

FOSTERING R&D AND PROMOTING ACCESS TO MEDICINES

Introduction

The patent system has traditionally been regarded as the main stimulus for the development of new drugs. Indeed, the pharmaceutical industry is strongly dependent on the use of patents, as evidenced by its global activism and the multiple forms of pressure they exert in favour of ever increasing levels of patent protection for pharmaceutical product.¹

Such activism -which explains to a large extent the adoption of the TRIPS Agreement in the framework of the World Trade Organization (WTO)²- is often justified by the idea that more protection (of patents and test data) will lead to more innovation. However, this is not valid either in general³ nor in the particular case of pharmaceutical products. The number of new chemical entities of pharmaceutical use has drastically declined in the last five years despite the sustained public and private investment in R&D, the extension of patent and test data protection to all WTO Members and the additional income obtained by pharmaceutical companies in developing countries in the post-TRIPS era. Moreover, the availability of new research tools (such as those provided by combinatorial chemistry, proteomics and genomics), the constitution of mega-companies through mergers and acquisitions, and the restructuring of R&D laboratories of large pharmaceutical companies have not halted the decline in the rate of innovation.

Innovation bias

The reasons that explain the declining productivity in innovation by pharmaceutical companies - notwithstanding the proliferation of pharmaceutical patents⁴ are possibly multiple and complex, and have not been adequately studied so far. They are likely to include both scientific and technological barriers and organizational issues⁵. Interestingly, large pharmaceutical firms increasingly depend for new drugs on advances made by small biotechnology companies⁶.

Although pharmaceutical patents allow title holders to generate a significant profit, this does not seem sufficient to sustain high levels of innovation, particularly in relation to diseases prevalent in developing countries, where buying capacity is low. As found by the Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH), patents tend to encourage R&D projects that address diseases that affect rich countries. They work as incentives where profitable markets exist. As noted by the CIPRH':

where the market has very limited purchasing power, as is the case for diseases affecting millions of poor people in developing countries, patents are not a relevant factor or effective in stimulating R&D and bringing new products to market...For developing countries where the demand is weak – not the need — there is little incentive to develop new or modified interventions appropriate to the disease burden and conditions of the country⁷.

It has been argued that large developing countries, such as India, might fill the gap in R&D in the areas of diseases prevailing in developing countries (generally known as Type II and III diseases)⁸. However, despite an increase in R&D expenditure by large Indian pharmaceutical

companies, their efforts are concentrated on drugs of interest to rich markets⁹, not those needed by the poor.

Patents do contribute to the development of new treatments where large profitable markets exist. Lack of effective demand (in economic terms) makes patent protection irrelevant for Type III diseases and only relatively relevant for Type II diseases. Hence, patents may deepen the existing inequalities between rich and poor, as they generate an incentive to develop and market profitable drugs and not those badly needed to address the health problems of the greatest portion of the world population. There is a growing consensus that alternative mechanisms are required to promote pharmaceutical innovation for diseases of the poor.

The World Health Organization has set up an intergovernmental group¹⁰ to implement the recommendations of the CIPIH Report, including the discussion of possible alternative mechanisms to promote innovation in pharmaceuticals. The World Health Assembly Resolution WHA60.30 adopted in May 2007¹¹ requested WHO to get more involved in supporting member states to improve access to treatments, and to encourage discussion of new incentive mechanisms for research and development.

Several mechanisms have been discussed to promote R&D in pharmaceuticals, particularly those needed in developing countries. They may consist of *push mechanisms* (e.g. grants, equity participation, tax credits) that subsidize research costs, or of *pull mechanisms* (e.g., advance purchase, prizes) that pay for research outputs. States have traditionally used push mechanisms, but growing attention has been paid to pull mechanisms, especially in order to encourage research on vaccines where the social returns to research are much higher (up to ten times) than the private returns¹².

