

**Commission on Intellectual Property Rights**

**Study Paper 2b**

**Using Innovative Action to Meet Global  
Health Needs through Existing Intellectual  
Property Regimes**

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## **Executive Summary**

A key challenge facing all stakeholders in the global health arena is how to simultaneously encourage more innovation and R&D into new, more effective products and ensure that those needing these products can afford and have access to them. Intellectual property rights (IPR) sits at the center of this debate.

This report investigates the literature and on-going political debates surrounding two issues: the link between IPR and R&D, especially in diseases prevalent predominately in the developing world (henceforth, neglected diseases); and the link between IPR and patient access to finished products.

The key findings are:

1. IPR is a necessary but insufficient incentive to encourage companies in the developed or the developing world to commit R&D resources towards neglected diseases;
2. IPR, to the extent that it affects the price on on-patented drugs, negatively affects poor patients' ability to afford and therefore access new drugs and vaccines.
3. Affordability does not ensure access as many other barriers exist. A comparison of the experience to date of HIV drug access in India, Brazil, and South Africa demonstrates the relative importance of IPR laws, government commitment to fighting the disease, and financial resources in ensuring access to HIV treatments.

Evidence suggests that win-win solutions can be developed to work within the current IPR system but all parties must still commit much more work and resources. New global norms of technology licensing agreements and pricing must be adopted. These include: differential pricing, controlling for the flow back of the cheaper priced products to the industrial countries in disease cases where there are global markets; and commitments by companies in technology licensing agreements that in exchange for IPR they will help ensure that any future products gaining market approval in neglected diseases, get to the patients who need them. In addition, governments in developed countries must make substantive financial commitments to help fund the development and purchase of new products.

## **The R&D Problem**

Neglected diseases such as malaria, TB, and leishmaniasis are a low priority of both public and private investors in pharmaceutical R&D because of the perceived small paying market and thus low expected returns from any product developed. In an attempt to design effective solutions to this problem, attention has been given to what role IPR plays either as part of the problem or as part of the solution.

The pharmaceutical industry is generally seen as a textbook case of where patents are an essential mechanism of appropriating the economic returns on innovation. Two features of pharmaceutical R&D explain why. First, the sunk costs of R&D are high, averaging \$300-600 million per new product. Second, the marginal cost of production of

pharmaceutical products is often low. The R&D process is lengthy and risky but most pharmaceutical products once launched are relatively cheap and easy to reproduce. This second feature is what permits generic firms to be able to produce products at prices well below the price of a branded product.

Over time, the form of innovation and the role of IPR in the pharmaceutical industry have evolved. In the present era, characterized by a mix of large, vertically integrated multinational corporations and small and medium sized technology and/or product focused biotechnology companies, product and process patent protection are one of a combination of regulations and competencies deemed necessary for competitive success through innovation.

IPR is paradoxically both essential and potentially burdensome for small biotech companies. To get started and for years to come, scientists turned entrepreneurs rely on external funding with no evidence of competence but their publication record and the patents from their research. At the same time, in order to develop their ideas into marketable products, they depend on gaining access, sometime only through costly and lengthy negotiations, to technologies and ideas developed and patented by others.

Evidence of the importance of patents for pharmaceutical innovation can be drawn from country cases such as Canada, where the strengthening of IPR (through the abolishment of compulsory licensing) in combination with tax incentives produced an up turn in R&D investments by local and foreign companies. Surveys of MNCs also suggest that patent policies rank high in the decision criteria for foreign direct investment by pharmaceutical companies. Finally a significant factor determining the successful development of the US biotech industry since 1981 and the absence of one in (west) Germany, despite their comparatively strong and competitive MNCs, was the reform in the US of shifting the rights of publicly funded research to the universities. In Germany, the rights remained with the scientist who, on her/his own, lacked the resources to patent and commercialize their research. As a result, German scientists, until recently, worked with established companies as consultants rather than attempting to set up their own companies.

With regard to the impact of introducing TRIPS compliant IPR laws for less developed country (LDC) infant pharmaceutical industries, it is still too early to judge. Predictions for a case such as India are that the introduction of product patent protection will put out of business hundreds of small local generics companies but may provide new opportunities for those willing and able to invest in R&D capabilities and larger generics companies who will be able to enter global markets as products go off patent. In the absence of significant injections of funds for basic research, training, and technology transfer it seems unlikely that in and of itself IPR will create new innovative companies. That said, it will improve the prospects for cross-national joint ventures and opportunities for scientists trained in the US and Europe to return home and make a significant contribution to the building of their own companies.

There is even less evidence that the introduction of TRIPS will encourage companies and scientists in endemic countries to invest in treatments for neglected diseases. In one focused study of “new research activity” globally post 1980 in tropical diseases found

only slight changes developments in malaria. Patent and investment behaviour in all others was stagnant despite new entrants to the R&D pharmaceutical industry.

Explicit, targeted policies and initiatives are needed above and beyond IPR to channel some of the resources and capabilities of the pharmaceutical industry towards neglected diseases.

### ***Policy Options***

A number of new product development *public private partnerships* (PPPs) have been set up to develop drugs or vaccines to address specific diseases. All rely on contracts with industry and specify terms in those contracts to address the problem of future affordable access up front. In exchange for funds and other support, the PPPs tend to secure the IPR rights to develop and deliver any final product at affordable prices to the developing world markets<sup>1</sup>. In some cases, such as leishmaniasis, that may imply the entire market. In others, such as malaria, there is a paying travelers' market that the industry partner may have first rights to.

High attrition rates and the limited budgets mean that PPPs must be considered only part of the R&D solution for any one disease. Their efforts by no means fill any box in an "intervention-disease" matrix. Attempts to legislate *national policies* in the US and the UK to *incentivize* companies to invest in neglected diseases along lines similar to orphan drug policies have been less successful<sup>2</sup>. The idea, in theory, is to combine cost-saving policies, such as grants and tax credits, and revenue-enhancing policies, such as the creation of a purchase fund.

Another "pull" proposal is to offer companies a patent extension on a product of their choice in exchange for their successfully developing and marketing, at affordable prices, a product for a neglected disease. While attractive from a research orient company's standpoint, such a policy is unlikely to find favour with the patients using the other drug or the generics industry whose portfolio strategies depend on predicted dates of product patent expiry in large, profitable markets. An interesting and as yet unexplored question is how companies in the developing world such as India, China, or Brazil would respond to the creation of a global fund or nationally based tax incentives to address disease of concern to their own populations.

### ***The Impact of IPR on Product Access***

Patents are one of several important factors that help determine access to new medicines in LDCs. The current literature and lessons from India, South Africa and Brazil demonstrate that the presence or absence of patent protection has affected drug prices and

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<sup>1</sup> In the case of the International Aids Vaccine Initiative, the company retains the patent rights to all markets under the conditions that it will guarantee access at affordable prices to developing country markets.

<sup>2</sup> The UK included tax credits for vaccine research in neglected diseases in the 2001 budget but the treasury has not yet approved the measure.

access, as well as development of domestic industry. But though patents are important, it is possible to overemphasize their effect on drug access and ignore other important factors such as the availability of international and domestic financial resources for health care, infrastructure needs, and political leadership.

The move towards stronger IP protections through the TRIPS agreement presents complex issues. There is evidence that strong patents can have a negative effect on affordable prices by delaying the entry of generic options. Industry continually raises concerns that the erosion of patent protections will undermine incentives for product development. Since Africa represents only 1.1% of the global pharmaceutical market (Attaran, 2001) it is difficult to see how lower prices in this market significantly impact MNC profits.<sup>3</sup> The real fear is that lower prices will undercut acceptance of higher prices elsewhere, and could lead to importation of comparatively cheap drugs to richer markets. Criticism by elected officials in the United States regarding differential prices for drugs commonly purchased by the elderly is a recent example of the political pressures working against differential pricing.

