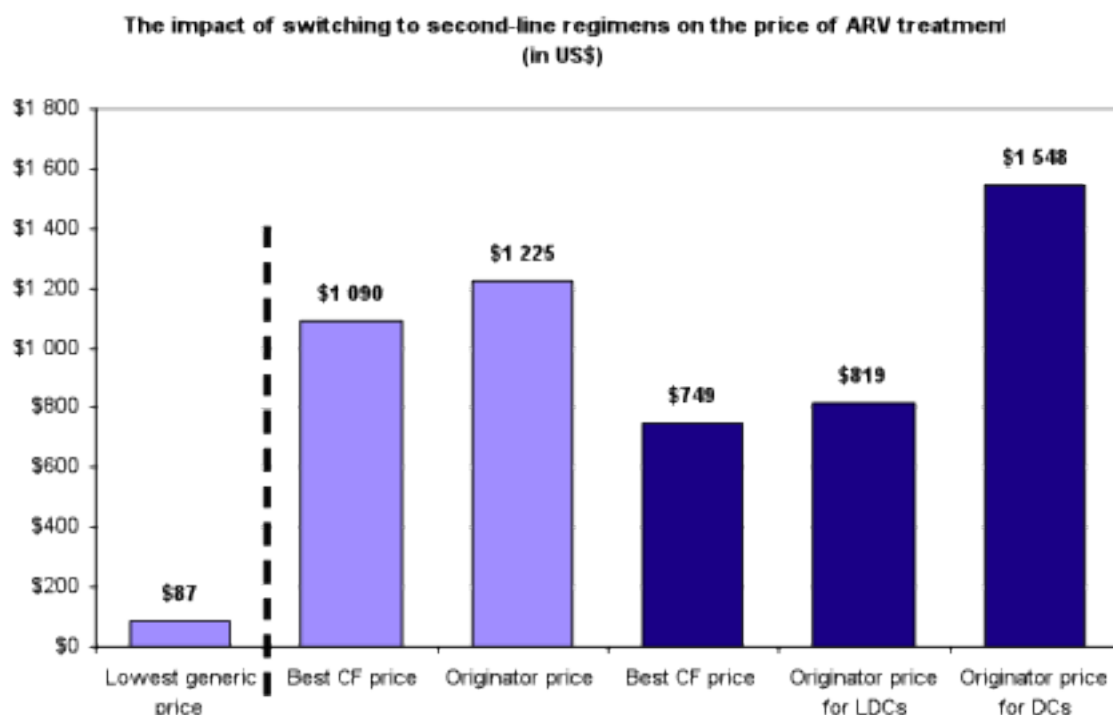
However, the second half of the 2000s got off to a much worse start. Prospects were considerably darkened by the convergence of a number of factors.

As stated above, 2005 was the deadline for those developing countries that had not already done so to make their national laws compliant with TRIPS. The essential effects of full application of the agreement concern the most recent drugs, those that were not produced in generic form before 2005 – or for which generic producers had not yet made significant investments. In practice, this involved almost all the second-line anti-retroviral drugs<sup>12</sup>. The consumption of these drugs is already substantial and is certain to grow strongly over time. It has been estimated by the Clinton Foundation that each year, 10% of any given cohort of patients on first-line treatments will have to move to second-line treatments. Since the purchase cost of second-line drugs is 7 to 12 times higher than that of first-line drugs (depending on the countries and the combinations administered to patients), the impact of 2005 TRIPS compliance in this domain has been staggering<sup>13</sup>. The graph below illustrates the differences in prices between first- and second-line treatments. In some middle-income countries that cannot access the generic products because of patent protection, the price hike could be as much as 17-fold.

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<sup>12</sup> The so-called 1st line treatments are recommended for “treatment-naive” patients. They all entail a triple combination of ARV, which may vary according to the patient’s viral load, profile and tolerance to the treatment. But in the event of treatment failure or virus mutation (which occurs regularly after a number of years of first-line treatment), new drugs must be prescribed. Hence the second-line and even third-line treatments.

<sup>13</sup> The arguments presented in this chapter are an update of those set out in Orsi et al. (2007).