Alternative R&D incentives

Mechanisms to encourage R&D of pharmaceutical products suitable to address the diseases prevailing in developing countries include¹³:

Public-private partnerships (PPPs)

PPPs provide a framework for cooperation among governments, public research institutions, the private sector and non governmental organizations (NGOs). They carry out focused research agendas¹⁴. Several PPs have been established to develop products needed in developing countries (see Box 1). In the framework of a partnership between DNDi (Drugs for Neglected Diseases Initiative) and Sanofi-Aventis, a fixed-dose combination of artesunate-amodiaquine (ASAQ) has been developed and submitted for registration in 23 sub-Saharan African countries¹⁵. The TB Alliance has developed methodologies to accelerating the preclinical phase and speeding the front and back ends of the clinical trial phase in order to reduce costs. It expects to deliver affordable treatment in the next five years¹⁶.

There are, however, serious concerns about the sustainability of PPPs, which strongly depend on funding from charitable foundations¹⁷. Moreover, since PPPs' strength lies in their R&D capacity, doubts have been casted on their capacity to effectively make accessible drugs to those who are in need thereof :

Product development partnerships [PDPs], as currently constituted, have a limited capacity to ensure access by individuals in poor populations to any products that may emerge from their efforts. Most attempt to assure future access through interactions with various partners ‘downstream’ to product development itself... Typically PDPs concentrate on ‘core R&D’ although they may have secondary activities in other areas¹⁸.

Box 1
Public-private partnerships in pharmaceuticals

- **HIV/AIDS**
- International AIDS Vaccine Initiative (IAVI)
- HIV/AIDS vaccines
- South African AIDS Vaccine Initiative (SAAVI)
- HIV/AIDS vaccines
- International Partnership for Microbicides (IPM)
- Global Microbicide Project Microbicide Development Project
- Anti-HIV microbicides
- **Malaria**
- Medicines for Malaria Venture (MMV)
- Malaria drugs
- Malaria Vaccine Initiative (MVI)
- Malaria vaccines
- European Malaria Vaccine Initiative (EMVI)
- Malaria vaccines
- **Tuberculosis (TB)**
- Global Alliance for Tuberculosis Drug Development (TB Alliance)
- TB drugs
- Aeras Global Tuberculosis Vaccine Foundation (Aeras)
- TB vaccines
- Foundation for Innovative New Diagnostics (FIND)
- TB and (later) other diagnostics
- **Other diseases**
- Drugs for Neglected Diseases initiative (DNDi)
- Trypanosomiasis, Leishmaniasis
- Institute for OneWorld Health (IOWH)
- Trypanosomiasis, Leishmaniasis, other
- Pediatric Dengue Vaccine Initiative
- Human Hookworm Vaccine Initiative
- Rotavirus vaccine Accelerated Development and Introduction Plan
- Pneumococcal Vaccine Accelerated Development and Introduction Plan

Source: Widdus, R. (2006), op. cit., p. 206.

Market exclusivity

The granting of a market exclusivity period modelled on the “orphan drug” scheme applied in the US under the Orphan Drug Act of 1983 has also been considered as a possible mechanism to promote R&D in the area of the so-called ‘neglected diseases’. Although this approach has been

often regarded as successful in the US¹⁹, it is likely to work only in countries where purchasing power is high. In addition, the conferred exclusivity may — unless other measures are implemented — deny low-income patients access to the new drugs. The system is also vulnerable to abuses by the beneficiaries of the exclusivity period²⁰.

Prizes

Rewards to encourage R&D in pharmaceuticals particularly needed in developing countries may be given in the form of prizes, as an alternative or supplementing intellectual property rights. Thus, Stiglitz advocates the establishment of a medical prize fund:

The international community could get together and say we will provide a prize for those who come up with a vaccine or cure for the kinds of diseases that afflict those in developing countries. With that prize there would be incentives for drug companies and researchers all over the world to do research to find the cures and vaccines against these diseases. But then, once the cure or the vaccine has been developed, we would use the force of the competitive marketplace. Under the current intellectual property regime, monopoly dominates, so that high prices restrict usage. In the competitive market place there would be low prices and each would be using whatever they could do to make sure the drugs are disseminated as widely as possible at the lowest cost possible.²¹

The implementation of this approach may pose difficult but not insurmountable problems, such as defining the size of the prize and the credibility of government's commitment. Given the amount possibly required to make the prize attractive to industry, it may not be a viable option for individual developing countries²². A shortcoming is also 'the possibility of paying more for an innovation than would be the case under a patent regime, or an amount insufficient to stimulate innovation, or to rewarding a product which then could be withdrawn from the market when unforeseen side effects are discovered'

Advance purchase commitments

Advance purchase commitments guarantee the future purchase of certain quantities of a product to be developed at an agreed price (with further price reductions after a period of time) provided that the product meets targeted standards and countries demand the product. This mechanism is likely to work best when a molecule has already been identified and the risk involved in R&D is relatively low²³.