### **Policy Options**

In looking for a coherent policy that addresses the needs of LDCs, examples from the three countries mentioned above can be useful. They each demonstrate the critical importance of a *combination of factors, including health funding, political commitment, and flexibility in implementation of IP law*. Of the three countries, Brazil has shown the most impressive successes at extending drug access to its population. In that country, development of domestic public manufacturing capacity and willingness to use options in trade law have allowed the government to be a powerful negotiator with patent-owning MNCs. IP policy should encourage flexible policies within the context of TRIPS, and affirm a variety options that strengthen the negotiating hand of LDCs with MNCs.

The Brazil model is less applicable to lower income countries without domestic industry. In these countries, significant injection of resources is absolutely necessary, combined with greatly reduced prices for pharmaceuticals. Political and economic incentives for *differential pricing* (particularly for essential medicines) can and must play an important role here. For example, expanded efforts by industrialized and LDC governments will be needed to prevent re-importation of cheaper drugs to wealthier markets.

*Generic competition, or its threat*, has been a crucial element in achieving reduced drug prices in LDCs. It would be irresponsible to constrain the ability of LDCs to use compulsory licensing for in-country production or importation of generic products necessary to address health priorities. The question of compulsory licensing for product import was left unresolved at the WTO consultation in Doha in November 2001. LDCs without production capacity clearly need to be able to use compulsory licensing for drug importation if they are to meet the health care needs of their populations. It also makes little sense to expect each LDC in the world to have its own production facility for every

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<sup>3</sup> Given comparatively low per capita incomes in most African countries, there is little to suggest industry is hoping for significant market expansion in these countries at industrialized world prices.

essential on-patent drug, particularly given the economies of scale in pharmaceutical production.

That said, compulsory licenses should not, however, be seen as a “magic wand” for obtaining affordable access to patented medicines in developing countries. Scherer and Watal (2001) have highlight three limitations. First, compulsory licensees must have the capability to “reverse-engineer” or import the product without the co-operation of the patent owner<sup>4</sup>. Increasingly, larger domestic companies in developing countries are raising their R&D investments and are collaborating with multinational companies to achieve advanced capabilities and reach more markets. Sustainable cooperation will not allow for these companies to undercut their “partners” in other products areas with generic copies.

Second, exports of compulsorily licensed products from large markets destined for small, least-developed countries can only work where the disease patterns are common to both markets.

Third, compulsory licensees will be only attracted to large and profitable drug markets, and so essential medicines with small potential volumes or mostly poor patients will not attract many applicants, however important it is from the perspective of public health (31). Thus, existing and future drugs for most of the neglected diseases discussed earlier in the report are not likely to be the focus on private generics producers either.

The AIDS pandemic demonstrates the desperate need for policies that foster early and broad access to life saving drugs, as well as the promotion of research on future technologies needed in LDCs. This is the difficult and urgent challenge to policy makers. As LDCs increasingly demand funding and policy options to increase health care access, and policy makers begin to appreciate the role of health status in creating a more stable world, this challenge of balanced and equitable IP policy becomes ever more important.

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<sup>4</sup> Transfer of technology, often recommended as a solution, requires the active cooperation of the patent owner or, in the context of South-South cooperation, of his competitors.

## A. The Introduction

### A.I. IPR Debates in a New Global Context – The Cipro Case

In February 2001, journalist Julian Borger of the Guardian wrote, “US public ignorance was in part to blame for why the pharmaceutical industry was controlling the policy debate on intellectual property for global health”. One could argue that the anthrax attack in the US in October has changed this. Certainly there has been first hand experience with the complexities of the issue. The US was suddenly faced with a situation where there was a perceived need for immediate access to a product still on-patent, where the exclusive owner of that patent, Bayer in this case, appeared unable or unwilling to offer enough supplies to meet immediate demand. The US government’s first instinct was to consider the compulsory license option and seek out alternative manufacturers. At the same time new R&D and manufacturing help is also needed from the pharmaceutical industry to develop vaccines and drugs to fight this and other bioterrorist threats. The “Cipro case” captures, in many ways the complexities of the debates of IPR tradeoffs faced within the global health arena.

Proposals from other manufacturers, Cipla in Indian in particular, claimed to be able to both meet that need in a shorter period of time and offer the product at a lower price to the government. The US government did not, in the end, follow through on its threat to seek a compulsory license but instead managed a deal with Bayer<sup>5</sup>. By contrast, the Canadian government moved immediately to grant a compulsory license to a Canadian generics company (NYT, 10/19)<sup>6</sup>. But the implications for the US and the pharmaceutical industry of the actual (and perceived) bioterrorist threats far exceed the immediate access to this one product.

New research and development is needed and the government must call upon biotechnology and pharmaceutical companies for help to deliver on their promises. There is concern, for example, that over-use of Cipro will lead to drug resistance and thus other antibiotics must be tested for their efficacy in treating anthrax<sup>7</sup>. More importantly, additional research is needed to bring a safe and effective anthrax vaccine to market. The one product in clinical trials, that of BioPort, has what are considered to be unacceptable sides effects including chronic fatigue, bone and joint pain, memory loss and other problems (some believed to be but not proven to be associated)<sup>8</sup>. There has also been a move to boost stocks of the small pox vaccine. Many of the leading vaccine producers have stepped forward to help add to the supplies that Acambis (UK firm) was already in

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<sup>5</sup> In the deal, Bayer would charge 95 cents/tablet for the first 100 million down from existing selling price of \$1.77; 85 cents for second million and 75 cents for third million. Bayer also donated 4 million Cipro tablets to police, firemen and postal workers (source).

<sup>6</sup> In the end, the move by the Canadian government did not follow legal requirements, was withdrawn, and the government, like the US, reached an agreement with Bayer.

<sup>7</sup> Other drugs already do exist. Doxycycline, in particular, has CDC support as “treatment of choice. Pharmaceutical companies including Bristol-Meyers Squibb, Johnson and Johnson, Eli Lilly, Pfizer and GlaxoSmithKline have all offered medicines for free if the FDA approves them for this use (NYT, 10/26).

<sup>8</sup> BioPort, the Pentagon’s sole supplier of anthrax vaccine has been also unable to ship any since 1998 because its renovated factory has not met FDA safety standards (WSJ, 10/19).

the process of manufacturing for CDC<sup>9</sup>. The government has earmarked \$509 million to finance the manufacture of these additional doses.

Additional legislation is pending that would make \$5-10 billion available to hasten vaccine production and ease regulatory restrictions (WSJ, 10/21). The government has already approached a number of biotech companies to initiate new public funded products to further R&D in relevant infectious diseases. There is an expectation by some industry experts “that in the future the government is likely to pour funding into research for new vaccines, drugs and biowarfare-detection tools and to identify other promising areas of research. Most of the answers to bioterrorism are in the hands of the biotech and pharmaceutical world” (Contra Costa Times, 10/24).

And in the rush to work, public offices and companies have discovered legislative and infrastructure bottlenecks barring progress in these, until recently, non-priority areas. The specialized skills of conducting animal model tests in monkeys, for example, is concentrated in very few institutes, Army Medical Research Institute of Infectious Diseases at Fort Detrick being one of them. Companies with products in the pipeline find their requests are but one in a very long queue. Amendments to FDA regulatory proceedings for fast-tracking products have also been delayed (NYT, 11/13). Finally, the new public investments into specific product research and development in “classified” areas may imply a move into a new era of public-private investor-research relationships. The outcomes are, at the moment, unclear and untested (NYT, 10/21).

Over the course of a few weeks, therefore, the US national headlines have portrayed the pharmaceutical industry and the patent systems that serves as “the bedrock to its business” as the key barriers to “national security” while at the same time identifying them as the best opportunity for quick, innovation solutions to up until now non-priority and under-researched scientific problems. Public funds, infrastructure and support are essential but not enough to meet the existing and future demands. Private company participation is essential.

