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Some Assumptions On Patent Law And Pharmaceutical R&D

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Introduction

The debates on IPRs and pharmaceuticals often address the role that patents play as an incentive for industry to undertake costly and risky R&D. Thus, according to the research-based industry "effective" IPRs protection is critical for it to recoup its large R&D expenditures (FIM/IFPMA, 1998, p. 9).

The pharmaceutical industry is among the most R&D intensive industries, measured by the percentage of sales devoted to such activities (OECD, 1992). 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 note addresses some of these assumptions.

Public involvement in pharmaceutical R&D

Though the development of new drugs is often claimed as a distinct contribution by the private pharmaceutical industry, in many 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).

In addition to direct involvement in R&D, many developed countries 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 have been granted for the development of "orphan drugs". According to one study, pharmaceutical companies received $ 106.9 million between 1983 and 1993 in tax credits[1]. The US government paid for the initial development, pre-clinical research, and clinical research of many important drugs, including many used for cancer and HIV-related diseases.

Thus, 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 [2] for 34 of the 37 drugs (Chabner and Shoemaker, 1989).

There are many examples of public funding of drugs important for the treatment of HIV infection and related diseases. 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. The drug 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).

In the case of AZT, the drug was first synthesized by Dr. Jerome Horowitz at the Michigan Cancer Foundation in 1964, using a Government grant. The first demonstration of an effect against animal retroviruses was done at the Max Planck Institute in 1974. Its possible use for the treatment of acquired immune deficiency syndrome was identified in 1985 by the staff of the National Cancer Institute working with staff at Duke University[3].

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[1] See http://www.cptech.org.

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

[3] In a 28 September 1989 letter to the New York Times, NIH and Duke University scientists held that "there are few drugs now approved in this country that owe more to Government-sponsored research". It added that Burroughs Wellcome (who obtained a patent on the use of AZT as retroviral) "did not develop or provide the first application of the technology for determining whether a drug like AZT can suppress live AIDS virus in human cells, nor did it develop the technology to determine at what concentration such an effect might be achieved in humans. Moreover, it was not first to administer

It seems possible to conclude, pending a more systematic work on this subject, that the public sector makes a significant contribution to pharmaceutical research, including the discovery and/or development of many important drugs. The public sector role is not substantially dependent on the availability of IPRs.

However, in some countries explicit policies have been applied in order promote the use of patents and licensing as a means to promote 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.

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:

"BayhDole 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[4].

Efficiency in R&D activities

AZT to a human being with AIDS, nor did it perform the first clinical pharmacology studies in patients. It also did not perform the immunological and virological studies necessary to infer that the drug might work, and was therefore worth pursuing in further studies".

[4] See also on this subject Mowery, Nelson, Sampat and Ziedonis, 1999, p. 269-306.

Another 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[5]. 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).

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. 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 (Gambardella, 1995, p.23; 79). The scale of laboratories is no longer a critical advantage, as it probably was when drug discovery was substantially based on mass screening.

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).

Finally, 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. 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)[6] does not correspond to actual expenditures, but to expenditures adjusted for cost of capital and to compensate for R&D failures. 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).

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 on the real magnitude of expenditures involved and on the

[5] For arguments about the greater efficiency of the private industry vis-à-vis the public sector in undertaking R&D, see Kealey, 1996, pp. 242.
[6] See, e.g., FIM/IFPMA, 1998, p. 9.

cost- efficiency of the dominant organization for drug R&D.

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. 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.69)[7]. 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 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 are granted. 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, strong patent protection may be of little relevance for the solution of the dramatic problems of poor people in the developing world.

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

[7] 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).

provided curative or preventive tools[8] 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 encourage 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. An important question is, in this context, the extent to which 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.

Several authors 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; Deardoff, 1992)[9].