For some analysts, advance purchase commitments are the main solution to the lack of R&D where no market exists²⁴. Thus, Sachs has argued that

[T]his idea of creating a virtual market where there is no market, in my view, is really the only solution that has been so far proposed, that realistically carries product development from the initial basic science all the way through clinical testing, all the way to the final market. And that is what has been missing in twenty years of discussion about vaccine development. It is not good enough just to support some R&D, you will never get the product brought to market that way, unless there is a real market out there²⁵.

The International AIDS Vaccine Initiative (IAVI) applied an advance purchase commitment to AIDS vaccines in 2005, and has since collaborated with GAVI, the World Bank, and other

vaccine public-private partnerships to support the design and implementation of a pilot program. A pilot program for pneumococcal vaccines was launched by the governments of Canada, Italy, Norway, Russia and the United Kingdom, as well as the Bill & Melinda Gates Foundation, in February 2007²⁶.

However, this scheme may be difficult to apply in the case of vaccines, as companies that already sell a medicine for the same disease and that, consequently, are the best equipped to undertake vaccines research, may have no incentives to do so. The discovery of a vaccine may lower the price of the medicine or threaten the very existence of its market as the epidemic may progressively disappear²⁷. In addition, the necessary funding may be substantial and beyond the reach of developing countries. In accordance with Sachs, for instance, there might be a need for a 2,5 to 3 billion dollars fund²⁸.

Patent buy-outs

Governments may, directly or through an organization in which they participate (such as the World Health Organization) commit to buy the future patent on a product of research, in order to distribute it freely or at low cost. Kremer developed a possible scheme for patent buy-outs; a markup would be recognized in accordance with the estimated typical ratio of the social and private values of inventions. In order to induce bidders to reveal their valuations, patents would be sold to the highest bidder²⁹.

While patent buy-outs could eliminate monopoly price distortions, they are potentially vulnerable to collusion. Determining the value of the patent may also be a complex matter, as several methods (with their own limitations) may be applied³⁰.

Open source schemes

Open source schemes can be used to undertake medical R&D research in a collaborative way. These schemes may be particularly useful for the identification of new candidate molecules³¹. They may foster advances in early phases of the R&D cycle of pharmaceuticals, but may be difficult to implement or inapplicable for later stages of R&D.

Medical R&D treaty

A new international treaty on medical research has been proposed by a number of NGOs and experts to ensure sustainable funding for R&D in pharmaceuticals³². The main features of the proposed treaty are as follows³³:

- it provides new obligations and economic incentives to invest in priority research projects;
- the core country obligation is to support medical R&D;
- the mechanisms to support R&D include public sector funding, tax credits and purchases of patented medicines (measured by the R&D stimulated by such purchases), as well as medical innovation prize funds and open source collaborative research projects;
- country obligations are pegged to a fraction of GDP, under a progressive rate, with minimum investments for priority research projects, such as investment in neglected diseases or global

infectious

diseases;

-the proposal creates a system of credits to reward and stimulate investments in research projects considered socially important;

-as in the the Kyoto climate treaty, credits could be traded across borders and countries that exceed the benchmark obligations could sell excess credits.

The implementation of this idea will depend on the political support it might receive and on the additional funding it might generate for R&D activities.

Patent extensions

A proposal has been made to provide a patent extension³⁴ on an unrelated product (transferable intellectual property rights -TIPRs) in order to promote innovation in neglected diseases. If implemented, companies might receive substantial additional income (generated by patients, health insurances and governments) but will retain control on its use, including the choice of products to be developed and the methodologies to be applied.

This proposal has encountered considerable criticism. It has not received support even from the pharmaceutical industry³⁵.