## **A.II. The Research Questions**

So we come to the question of how to both encourage the private companies to participate (which means making it affordable, especially for small biotech companies who are not in a position to pursue projects just out of patriotic duty) while at the same time ensure affordable supplies of products, new and existing, some on-patent, some not; some in stock, some not. The US has demonstrated the political and financial means to mobilize the resources needed to respond to this national “emergency” (though of course results are not guaranteed given the risks and uncertainties inherent in the science of drug and vaccine development). At a global level, we face the exact same types of questions within the intellectual property right (IPR) debates over how to improve health in the developing world. These countries cannot mobilize the resources to “solve” their regional problems and depend on global solutions. However, the instinctive view of IPR is as a

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<sup>9</sup> Acambis received a contract in September 2000 from the US government to manufacture 54 million doses. The deal originally had a 5 year time frame. That has been pushed up to 2 years.

barrier to access for drugs that already exist. Yet recognition that is crucial to providing incentives to develop new drugs is still at the core of the problem. As a recent report by Working Group 2 of the WHO Commission for Macroeconomics and Health has demonstrated, methods to realize the production of these global public goods have yet to be found.

This report looks at the role IPR plays in the achievement of two demands in the context of developing countries: affordable access to existing products and investments in new R&D for a limited number of diseases that predominately affect populations in the developing world<sup>10</sup>.

### **A.III. The Report Layout**

The first section examines the R&D problem. For a set of infectious and communicable diseases, henceforth referred to as *neglected diseases*, the lack of market opportunities makes them a low commercial priority for the public and private organizations contributing to drug and vaccine development. How IPR plays a role in possible solutions to this problem is linked to its role as an incentive for companies to innovate and invest in R&D.

We review literature on the nature of the relationship between innovation and patent protection in the pharmaceutical industry in general, before turning to the questions of what impact the strengthening of IPR is likely to have on the developing countries' capability to do R&D and, more importantly, on the likelihood that any company, from developed or developing countries, will contribute more resources to the neglected diseases of the poor. A relatively new set of questions have arisen about how the development of the biotechnology industry and its changes to the structure and organization of R&D and patenting strategies should influence the standard assumptions about patents and innovation in the pharmaceutical industry. Nonetheless, there is a general consensus that strong IPR is a necessary component of a broader set of institutions, regulations, and competencies that encourage innovation.

Our analysis points, however, to the need for explicit public policy above and beyond IPR policy to encourage the necessary level and emphasis of R&D investments to treat neglected diseases. Three models of R&D have been considered in the policy literature – a private, public-private, or public model of R&D. Given the skills, resources, and experience that sit with in the pharmaceutical industry and are essential for the R&D progress, the first two, applied in combination, have the greatest prospect of success. IPR can be used as a constructive incentive and negotiation tool in both.

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<sup>10</sup> Over the past couple years, an extensive literature has emerged on the issues of how to incentivize new R&D into diseases of the poor and secure better access for these new and existing products. A report based on a joint Institute for Global Health and Wellcome Trust meeting in December 2000, focuses explicitly on the importance of IPR in these issues (IGH, 2001). We endorse and refer to many of the views expressed in that report. Other valuable contributions to the broader literature include Kettler, 2000, PIU, 2001, CMH Working Group 2 Report (forthcoming), WHO-IFPMA, 2001, IGH, 2000).

The second section of the paper reviews the literature about the affect of IPR on drug prices and patient access to essential medicines in the developing world. We focus on the cases of the effects of IPR on access to HIV/AIDS drugs in three different countries - India, Brazil and South Africa. These three countries are large regional leaders, and are characterized by different IPR regimes and stages of industrial development. A key conclusion drawn from this review is that patents have definite affects on the price of newer therapeutic drugs, and in resource-constrained environment these higher prices inhibit drug access.

Today, generic drugs play a crucial role in controlling drug prices. Looking to the future, to the extent that newer, on-patent treatments represent significant therapeutic advances over older off-patent drugs, the personal health of millions may be affected by patent policy. The section also finds that the relative importance of IPR in the affordability debate in any one country depends on the strengths of at least two other factors – financial resources and government commitment. IPR is less of a problem for countries where there are plentiful resources for health spending. IPR is also relatively unimportant in cases where there is no government commitment to providing care and no available financial resources to purchase drugs.

Recognizing the importance for disease specific and country specific solutions, our analyses support a movement towards at least two new global “norms” within a TRIPS compliant world to facilitate access:

1. differential pricing (in the absence of exhaustion in industrial countries) in cases where there are global markets; and
2. technology licensing agreements that include access conditions for global health applications for product in the R&D pipeline. “An essential goal is to establish a precedent in deals where access conditions come to be seen as standard – conditions faced by any individual company’s competitor”.

Success in both of these endeavors requires commitments, learning and participation from developing and developed country governments, pharmaceutical companies, university technology transfer offices and so on. They are part of global solutions going forward.

## **B. Using IPR to Solve the R&D Problem**

### **B.I. Defining the Problem**

Developing new drugs, vaccines and diagnostics is a critical part of a package of steps needed to treat and ultimately eradicate the infectious diseases prevalent predominately among the poorest segments of the peoples of the developing world. Table 1 shows the disease areas where the majority of cases occur in the developing world (all tables and figures are found at the end of Section B).

As we show in Figure 1, the primary actors involved in the research and development (R&D) of pharmaceuticals and vaccines are public research institutions in developed countries and private pharmaceutical companies in developed countries. The public researchers contribute primarily to the early discovery stages; private companies invest in all stages but dominate the processes of development, production and commercialisation. The division of labor has changed somewhat over the past 20 years though the relative comparative advantages have stayed the same (see below).

There is much evidence that diseases such as malaria, TB, leishmaniasis and others are a low priority. Surveys of company pipelines and alliance databases add to the much cited figures of only 5-10 per cent of health R&D going to LDC diseases, with 1 per cent of new products between 1975-1997 developed specifically for tropical diseases (summarized in Kettler, 2000). For example, according to the PhRMA website, there are two products in its member company's pipelines for malaria, one for leishmaniasis, one for African Trypanosomiasis and three for TB. According to the ReCap.com alliance website there are currently 12 alliances in research that might relate to malaria, 17 to TB and 6 to HIV vaccines. Also see Cockburn and Lanjouw (2001) for measures of R&D in these disease areas including growth of worldwide patents, growth of worldwide publications, growth of NIH research awards and a survey of Indian pharmaceutical companies.

Private companies are not the only actors neglecting these diseases. It is difficult to assign some of the NIH research investments to specific diseases. But in 2001 only 0.21 per cent of the total \$41,887 million going to research initiatives and programs went to TB and 1.13 per cent to AIDS vaccines compared with 10 per cent to cancer, the disease with the largest budget (NIH). See Table 2. A joint WHO/IFPMA group has conducted a thorough investigation of the public and private involvement in neglected diseases (WHO/IFPMA, 2001)<sup>11</sup>.

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<sup>11</sup> The goal of this study was to identify which disease would most benefit from new R&D. Two tiers with nine diseases are found wanting of effective products on the market or under development in the pipeline: malaria, TB, lymphatic filariasis, onchocerciasis, leishmaniasis, schistosomiasis and African trypanosomiasis (WHO/IFPMA, 2001).

Studies have been conducted to identify the reasons for the lack of new private R&D into these diseases (Kettler, 2000, Kremer, 2001, PIU, 2001, Europe Economics, 2001). Assuming, to start, similar cost structures and scientific hurdles for neglected diseases as for the developed country diseases, a key factor that discourages private investment is the poor expected return. Despite high need – a large number of patients – these patients are unable to pay for medicines and thus expected demand is very low.

In 1998, for example, the peoples of Africa made up 10 per cent of the world's population but suffered 25 per cent of the disease burden, measured in terms of disease adjusted life years (DALYs). Sixty eight per cent of those DALYs lost were linked to communicable diseases (World Bank, 1999 and WHO, 1999).