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

The pharmaceutical industry did not suffer in the last 20 years from any demonstrable shortage of funds for R&D. It invested a high percentage of its sales in R&D, and was one of the most profitable sectors in the developed countries, notably in the USA[10]. All this was possible despite the fact that a large number of developing countries (including those with the largest pharmaceutical markets, such as Argentina, Brazil,

[8] 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).

[9] 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).

[10] See, e.g., "Fortune Global 500", Fortune Magazine, August 2000.

Egypt, India, Mexico) did not grant product patent protection at all during that period, or only introduced it during the 1990s.

It may well be the case that the cost of R&D is bound to increase in the future, perhaps as the large firms start to exploit the new possibilities opened by "genomics" and "proteomics"[11], or because it becomes more difficult to develop new products[12]. It is also true, however, that all countries are obliged to recognize pharmaceutical patents, and most developing countries already grant them despite the transitional periods provided for by the TRIPS Agreement[13]. Therefore such firms will be able to generate patent-based income almost universally, since practically the whole world is 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[14]. 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[15].

Patents and innovation

Finally, 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 encourages genuine "inventions".

Though the patent system was devised in order to reward inventiveness, encourage technical progress and foster the dissemination of innovations, patents are used in many cases as commercial tools in order to restrict or delay legitimate competition. For instance, in the United States thousands of patents are granted each year 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 Office granted over 160 000 patents, twice the number granted ten years ago.
This is the fruit of loose criteria for patentability,[16] of the excessive flexibility of the

[11] The impact of these new developments on the cost of R&D have not been investigated yet.
[12] In fact, the innovation rate (measured by the development of "new chemical entities") has substantially decreased since the 1990s. See, e.g., FIM/IFPMA, 1998, p. 21.
[13] 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.
[14] 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.
[15] See www.ims-global.com/insight/report/global/report.htm .
[16] 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

Patents Office in assessing the degree of non-obviousness, novelty and usefulness of the applications submitted to it and of shortcomings in the examination procedures[17] (Gleick, 2000, p.44).

In the pharmaceutical field, only a few "new chemical entities" (i.e. molecules not pre-existing) are developed and patented each year, but a significant (but undetermined) part of R&D activities are devoted to the modification of known chemical entities, including the patenting of formulations or dosage forms, combinations, crystalline forms of known molecules, etc.. In addition, "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 drugs ("me-too drugs") which do not represent a significant therapeutic progress. 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).

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 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.[18] 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.[19]

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

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widely used by indigenous communities in developing countries (Correa, 1999; The Crucible Group, 2000).

[17] 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.

[18] The chemical and pharmaceutical industry accounts for about one third of the around 160.000 patents granted each year in the USA (Aharonian, 2000).

[19] See, Zaveri, 1998; Keayla, 1999; Cook, Doyle and Jabbari, 1991.

denied access to the drug at more competitive prices when the original patent expired.

Conclusions

It seems undeniable that the pharmaceutical industry has an important role to play in the future development of new drugs. However, several assumptions generally made with regard to pharmaceutical R&D and the patent system need to be objectively reviewed.

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. Patenting and licensing practices applied by public R&D institutions should be reviewed, since they may restrict rather than foster innovation.

The consideration of the level of IPRs protection in pharmaceuticals needs also to take into account the appropriateness of current R&D structures, and the extent to which large scale firms can provide an efficient organization for such activities. It seems clear that commercially driven R&D organizations are unlikely to provide solutions for the diseases that mainly affect the poor.

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.

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 provide a basis for blocking genuine competition, particularly after the expiration of the basic patents on a given drug.

In sum, in view of the important intervention of the public sector in pharmaceutical R&D, of the scope and objectives of a great part of private R&D, and of the nature of the measures that countries can adopt to improve current access to medicines, there is little foundation to think that the use of such legitimate measures by developing countries threaten in any significant way future R&D in pharmaceuticals. Limitations on the use of such measures, which can save the life or improve the health conditions of a large part of the world population, cannot be reasonably justified on the risks posed to future R&D.

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