Fast track of regulatory review

Another proposal has been made to provide an advantage to firms that would invest in R&D on diseases prevailing in developing countries through PPPs, in the form of faster approval of drugs of their choice³⁶. Although it would not extend the exclusivity period, a risky aspect of this proposal is the potential distortion of decisions by regulatory agencies. The viability of this scheme is arguably low after the ‘Vioxx debacle’³⁷ that has put into question FDA procedures. As noted by one commentator:

the FDA was once considered too slow and deliberate in approving drugs. Those days are gone. It now generally approves drugs faster than counterpart agencies in Europe and elsewhere. But in its rush, it is demanding less evidence of safety and effectiveness. While shortcuts are sometimes warranted for truly innovative drugs, they are now too frequent. Furthermore, although quick to approve drugs, the FDA is slow to take them off the market when they prove dangerous...³⁸.

Patent pools

A “patent pool” is an agreement between two or more patent owners to license one or more of their patents to one another or third parties. Although patent pools usually raise competition concerns, they may be used for pro-competitive purposes. For example, the United States Patent and Trademark Office identified a number of advantages, such as greater efficiency in obtaining rights to patented technology through “one stop” licensing mechanisms; the distribution of risks associated with research and development; and the elimination of “blocking” patents or “stacking” licenses, and the consequent encouragement of cooperative efforts³⁹.

The setting up of patent pools may facilitate access to existing technologies and products. They may be mandatory or based on a voluntary agreement entered into by participants therein. Patents pools have raised anti-trust concerns in some circumstances as they may lead to collusion and the market exclusion of would be competitors.

Conclusions

The patent system does not work in the absence of profitable markets. Rather than a typical situation of ‘market failure’, the case of diseases prevailing in developing countries evidences the lack of interest of the pharmaceutical industry and States’ failure to address the problem.

None of the various proposals mentioned above is likely to provide by itself a solution to the insufficiency of R&D to address such diseases. A combination of two or more mechanisms may be needed, taking into account the type of products involved and the possible cost of clinical trials. A key issue is to ensure that the outputs of research are available without restrictions imposed by patents and other rights (such as data exclusivity). In this sense, some of the proposals may be seen as alternatives to the intellectual property system, although their proponents have generally regarded them as supplementary to that system.

It is difficult to suggest which proposals hold the greatest promise for being operationalized on a sound basis, given their costs and political viability. The sustainability of PPPs may be enhanced if governments decided to effectively support them. There are already pilot experiences with advance purchase commitments, as mentioned above, and there have been proposals to implement prizes for drug R&D⁴⁰. The latter are perhaps the most likely candidates for international action in the short term.

In addition to the ongoing work under the auspices of WHO, some of the examined proposals, particularly the possible use of open access initiatives, may be further explored as part of the WIPO Development Agenda⁴¹ in the context of broader policies to promote innovation.