CF is put for drugs combining in one pill two or three ARV

Source : MSF compilation based on WHO “Price Reporting Mechanism” and WHO report, available at <http://www.msfaaccess.org/resources/key-publications/>, 2009

The situation is all the more worrying because second-line treatments are not the only drugs affected. Already, and even for countries with limited resources, WHO treatment guidelines include some of the “new” ARVs, the production and sale of which are therefore subject to the restrictions entailed by full application of the TRIPS. In recent years (2006 and 2009), the WHO has modified twice its treatment guidelines for poor countries. To take into account the experience acquired in terms of the tolerance and toxicity of the first-generation ARV and the contribution made by new drugs (and the new combinations they make possible), the new WHO guidelines now include a number of new important drugs, none of which can be produced in generic form (except under exceptional circumstances).

This trend is bound to intensify over time. In the future, good medical practice will include an increasing proportion of new-generation ARV, even in first-line regimens for

treatment-naïve patients. As a result, the framework that allowed mass access to treatment (about 5 million patients at the end of 2010) at low cost is rapidly disintegrating.

The situation can only be aggravated by the fact that the cost of ARV is not the only factor that is going to weigh more heavily on budgets. The follow-up care of patients (for the early detection of treatment failure, due to virus mutation of other reasons), requires regular monitoring of their immunological and virological status. Every six months (according to the standard WHO guidelines for developed countries) patients must be tested to measure their viral load. The cost of buying the equipment, conducting the tests and training staff to carry out and interpret the tests or to manage and maintain the equipment constitutes a considerable extra burden. All the more so since this type of equipment (and the personnel capable of using it) are lacking in most Southern countries.

Furthermore, unlike the ARV market, which is relatively transparent and competitive, the market for tests and monitoring equipment is very opaque and oligopolistic: as a consequence, the cost of monitoring assays and installing laboratory networks capable of using them are inflated.

Last but not least, while huge extra investments are now needed, there are serious threats hanging over the funding of public health budgets. First, the international financial crisis is prompting donor countries to tighten their purse strings. Thus, for the first time ever, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) has reported a funding deficit of more than 4 billion USD for the 2009-2010 period)<sup>14</sup>, <sup>15</sup>. Finally the campaign for the third

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<sup>14</sup> Global Fund against AIDS, TB & Malaria (GFATM). Report of the Executive Director. Twentieth Board Meeting. Addis Ababa, Ethiopia.

<sup>15</sup> The prospects for the future are even more worrying. The big NGO *Médecins Sans Frontières* notes in a recent document that: “The most glaring sign of the decreasing political commitment to HIV/AIDS is a major funding deficit. The Global Fund to Fight AIDS, Tuberculosis and Malaria Board is considering a motion to cancel the funding round (Round 10) for 2010; if accepted, no new proposals will be considered until 2011. Similarly, the US President’s Emergency Plan for AIDS Relief (PEPFAR) plans to “flat-fund” its programs for the next two years, renegeing on promises made last year to support expanded treatment access”. In “Punishing Success? Early Signs of a Retreat from Commitment to HIV/AIDS Care and Treatment”, **5th November 2009**. Available at <http://www.msfaccess.org/resources/key-publications/>

replenishment of the GFTAM (covering the period 2011-2013) ended with very results. With only 11,7 bn\$ collected for 3 years the Fund even not reached its lowest expectations<sup>16</sup>.

Thus, at the very moment when the cost of access to health care is doubly burdened by the shift to new drugs - now protected by patents over which competition cannot exert any moderating influence – and by the need to set up monitoring networks and purchase the vast amounts of equipment required, there is a grave risk that international funding of public health will be cut.

### **3.3 The reaction of Southern countries: the case of Thailand and Brazil**

To deal with the new situation, after 2005 the Southern countries most involved in the fight against AIDS had to find new solutions. After refraining from doing so for a long time, Thailand, soon followed by Brazil, have started issuing compulsory licenses.

Although Thailand was not the first country to issue compulsory licenses<sup>17</sup>, the initiative taken by this country was crucially important, because it is both a large producer of generics and heavily engaged in the fight against AIDS at a national level.

It was only after lengthy deliberations inside the country, leading to the establishment of a powerful coalition of social forces in favour of generics that the country finally took the plunge (Tantivess et al. 2008, Krikorian 2008). After several unsuccessful attempts to negotiate price reductions with the patent-holder companies, the Ministry of Health proceeded in two stages, issuing two series of compulsory licenses<sup>18</sup>. The first, in November 2006, was for Efavirenz, and the second - two months later - was for Lopinavir/r. These licenses were issued for

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<sup>16</sup> The lowest expectations (known as “scenario 1”) was designed to allow for the continuation of funding of existing programs. New programs could only be funded at a significantly lower level than in recent years. The resources required for this scenario were estimated at US\$ 13 bn

<sup>17</sup> In fact, several African and Asian countries “with limited resources” or classified as “intermediate” issued compulsory licenses before 2005. They include Zimbabwe (2002), Indonesia, Malaysia, Mozambique and Swaziland (2004). Ghana, Guinea and Taiwan issued such licenses during 2005.