Taking the case of malaria, The Medicines for Malaria Venture (MMV) has estimated that “a new drug that sold well in endemic countries, with a low margin, and achieved an aggressive 30 per cent market share in the travelers market, at a 50 per cent margin, would result at most in \$50 m annual returns, not enough for pharmaceutical companies seeking annual sales potential of \$250m-\$300m for a new drug” (MMV Business Plan). The Global Alliance for TB Drug Development (GATB) has recently published a study that estimates the market for new TB drugs at \$700 million by the year 2010 (NYT, 11/15).

The public policy challenge is to construct incentives to engage public and private researchers to invest more aggressively in R&D for new products in the neglected diseases of the poor. In addition to new products, extensions to existing compounds to make them more suitable for the specific circumstances of the country of focus is also needed. Adjusting the dosages to local needs, finding combinations more appropriate for local medicine practices are among the examples of “local development work” (Europe Economics, 2001, 8). The policy discussions focused primarily on two alternative solutions<sup>12</sup>.

- (i) The first model – the commercial approach - strives to make neglected diseases as attractive as other, non-neglected, diseases to private companies looking to make investment decisions. By improving their expected profitability a package of cost reducing (“push”) and market enhancing (“pull”) policies would incentivise more R&D into these diseases;
- (ii) In the second model, public-private partnerships (PPPs) are set up to address disease specific R&D gaps.

Both of these models are based on the assumptions that private industry plays a critical role in the R&D process, that strong IPR, especially patent protection, is required to incentivize companies to participate. This implies that we are operating within the current

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<sup>12</sup> The third possible alternative – the purely public model – has, until now received less serious attention, in part because of the lack of resources and expertise within the public sector to conduct specific stages in the R&D process.

IPR environment where countries with pharmaceutical industries have or are in the process of introducing TRIPS compliant IPR legislation. Within both models creative patent and licensing arrangements above and beyond the base protection rules should be employed to ensure success. We discuss the specific details of this below.

## **B.II. Innovation through Patenting, Some Theory**

Our first task is to examine the presumed link between strong IPR, patent protection in particular, and R&D and innovation in the pharmaceutical industry. The pharmaceutical industry is generally seen as a textbook (and exceptional) case of “where patents are considered an important mechanism of appropriability of the economic outcomes of innovation. Absent such protection, profit-seeking firms would not invest in research or would under-invest as compared to social optimum” (Lacetera and Orsenigo, 2001, 6)<sup>13</sup>.

The message from research-based pharmaceutical and biotechnology companies is clear - without patent protection, there will be no R&D. Two features of pharmaceutical research and development explain why. First, the sunk costs of R&D are high, averaging \$300-600 million per new product. (This estimate includes the cost of failures and the opportunity cost of funds during the R&D process) (Kettler, 1999). This amounts to more than thirty percent of the total cost of developing, producing, and marketing the typical product. Second, the marginal cost of production of pharmaceutical products is often low. Although the R&D process is lengthy and risky, most pharmaceutical products once they exist are relatively cheap to produce. This feature is what permits generic firms to launch products at prices well below the cost of a branded product, immediately following expiration of the patent. Without patent protection and the secured period of market exclusivity, generic products would enter the market immediately following product launch, and bid down prices to marginal cost. Since marginal costs do not cover the fixed costs on R&D, the likely result would be a decrease in R&D, and hence a decrease in new products brought to market by the research-based industry.

The Joint Economic Committee to the US Senate in a report on the contribution of the NIH to the drug development process, sums up the importance of IPR as follows:

“Once knowledge discovered by basic research has been disseminated, any one can use it without charge. Therefore investment in basic research can be unprofitable for private industry except insofar as it has well-defined links with applied research. However, this implies that the economy wide rate of return on basic research is higher than the private rate of return that industry can capture – a situation that creates a case for government support of basic research, such as medical research. Federal research and private research are complimentary. Private research in the United States has produced a cornucopia of medicines,

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<sup>13</sup> For reviews of the literature on the presumed causation between patenting and innovation see World Bank (2001) and Europe Economics (2001). On the economic theories of the costs and benefits of patents see Nelson and Mazzoleni (2000).

medical devices, and techniques. Private research has built on a foundation funded by federal research. Many of the ideas underlying private research and commercialization were developed by federally funded research. Together, federal funding and private funding have produced networks of innovative research that have served the American public well.” (JEC, 2000, 9)

The organization of R&D, the form of successful innovation, and the role of IPR have evolved over time in the pharmaceutical industry. Lacetera and Orsenigo (2001) have conducted an excellent study of the interplay between “policy regimes”, of which IPR is a part, and “technological regimes”. They explore how these interactions have contributed to the nature of innovative performance and competitive success in the US and Europe in each of industry’s three phases of historical development: the early emergence and development epoch (pre WWII); the Golden Age and Welfare State Era (WWII until mid 1970s); and the Age of Molecular Biology and Cost Containment (mid 1970s until the present).

Their account makes a number of key contributions to our IPR discussion:

1. IPR, especially patents rules are one of the key factors in each stage, but its structure and form of influence as an incentive has varied and evolved as the science, technological competencies and business strategies have evolved. So, for example, German companies tended to lead the industry in the first epoch, supported by process patents only at a time where limited scientific and technological advance meant product patents held rather than advanced innovation. By clear contrast, strong, targeted product patent protection in the modern era is one of the central contributors to the US’ success (and its absence a factor for the Germans’ problems (Kettler and Casper, 2000)).
2. That said, there is also no one “best practice” in anyone time period and also no linear relationship between one type of regulation and competitive success. It is the composition of regulation and competencies that are important. Other important components of the supportive system above and beyond IPR include price, market size, safety and approval regulations, and scientific resource. “More generally, these observations suggest the conjecture that strong patent laws do indeed confer an advantage to innovators, but they are not enough to promote innovation in contexts where innovation capabilities are low or missing altogether. Similarly, high degrees of appropriability are likely to be particularly important for sustaining innovation in highly innovative and competitive environments rather than in situations where little innovation takes place anyhow. In other words, patents magnify the incentives to innovate but do not create them in the absence of competencies to make innovation possible in the first place” (26). There are cases where countries with companies that have managed to innovate despite relatively weak patent systems at home (Germany and Switzerland) and others where companies have failed despite strong patent systems (Italy and Japan).

3. The account demonstrates there is not necessarily only one sustainable business model. While not the industry's leaders in terms of R&D innovation or profits, companies in countries like France for example, have, at least until recently, survived pursuing a less innovative domestic market oriented strategies of me-too production, process imitation, inventing around and the production and marketing of drugs under license or after patent expiration (23)<sup>14</sup>.

These findings raise important questions for the developing countries considering changes to their IPR system.

- A. They imply that we must at least address the question of whether we can predict how companies in countries with emerging but relatively underdeveloped industries will respond to the introduction of the globe's leading companies' IPR standard.
- B. They imply that in the absence of necessary competencies and institutional support, IPR regulation in and of itself will not necessarily have an effect on developing countries' abilities to conduct R&D and innovation to a global standard.
- C. The extent to which countries can pursue "national company strategies" will depend on their dependence on global markets, resources, and competencies to survive.

We return to these issues in Sections B.V and B.VI.

Lacetera and Orsenigo (2001) describe in considerable detail the role IPR play in the current "biomedical" epoch of pharmaceutical development. "The molecular biology revolution radically transformed the ways research is organized and conducted and the structure of the industry". The next section explores the opportunities and potential problems for innovation through patenting in this new organization form.