Endnotes

- ¹ See, e.g., Schaffer, G. (2003), Defending interests. Public-private partnerships in WTO litigation, Brookings Institution Press, Washington D.C. (describing lobbying and other kinds of pressure by the US pharmaceutical industry).
- ² Ed Pratt Jr., CEO Pfizer's (1972-91) was reported to say: 'The current GATT victory, which established provisions for intellectual property, resulted in part from the hard-fought efforts of the US government and US businesses, including Pfizer, over the past three decades. We've been in it from the beginning, taking a leadership role'.
- ³ As noted by Prof. Boyle 'The assumption seems to be that to promote intellectual property is automatically to promote innovation and, in that process, the more rights the better. But both assumptions are categorically false. Even where intellectual property rights *are* the best way to promote innovation, and there are many areas where they are not, it is only by having rules that set the correct *balance* between the public domain and the realm of private property that we will get the innovation we desire' (Boyle, J. (2004) 'A Manifesto on WIPO and the future of intellectual property', Duke Law & Technology Review No. 9, available at <http://www.law.duke.edu/journals/dltr/articles/PDF/2004DLTR0009.pdf>, p. 2).
- ⁴ Such a patenting reflects aggressive strategies to acquire and enforce 'evergreening' patents rather than significant contributions to the state of the art.
- ⁵ Companies are streamlining their pipelines, focusing on fewer diseases and licensing-in (that is, obtaining more drug candidates from other companies). Thus, many large pharmaceutical companies have drastically reorganized their R&D activities. GlaxoSmithKline took the lead by dividing R&D into therapeutic areas and setting up seven Centres of Excellence for Drug Discovery. Roche will also create five Disease Biology Areas for oncology, virology, inflammation, metabolism and central nervous system, which will cover everything from drug discovery to medical proof of concept to marketing.
- ⁶ See 'Billion dollar pills', The Economist, January 27, 2007.
- ⁷ CIPIH, op. cit. p. 34 and 36.
- ⁸ Type II diseases (often termed *neglected diseases*) are incident in both rich and poor countries, but with a substantial proportion of the cases in the poor countries (e.g. HIV/AIDS and tuberculosis). Type III diseases (often called *very neglected diseases*) are those that are overwhelmingly or exclusively incident in the developing countries, such as African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis). See CIPIH, op. cit. p. 28-29.
- ⁹ See Chaudhuri, , The WTO and India's pharmaceuticals industry. Patent protection, TRIPS and Developing countries, Oxford University Press, New Delhi, p. 166.
- ¹⁰ The first meeting of the Working Group took place in December 2005. See, e.g., <http://www.cptech.org/ip/health/who/igwg.html>.
- ¹¹ Available at http://www.who.int/gb/ebwha/pdf_files/WHA60/A60_R30-en.pdf.
- ¹² See Kremer, M (2001), "Creating Markets for New Vaccines" in Adam B. Jaffe, Josh Lerner, and Scott Stern (eds.), Innovation Policy and the Economy, MIT Press, Volume 1; Roy, P. (2001), Research incentives in competing markets: a model of the development of new vaccines, Tesina Centro de Estudios Monetarios y Financieros (CEMFI) N.º 0102, Madrid.
- ¹³ For a more detailed discussion, see CIPIH, op. cit. 2006, p. 86-91.
- ¹⁴ See, eg. Widdus R and White K (2004), Combating diseases associated with poverty: financing strategies for Product development and the potential role of public-private partnerships (Abridged version), Initiative on Public-Private partnerships for Health. Global Forum for Health Research, Geneva; Kettler H and Towse A (2002), Public-private partnerships for research and development: Medicines and vaccines for diseases of poverty. Office of Health Economics, London.
- ¹⁵ The product is already registered in 12 of these countries. See www.actwithasaq.org.
- ¹⁶ See Next Steps Now. Preparing the World for Rapid Uptake of a. Faster, Better TB Cure. TB ALLIANCE. GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT. 2005/06 Annual Report, available at <http://www.google.com.ar/search?q=tb+alliance+annual+report+2005&ie=utf-8&oe=utf-8&aq=t&rls=org.mozilla:es-AR:official&client=firefox-a>.
- ¹⁷ See CIPIH, op. cit. p. 70-77.

¹⁸ Widdus, R. (2006), 'Product development partnerships on 'neglected diseases' intellectual property and improving access to pharmaceuticals for HIV/AIDS, TB and Malaria', in P. Roffe, G. Tansey and D. Vivas (Editors), Negotiating Health. Intellectual Property and access to medicines, Earthscan, London, 2006, p. 214.

¹⁹ See CIPIH, op. cit., p. 86.

²⁰ It has been noted that although the Orphan Drug Act covers diseases of fewer than 200.000 patients, it has been applied to many highly profitable drugs, such as AZT (Zidovudine) for AIDS, Epogen (EpoetinAlfa) for certain types of anemia (with \$2 billion in annual sales paid for by Medicare) and Human Growth Hormone for short stature (Schultz, W. *Incentives for breakthrough drugs*, available at <http://www.iom.edu/Object.File/Master/30/665/schultz.pdf>).

²¹ Stiglitz, Joseph (2007), Times Online MBA Podcasts in association with IBM: Week 1 - Making Globalisation Work, available at <http://www.google.com.ar/search?q=Times+Online+MBA+Podcasts+in+association+with+IBM%3A+Week+1+-+Making+Globalisation+Work+by+Joseph+Stiglitz&ie=utf-8&oe=utf-8&aq=t&rls=org.mozilla:es-AR:official&client=firefox-a>.