<sup>18</sup> ARVs are not the only drugs concerned by such licenses. They have also been issued for other drugs of public interest, notably anti-cancer drugs.

“governmental use”, on the grounds of public interest, a “flexibility” provided for in the TRIPS. The effect on the procurement costs of these two ARVs was an immediate reduction of 44% for Efavirenz and even more for Lopinavir/r. The production of these generics was entrusted to the national public laboratory GPO.

Drawing on the experience of Thailand, the Brazilian Ministry of Health issued a compulsory license for Efavirenz in April 2007. Like Thailand, Brazil entrusted the production of generics to its public laboratory, Far Manghinos. While waiting for the latter to enter into full production<sup>19</sup>, the generics were to be imported from India. The reduction in procurement costs was huge, falling from USD 1.59, (price at which Merck sold its proprietary drug) to USD 0.43, the price of the generic (d’Almeida et al. ,1998).

Yet, the evidence shows that these measures are not enough. A detailed and exhaustive study of the issuing of compulsory licenses (d’Almeida et al. 1998) highlights the limits of these initiatives :

- the process of issuing such licenses is long, expensive and politically very sensitive;
- even if significant reductions are obtained for the drugs produced under compulsory license, the impact on the overall cost of treatment remains slight, because of the very small number of ARVs produced under compulsory license;
- lastly, the process is subject to dispute and legal challenge; in practice the provision of drugs depends on the vagaries of legal procedures and court rulings, creating a situation of uncertainty that is unacceptable when tens of thousands of patients need to be supplied with different types of drug combinations on a daily basis.

All in all, compulsory licensing is therefore ill-adapted to dealing with a disease like AIDS. Because it is a chronic disease caused by a virus capable of mutation, changes in treatment are regularly needed to take into account the evolution of the epidemic and the continual arrival of new drugs. But each time such a change is needed, the flexibilities currently

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<sup>19</sup> At the same time as the compulsory license was issued, local public-private partnerships were set up as a means to ensure the relatively rapid production of the active principles required to manufacture the Efavirenz.



codified in TRIPS require governments to issue new licenses, to locate producers, to negotiate the terms of the contract and to place the necessary orders... without any guarantee that they will not, at one stage or another, encounter obstacles that compromise the procurement.

For all these reasons, the use of compulsory licenses – under the conditions currently governing their issue – is an unwieldy, expensive and ultimately ill-adapted process. Clearly if the issue is to face the pandemic, more appropriate tools are needed, and the TRIPS flexibilities need to be significantly enlarged

#### **4. CONCLUSION**

The IPR system governing pharmaceuticals has become increasingly dysfunctional — even in countries like the U.S. Thus, the efficacy and desirability of extending strong IPR protection in the rest of the world raises very legitimate doubts. The consequences of the TRIPS as regards access to care in developing countries – as illustrated by the case of the fight against the HIV/AIDS pandemics - could be dramatic.

Strong patent laws do, indeed, confer an advantage to innovators in the pharmaceuticals industry, but the magnitude and even the shape of such effects is difficult to assess, both theoretically and empirically. In any case, they may not be enough to promote innovation in contexts where innovative capabilities are low or missing altogether. Conversely, excessively tight IPRs have strong negative effects on prices and access to health, especially in developing countries.

How can the negative effects of stronger patent protections be offset? Or alternatively should we think to redesign the whole system of IP protection currently enforced in the pharmaceutical sector<sup>20</sup>? A series of measures (like advanced purchase commitments and

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<sup>20</sup> Among the contributions focussing on this issue two, especially may deserve attention. The first one emanates from the US National Academy of Science, (Merril et al, 2004 ...), the second from a group of developing countries led by Argentina and Brazil aiming at opening a discussion inside the WIPO arena on IP issues (WIPO, 2004)

product development partnerships) have been introduced and several schemes for the design of alternative incentive mechanisms to innovation (e.g. prizes) have been proposed. Their efficiency and feasibility remains controversial. Key research questions – with strong practical implications - are urgent on the agenda.

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