### **B.III. New Patenting Issues in the Molecular Biology Age**

At least three important changes have come with the new biomedical epoch. First a new set of actors have entered into the R&D process, specifically the new start-up biotechnology companies which, at least in their infancy, focus on specific stages of the discovery stage of product development, and the venture capitalists, who help support these entrepreneurial biotech companies. Second, IPR has become central to the universities' contribution to R&D as well as to the biotech company's ability to attract funds, do deals, and survive. Third, there has been a shift towards patenting inputs, namely research tools, as well as final products. It is beyond the scope of this paper to elaborate in detail the effects of these three developments on position of IPR in the

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<sup>14</sup> Recent debates in the EU and elsewhere have focused on the question of whether national health care budgets are well spent on the purchase of "me-toos" that add relatively little innovative value to existing products (Kettler, 1998).

pharmaceutical industry's overall strategy (though it would make a fascinating study, well worth developing if it has not already been done). We focus on a few key points and debates of relevance to our ultimate question of how to solve the R&D problem.

1. Pharmaceutical discoveries have always drawn on academic research and close ties between industry and universities are fundamental to commercial success. But the nature of the universities role has now changed as it has taken over the business of commercializing its research by way of patenting, licensing and the creation of spin-offs, enabled by changes in the IP rules<sup>15</sup>. In the US at least, patents are now fundamental to innovation in both universities and companies (Nelsen, 2000). **[In final draft include table listing key IP amendments in US, UK, Germany that play a role in technology transfer as well as policies that enhance IP protection for pharmaceutical industry over all].**

2. IPR is central to the survival of the new independent biotech companies. Venture capitalists, potential alliance partners, and the stock market all evaluate companies according to their IP profiles, among other things, in the critical decision on whether to fund the risky R&D that may eventually lead to product launch (and earnings income based on actual sales).

3. These biotech companies have moved into the business of patenting inputs, namely research tools, as well as research output – products. As these inputs become every more fundamental to the development of new drugs and vaccines, companies operating downstream in the R&D process, be that major pharmaceutical companies or other biotechnology companies need to do deals with these companies to gain access to the tools, resources, and inputs they need to construct products.

The move to patent inputs is the primary impetus behind new debates about the potential limiting effect of patenting in the biotech industry on bio-medical innovation. There are significant new costs involved. Due to the enormous number of technological processes that are required as inputs to product development, individual companies are simply not able to keep all processes in-house. For any individual company, acquiring the necessary licenses and sorting out the state of play of patents filed in order to obtain the "freedom to operate" without infringing on rights held by others is expensive and time consuming. For example, pharmaceutical firms must often negotiate with multiple parties (universities, consortia of institutions, non-governmental institutions, individuals, and corporations) to assemble access for licenses to the overlapping and interwoven claims to intellectual property rights needed to develop a single product. Where multiple parties are involved in developing a final product, they end up sharing the returns. Referred to as royalty stacking, the company launching the final product pays royalties to the multiple partners that have contributed to it.

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<sup>15</sup> A number of legislative amendments in the US have facilitated this technology transfer process. Most important was arguably the Bayh-Dole act which granted rights to universities and small business to patent inventions developed with public funds and authorized federal agencies to patent and license their inventions (IGH, 2001, 10).

There are arguments about what tools and resources should legitimately be patented and which should remain available for all researchers to use. Patenting and exclusive licensing, it is argued, blocks academic and private researchers access to technologies that are potentially applicable to a range of uses<sup>16</sup>. It's a difficult position to argue. On the one hand, a patent acquired by a company for a specific disease ensures the company access to rights to all uses for that patent, unless explicitly stated otherwise and that blocks others from using it (without a license from the "owner). But on the other hand, without exclusive rights companies may not be willing to invest the resources to develop ideas into useable tools and products given the risks that a competitor "gets there first" in a non-exclusive rights agreement.

Walsh et al. (2000) have conducted a study through interviews and archive research to explore the concern that "the biomedical innovation is susceptible to a tragedy of anti-commons". Here numerous property rights claims to separate building blocks for some prospected products or line of research. If negotiations necessary to their combination fail, pursuits of these lines of research or product development can be "quashed" (2). These authors find a dramatic increase in the number of patents on inputs to drug discovery. However, "we find drug discovery has not been substantially impeded by the increase in patents on inputs to drug discovery. There is evidence of delays associated with negotiating across to patented research tools and there are areas where patents over targets limit access. There are also cases where research is redirected to areas with more IP freedom. However, the vast majority of respondents say there are no cases where valuable research projects were stopped due to IP problems.

There is not as much breakdown as one might expect because firms develop "innovative solutions" that allows their research to proceed. These solutions combine taking licenses, inventing around patents, infringement, developing and using public databases and challenging patents in court. Finally the very high technological opportunity in this industry means that firms have a surplus of potential targets for drug development so that the walling off of some by patent holders while shifting the focus does not prevent firms from discovery drugs...Overall, we are optimistic about the industry's ability to accommodate the increased complexity of intellectual property. (1)

This is certainly not the final word on this issue. Further research must and will be done. For the purposes of our problem, a clear understanding of the new structures and organizations and motivations of R&D are essential for the devising of effective policy tools and initiatives. Section V considers the link between IPR legislation and the development of R&D capacity in developing countries. The points made in this section suggest that any country looking to succeed in the modern era of pharmaceuticals will need to have means to gain access to these now patented tools and technologies. They will also need to consider how their IPR policies affect not only private companies but also public researchers. Again, this is an area requiring new research.

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<sup>16</sup> For detailed discussion of the case of genomic patents and of PDAPP see Barton, 2000a and 2000b, Dunn, 2000.

## **B. IV Innovation through Patenting, Some Evidence**

Many studies have attempted to empirically test the causal link between patents and innovation (see Europe Economics (2001) and the World Bank (2001) for overviews of studies). We present results from three studies.

**[for final draft, add example of impact of Bahy-Dole on US biotech; the ownership structure of patents in Germany on its biotech industry; and Pammolli's findings of the role of IPR as a factor in explaining EU pharmaceutical competitive weakness vs US (2001 study for EU)]**

### *1. How Changes in Patent Policy Influence Patent Filing Behavior*

Lerner (2000) examines the relationship between changes in patent policy and “innovation” defined by new patents filed, for 60 countries over a 150 year time period (his study does not just focus on pharmaceuticals). Looking at 177 policy changes in all, Lerner found that the effects of patent policy shifts were far greater for foreign entities than for residents of the country undertaking the policy change. “In fact, adjusting for the change in overall patenting, the impact of patent protection-enhancing shifts on applications by residents was actually negative, whether domestic filings or those in Great Britain were considered” (30). Cross-sectional analyses suggest that the impact of patent protection-innovation enhancing shifts were greater in nations with weaker initial protection and/or with greater economic development.

He acknowledges the limitations of using “patents” filed as a measure of innovation. Many important innovations are not patented on the one hand while many relatively trivial changes to existing inventions are. That said, this study certainly represents an important contribution to the debate.

### *2. Abolishing Compulsory Licensing in Canada*

In a pharmaceutical specific study, Pazderka (1998) examines the impact of the 1991 abolishment of a compulsory license provision on the Canadian pharmaceutical industry. The 1969 provision aided in the development of a domestic generics industry (between 1969 and 1987 when the provision was first amended) 400 licenses were granted) but arguably had discouraged FDI and domestic investment in pharmaceutical and biotechnology R&D.

His analysis of R&D investment trends, taking into account the trends in Canada as a whole and the pharmaceutical industry worldwide suggest a positive response to the strengthening of the patent rules. A comparison of pharmaceutical R&D expenditure in 14 OECD countries over the post 1988 period, Canada's rate of growth of investment exceeded that of the other countries for example. He acknowledges, however, that exclusive links between the change in patent policy and R&D expenditure is not possible. Other factors, such as an R&D tax credit, and the commitment by pharmaceutical

companies to increase their ratio of R&D spend to sales as part of the negotiation with government over the licensing rule no doubt contributed as well.