²² See CIPIH, op. cit. p. 88.

²³ See, e.g., Barder O, Levine R (2005) *Making markets for vaccines – Ideas to action*, Washington, Center for Global Development, available at <http://www.cgdev.org/publications/vaccine/>.

²⁴ The UK government announced in December 2004 its intention to work with industry partners 'to develop proposals for Advance Purchase Commitments as a means to stimulate greater and accelerated research and development for HIV and malaria vaccines for use in developing countries' (DFID, 2005, Increasing people's access to essential medicines in developing countries: a framework for good practice in the pharmaceutical industry. A UK Government policy paper, London, available at www.dfid.gov.uk/Pubs/files/pharm-framework.pdf).

²⁵ Sachs, J. (1999), 'Mobilising science: medicines for development', in Medicines for the poor. The World Trade Organization and the Developing Countries. Report of a public debate held on 16 December 1999, Information & Communication Department, Information project 'The WTO and the Developing Countries', Ministry of Foreign Affairs, The Hague, p. 33.

²⁶ See <http://www.iavi.org/viewpage.cfm?aid=1377>.

²⁷ Roy, op. cit., p. 20.

²⁸ Sachs, op. and loc. cit.

²⁹ Kremer, M. (1997), Patent Buy-Outs: A Mechanism for Encouraging Innovation, NBER Working Paper No. 6304 December, available at <http://www.nber.org/papers/w6304>.

³⁰ See generally on valuation of intellectual property assets, Berman, B. (2002), From Ideas to Assets, New York: Wiley Intellectual Property Series.

³¹ See, e.g., Thomas B. Kepler, Marc A. Marti-Renom, Stephen M. Maurer, Arti K. Rai, Ginger Taylor, E, and Matthew H. Todd (2006), 'Open Source Research — the Power of Us', Australian Journal of Chemistry, 59(5) 291–294 available at http://www.publish.csiro.au/view/journals/dsp_journal_fulltext.cfm?nid=51&f=CH06095.

³² See, e.g., <http://www.cptech.org/workingdrafts/rndtreaty.html>.

³³ Based on 'Proposal for Treaty on Medical Research and Development (February 2005)' available at <http://www.cptech.org/workingdrafts/rndtreaty.html>.

³⁴ A precedent for this proposal is the 6-month patent extension awarded in the US to drugs that list pediatric uses in accordance with the FDA Modernization Act.

³⁵ See CIPIH, op. cit.

³⁶ Moran M. (2005), Fast track options as a fundraising mechanism to support R&D into neglected diseases. Geneva, CIPIH submission, available at <http://www.who.int/intellectualproperty/submissions/Mary.Moran2.pdf>.

³⁷ The anti-inflammatory drug was pulled off the market on Sept. 30, 2004, suspected of causing heart attacks in a large number of patients. At least 11.500 lawsuits were filed against Merck (Smith, A, 2006, 'Merck wins latest Vioxx case. N.J. jury finds drugmaker not liable in the seventh case over withdrawn

painkille', [CNNMoney.com](http://money.cnn.com/2006/07/13/news/companies/vioxx/index.htm), available at
<http://money.cnn.com/2006/07/13/news/companies/vioxx/index.htm>).

³⁸ Angell M (2004), *The Truth About the Drug Companies, how they deceive us and what to do about it*, Random House, New York, 2004, p. 209.

³⁹ See Clark J et al. *Patent pools: a solution to the problem of access in biotechnology patents*.(2000), US Patent and Trademark Office, available at <http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>.

⁴⁰ For instance, on January 26, 2005, US Representative Sanders introduced H.R. 417 - The Medical Innovation Prize Fund Act. This bill proposed the creation of a fund to reward innovators who develop new pharmaceuticals. Rewards would be paid out over ten years. See <http://www.cptech.org/ip/health/prizefund/hr417.html>.

⁴¹ The Development Agenda was proposed by Argentina and Brazil in 2004. The Provisional Committee on Proposals related to the WIPO Development Agenda (PCDA) considered 111 proposals in 2006. See, e.g., <http://www.southcentre.org/info/scielipquarterly/ipdev2007q1.pdf>; www.cptech.org/ip/wipo/da.html