Less time series data is available on the biotechnology sector. Drawing on a survey by Heller (1995), Pazderka shows that that Canadian biotech companies have tended to file patents in the US first and then Canada if financial resources allow, driven by the larger market prospects for any successful products in the US. The same survey found that the majority of Canadian filed patents are actually by foreign firms. “Heller hypothesizes that the strengthening of IP protection in Canada may contribute to the growth in Canada’s trade deficit in biotechnology products. He also found that “Canadian and MNC biotechnology companies have chosen not to commercialize their products in Canada because of the high cost of obtaining and developing patent protection relative to the small size of the market” (186-187). Here is additional evidence of the importance of a supportive composition of regulations and environment to support R&D.

### *3. FDI Decisions and Perceptions of IPR Weakness*

In two well-sited studies, Mansfield has analyzed the relative importance of strong patent protection regulation in MNCs foreign direct investment decisions in different industries. Quoting from the abstract of his most recent study (1995),

“In earlier studies, I found that the strength or weakness of a country’s system of intellectual property protection seems to have a substantial effect, particularly in high-technology industries, on the kinds of technology transferred by many US firms to that country [Mansfield, 1994]. Also, this factor seems to influence the composition and extent of US direct investment there, although the size of the effects seems to differ from industry to industry.

In this present paper, which includes German and Japanese firms, the findings indicate that, in relatively high-technology industries like chemicals, pharmaceuticals, machinery, and electrical equipment, a country’s system of intellectual property protection often has a significant effect on the amount and kinds of technology transfer and direct investment to that country by Japanese and German, as well as US, firms. Also, when a variety of relevant factors are held constant in an econometric model, the effects of such protection on US foreign direct investment are substantial and statistically significant”(1).

Table 3 summarizes the key findings from the survey of drug and chemical companies. One thing that stands out is the importance of patent protection in the manufacturing as well as the R&D stages in the process. Table 4 shows the countries considered the worst potential FDI and technology transfer partners by the German, Japanese and US pharmaceutical and chemical companies because of perceived weak IPR as of 1994. There were 14 countries considered in total, selected because of their size and importance “as well as the frequency with which they have been cited in connection with controversies over intellectual property protection” (5). India stands as the country of

greatest concern in all three categories. This reflects not only its weak IPR rules but also the perceived abilities of the companies there to exploit the limited protection rules.

Insert Tables 3 and 4.

### **B.V. IPR and R&D Capacity in the Developing World**

The historic accounts of the pharmaceutical industry have, until now, involved a limited number of countries and companies. The “rest of the world’s” role has been that of consumers. The situation is changing. Even before TRIPS, the production side of the industry has started to become more global. According to a 1991 UNESCO study, only six low and middle income countries (Argentina, India, China, Israel, Mexico, and South Korea) had industries with innovative capabilities and 8 others, including Brazil, Cuba, Indonesia and Egypt, could produce therapeutic ingredients and finished products, competitive in regional export markets. 59 countries had no industry at all and were totally reliant on imports to meet their pharmaceutical requirements. See Table 5. An important question for this report is how the globalization of patent protection will affect the global level of innovation and in particular the number of innovations in neglected diseases.

Many proponents of TRIPS argue that a key benefit for developing countries is that it will improve the conditions necessary to attract FDI and technology transfer, inputs necessary to help develop local R&D capacity. A list of expected long-term benefits from stronger IPR includes:

1. It will potentially globalize the effort to find cures for disease, spreading the effort to emerging economies that have core scientific skills but currently lack the incentives to use them. In countries with emerging pharmaceutical industries such as India, Korea, Brazil, and China, it should encourage researchers to switch from a strategy of molecule copying to one for innovative research of new drugs and LDC-versions of existing drugs;
2. It should improve the transfer of, and access to, technology and information from companies in established countries to LDC researchers;
3. It will create jobs for skilled labor and perhaps limit the “brain drain” from LDCs to established economies;
4. It will improve international credibility for, and prospects for joint ventures and direct foreign investment in, LDC research.

Mansfield’s studies presented above do suggest that weak IPR is a disincentive for FDI and technology transfer. Pharmaceutical companies refuse to bring products to market in countries where their patents are not protected (and domestic capacity exists for copying these products). In a 1996 study, only 45 of the 434 pharmaceuticals on patent in the UK were made available in India by Pfizer (Mossinghoff, 1996). And case studies of Canada, Mexico, and Korea suggest that introducing IPR can have a positive impact R&D investment. Again, according to Mossinghoff, “Rx industry consistently located R&D and manufacturing in developing countries that respect IPR”.

That said, the analysis of Lacetera and Orsenigo clearly demonstrate the need for both supportive regulations and competencies. In the end, the outcome will vary by country and depend at least in part on the current state of development of its pharmaceutical industry. India is a popular case study for these kinds of questions. The details are presented elsewhere (Lanjouw, 2000, Juma, year?, Lanjouw and Cockburn, 2000, Kettler and Modi, 2001), but the Indian case is particularly interesting because of its successes in developing an industry supported by, among many other things, a weak IPR system. It is seen as a country with potentially as much to lose as well as win from stronger patent rights. **[need to develop]**

#### *Local R&D Into Neglected Diseases*

It has been argued that developing countries stand to contribute extensively to the global R&D effort in general, and the effort to eradicate neglected diseases in particular. Cockburn and Lanjouw (2000), as a test of the incentive role of patent protection, conducted a study of whether the trend in global research into neglected diseases has changed significantly (and positively), as endemic countries implement strong IPR. Given identifiable differences in drug demands in these countries, they surmise that one might expect changes in the pattern of research expenditures as a result of the strengthening of the patent system that would be easier to detect and ascribe to policy reform than would be changes in overall levels of investment (2).

They do find some evidence of new “research activity” in malaria, in the 1980s and early 1990s, but none in other tropical diseases. Rather than test the incentive role of patent protection to conduct R&D in general, they may instead have presented excellent evidence to the fact that patent protection on its own is not enough to incentivize new investment in these neglected diseases.

#### *The Case of India*

One of us has argued elsewhere (Kettler and Modi, 2001), also relying on the Indian example, that the idea that the potential cost advantage of doing R&D in the developing would encourage emerging companies with R&D capabilities to focus on diseases neglected by the global players seems weak for a number of reasons.

In addition to the required investments, companies need to move along a steep and rapidly evolving learning curve in order to achieve the desired cost levels. Most Indian companies have done little or no extensive R&D of the type required to discover, develop, and market a new product. Moreover, even if companies were capable of achieving such low costs, moneymaking opportunities would still be much greater for rapidly growing global diseases than for neglected diseases, notwithstanding significant differences in cost structure between these two categories.

In interviews, executives of India’s leading companies revealed a global focus (*Lanjouw and Cockburn, 2000*). These companies seek to exploit their traditional experience and cost advantages in the generic drugs market or in improving the drug profile by modifying existing drugs or discovering new classes of molecules for well-understood

diseases. Those looking to increase their in-house R&D facilities emphasize the importance of major diseases in industrialized countries, e.g. cancer and diabetes. In the USA, for example, marketing approval by the Food and Drug Administration is quick and even a moderately important discovery is likely to be significantly profitable (Lanjouw, 2000). As of 1999, only 16% of research and development expenditure in India was targeted on tropical diseases or developing-country markets, and about half was focused on developing more suitable products for diseases of global incidence (Scherer and Watal, 2001).

The Indian Government has given priority to investment in new drug development for diseases of relevance to the Indian population. Among these diseases are tuberculosis, malaria, and leishmaniasis. Without explicit targeted incentives, however, such investment is unlikely to take place. The Pharmaceutical Research and Development Committee has proposed the establishment of a support fund through a tax on formulations sold in India (Lanjouw, 2000). This would help to fund research in areas of combined high cost and low return, e.g. neglected diseases. It is unclear who would decide how to allocate the money. Of particular importance is the question as to whether the estimated US\$ 22 million generated annually by such a scheme would serve as an adequate incentive. Another way of encouraging greater interest in priority disease areas might be to adopt the Government's tax-holiday proposal and focus on innovations in these areas.

Potentially large economic and social benefits could be gained by enabling private companies and research institutions in endemic regions to contribute to R&D work on new treatments. Furthermore, research facilities based in these regions may be comparatively well placed to achieve quick solutions. This is because the practice of health research relies heavily on close contact with other parts of the health sector, on the local epidemiological environment and on the clinical, behavioral, and social sciences that are tied to both national and global frameworks.

However, creating conditions for innovative and cost-effective drug discovery and development and for a critical mass of companies focused on R&D requires significant investment in facilities, institutions, and skill building. India is just one example - other countries with emerging industries face many of the same challenges in their own institutional contexts. The Indian companies most likely to survive the changes in patent laws are those that can exploit traditional strengths in areas of generic drug production and innovative process development, and find markets in industrialized countries. Driven by the need to earn profits, companies wishing to succeed in the field of drug discovery are likely to target growing and potentially profitable global disease areas.

## **B.VI Policy Solutions based on “Creative” IPR Steps**

Local solutions to local disease problems seems a long term prospect at best and will clearly require more than just the introduction of stronger IPR or even general incentives to conduct R&D. Once capable of managing intellectual property and conducting R&D

there is ever reason to expect that companies from low and middle income countries will focus on diseases where they too can earn a profit. There is universal agreement that additional incentives and explicit, disease and problem focused policies and projects are needed to increase the amount of R&D investment committed to neglected diseases and, more importantly, launch new products.

Policy discussions have focused on two different types of R&D models: the commercial model which seeks to incentivize “traditional actors” to replicate the R&D process applied to global diseases to neglected ones; the public private partnership model which proposes a new organization of R&D. Creative IPR policy can serve as an important incentive tool in both models.

### **Policies to Support the Commercial Model**

In the commercial model, the goal is to incentivize private companies to engage in neglected diseases as they do in other ones by increasing the expected return on these investments. As in all R&D projects, public and private actors will contribute, but the private profit motive will drive the process. As others have discussed at length (Kettler (2000), PIU (2001), IGH (2000), Working Group 2 (forthcoming), two types of policies are sought – push incentives to reduce the real cost of doing R&D in these diseases and pull incentives to increase the expected rate of return. A summary of the incentives considered is presented in Table 6. With our focus here on IPR, we focus only on the roaming patent exclusivity ideas as part of a “modified orphan drug act”<sup>17</sup>.

There are differences between the specifics of the orphan drug acts in the US, EU, and Japan but the common goal is to incentivize pharmaceutical companies to invest in orphan diseases where the small number of patients and thus total market expectations are too small to warrant investing in the costly R&D process. A critical component of the US act is that companies qualifying for orphan drug status are guaranteed seven years market exclusivity from the date the FDA approves the product regardless of the status of the patent. Kettler (2000) has argued that that opportunity alone has made the orphan drug option extremely attractive for biotech companies, especially those developed products based on unpatentable materials.

An attractive feature of the orphan drug act from the standpoint of our task to deal with neglected diseases is that it combines push and pull incentives. And technically, the neglected diseases qualify for orphan drug status in the US because of the limited number of cases, often zero<sup>18</sup>. But exclusivity over this limited number of cases or even over a global number is not an incentive because of the patient’s inability to pay.

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<sup>17</sup> Milne and Ronchi (2001) have written an extensive analysis of the modified orphan drug option for the CMH’s Working Group 2.

<sup>18</sup> Worldwide, of course, these diseases are by no means “orphan” except from the stand point that they are uncared for by the investment and research communities.

Some work has been done on the opportunities and costs of introducing a roaming patent exclusivity clause that would allow companies to extend the patent life of a product of their choice for a limited, pre-specified period of time in exchange for bringing a product to market in a neglected diseases (and making it “affordable” to patients who need) (Kettler, 2000, WHO-IFPMA, 2001).

In a hypothetical set up, a team of experts, perhaps housed at the WHO, would be responsible for preparing a list of qualifying disease categories. This list would have to be updated as new treatments are developed and new infectious diseases (or drug resistant strands) are discovered. This international body would approve applications for this special orphan designation but individual countries would be responsible for providing the research grants, tax credits, and exclusivity rights. The number of “extra” exclusivity months this company would be awarded for product B (their already existing drug) would depend on the expected R&D costs of product A (the new LDC drug) and the expected added revenue per month earned from sales of product B in an uncontested market. Alternatively, a cap could be set on the additional funds companies could earn from the granted market exclusivity.

The main problem with this proposal is that the burden of financing the roaming exclusivity measure falls predominately on the users of drug B. Developed country governments are likely to face opposition from strong domestic patient groups opposed to the idea of their being singled out, making such a measure hard to legislate<sup>19</sup>. Another problem with this proposal is it will only be of valuable to companies that already have approved products. This would exclude small biotechnology companies, for example, that have no other products to transfer the exclusivity rights.

There is little argument that under any policy, industrial countries will have to subsidize the costs for developing to benefit. The two key issues are first, whether the work is done by public or private organizations (in this case the private companies do the work) and second, whether the subsidy will be “hidden” (extra costs to payers and patients in the funding and using the products with the extra months of exclusivity) or “open” (a grant paid out of general taxation, say, to the WHO to set up a purchase fund for example).

A different, and relevant question arises as to whether the types of push and pull incentives that some European countries and the USA are considering, in relation to the R&D priorities of multinational corporations, would work in India or other countries with emerging industries. If one or many global purchase funds were set up, this being the leading pull option currently under consideration, Indian companies could theoretically compete for a share. However, to be most effective, incentives should probably take explicit account of the distinct cost structures, skills, and strategic capabilities of companies in the less developed countries, just as different policies are needed to encourage the participation of small, often loss-making biotechnology companies, as

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<sup>19</sup> A proposed remedy to this problem is to have the governments reimburse the patients the difference between the expected generics price and the protected price for the months of extended exclusivity. This would transfer the burden back to the general taxpayer. The generics industry might also demand compensation for the extra months they are denied access to the market.

opposed to multinational corporations. How global incentive packages should be designed and executed are topics for important research in the future.

### **Policies to Public Private Partnerships<sup>20</sup>**

IPR plays a critical role in these new disease-specific initiatives (see Kettler and Towse). PPPs must pursue an aggressive IP strategy designed to maximise the social value of product and process patents. This can be achieved by:

- acquiring rights over all IP arising from projects directly funded by the PPPs;
- trading rights to rich country markets and use in other indications for low price access for LDC target markets;
- ensuring there are incentives to deliver to these markets – such as requiring simultaneous launch in rich and poor countries;
- providing incentives to supply sufficient volume to LDC markets;
- retaining reversion rights, should commercial partners not deliver on their commitments.

The evidence suggests that the PPPs are pursuing some combination of these strategies.

Arguably the most important strategic tool is the partnership research contract and in particular the intellectual property (IP) ownership conditions. In the contract, the PPP can specify what it expects from the company in exchange for the funds. A win-win balance must be found. The PPP must be assured that its money will be used efficiently to further research in the global health problem of focus. At the same time the company needs enough leverage to use these funds to help further its own goals – to earn profits.

The critical negotiation point is that over the ownership of IP – both IP created with the PPPs resources and background IP that is essential for the production of the product.

IP is a key weapon for pharmaceutical companies in their pursuit of products and ultimately profits. PPPs must be as aggressive in the way they use IP as any commercial unit but for a different purpose – namely to pursue their social objective of getting quality, affordable products to developing country patients. This involves the negotiation of creative IP arrangements that do not scare off companies but also allow the PPP enough control to ensure their ultimate objective, a difficult challenge. The basic strategy has to be:

- A. Keep what you find. So MMV owns (or shares ownership) any of the IP created through research it has funded.
- B. Trade over any developed market for control of sales in developing country markets. So IAVI's commercial partners can retain control of the IP to use in the "paying world" provided that IAVI has access to it to meet demand in the developing world.
- C. Establish explicit volume deals with the company partner so that if the company does not want to manufacture the product at volumes needed to meet the developing

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<sup>20</sup> This section draws extensively on an analysis conducted by Kettler and Towse (2001).

country need, the PPP can get rights to the process and use contract-manufacturing organizations to meet the supply needs.

- D. Trade any other disease use for control of the IP for the neglected disease. An alternative option, especially for diseases where the “paying market” is low or non-existent is to give the company partner the right to the PPP funded IP in all but the neglected disease of focus.
- E. If the partner chooses not to use the IP in pursuit of the designated product, the PPP has the rights to take it back. The PPP has the right not to be held up. IAVI has also tried to arrange contracts where if the product reaches a late stage and the company chooses not to continue development that it also gains access to any background patents its needs to be able to produce the product and continue development through a new partner.
- F. Explicitly address the issue of royalty rights for products sold in the paying markets. Again, using the MMV example, they expect a share of any royalties coming back from IP their funds created. In cases where the IP already exists, prior to the company entering into a deal with MMV, they are more likely to negotiate control over the developing world market only, leaving the paying market to the partner as discussed above.
- G. Clearly determine the IP rights and conditions up front. In an early deal with an academic institute, for example, one of the PPPs took the attitude “we’ll sort the IP stuff out later”. The problem is that the research programme now involves a university, the funder of the early university research, the PPP that also contributed funding, a biotech company that has since been created based on the university research, and a device company whose technology they seek to combine with the product in clinical trials.
- H. When in-licensing products or technologies, seek control rights to out-source the project to third parties.

PPPs are breaking into completely new territory with their IP negotiations. Some experience can be learned from biotech companies, especially platform technology companies, which are in the business of doing multiple deals with different companies, licensing out the use of their IP. But the conditions PPPs place on IP negotiations – price guarantees, volume guarantees, and market specifications – are new and risky. In IAVI’s case, the IP agreements are also used as a mechanism to avoid delay in the introduction of vaccines to developing countries (in previous cases more than 10 years), by insisting that any vaccine will be made simultaneously available in developed and developing countries.

Companies might fear that if they enter into a deal with one of the PPPs, especially one that combines the PPP’s IP and some of their own background IP, and early tests fail, that this will limit opportunities to use the background IP for other uses. This is a risk companies take in any collaborative deal but the perception is that there are more risks in doing such a deal with a “public good” based organization. Second, and linked to this, is the fear that the PPP will breach the confidentiality agreements and transfer the knowledge they learned in a commercial deal to other ones. “If the PPP knows it, everyone else will” (Interview, Lita Nelsen, May 2001).

Another potential problem is that fact that the PPPs expect to need to do a series of deals with different partners to get products to market. So it is important for the PPP to hold on to IP rights in the early stages, so as to have more to bargain with in the late stage when a major pharmaceutical partner is especially important. So in cases where the IP has been split across diseases, IAVI, for example, must retain the rights to the IP for the HIV vaccine so it can license it out later.

Biotech companies need money and funding, especially if it helps validate their technologies that may be relevant for other diseases. So cash is a positive incentive. The same cannot be said for major companies. Money is not enough. So the challenge is how to make it attractive for major companies to do deals.

In summary, opportunities exist for employing IPR in creative ways to realize the R&D objectives. A critical difference between the commercial and the PPP model is in the former there are no guarantees that industry will respond. Disease focused PPPs are well funded and are in the business of making sure that product pipelines and eventually marketable and accessibly products are built. Because PPPs depend on major pharmaceutical company participation, however, especially in the expensive late clinical trial and manufacturing stages, a combination of incentives and PPPs are probably needed.

Consideration, especially by the Rockefeller Foundation, is also being given to the question of what disease generic initiatives could/should be established to help promote R&D in PPPs but also in private companies, be that in the developed or developing world. One idea under discussion is the establishment of an organization that would focus on the problem of Managing Intellectual Property for Global Health. It starts on the premise that IPR is necessary for R&D because the private sector is an essential player (i.e. is not promoting the idea of retaining “public ownership” of specific technologies). However, as the PPPs have demonstrated, there are ways to ensure both protection of ideas and future access through creative licensing, and a goal of this initiative is to educate and support all relevant actors (technology transfer offices, national and private research institutes) in the practice of these licensing agreements.

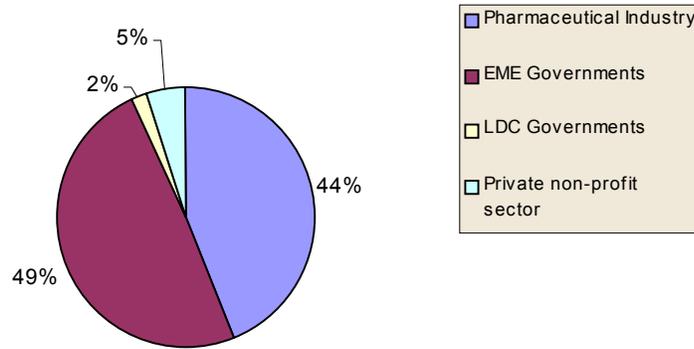
## Tables and Figures for Section B

**Table 1- Diseases of the Poor**

| <b>Disease</b>                      | <b>Developing Country<br/>Burden as a % of<br/>Total</b> | <b>Number of<br/>Suffers (1996)</b> |
|-------------------------------------|--|-------------------------------------|
| Chagas Disease                      | 100  |                                     |
| Dengue                              | 100  |                                     |
| Ancylostomiasis<br>and Necatoriasis | 100  |                                     |
| Japanese<br>Encephalitis            | 100  |                                     |
| Lymphatic<br>Filariasis             | 100  |                                     |
| Malaria                             | 100  | 24,672,000                          |
| Onchocerciasis                      | 100  |                                     |
| Schistosomiasis                     | 100  |                                     |
| Tetanus                             | 100  |                                     |
| Trachoma                            | 100  |                                     |
| Trichuris                           | 100  |                                     |
| Trypanosomiasis<br>Leishmaniasis    | 99.9   |                                     |
| Measles                             | 99.9   | 792,000                             |
| Polio                               | 99.9   |                                     |
| Syphilis                            | 99.9   |                                     |
| Diphtheria                          | 99.8   |                                     |
| Leprosy                             | 99.7   | 566,000                             |
| Pertusis                            | 99.6   |                                     |
| Diarrhoeal<br>Diseases              | 99.5   |                                     |
| TB                                  | 91%  | 167,000                             |
| HIV                                 | 65%  | 3,798,000                           |

Source: Lanjouw and Cockburn.

**Figure 1 – Who Invests in Global Health R&D**



Note: Total R&D Expenditure in 1992 = \$55.8 billion

Source: WHO, 1996.

**Table 2**  
**Budget Allocations to Tropical Disease Research at the National Institutes of Health**  
**(Millions of Dollars)**

| <b>Year</b>       | <b>NIAID<br/>Tropical</b> | <b>Other<br/>Institutes<sup>a</sup><br/>Tropical</b> | <b>Total Tropical in<br/>1997 dollars</b> | <b>Pct Growth in Total<br/>over Previous year</b> | <b>Share of Total<br/>Tropical in Total<br/>NIH</b> | <b>Pct<br/>Growth in<br/>Share of<br/>Tropical</b> |
|-------------------|---------------------------|--|---|---|---|--|
| 1990              | \$38.40                   | \$6.5  | \$57.6                                    | -   | 0.0053  |  |
| 1991              | 39.5                      | 7.8  | 57.8                                      | 0.4%  | 0.0051  | (3.8)%   |
| 1992              | 43.6                      | 8.4  | 60.9                                      | 5.3   | 0.0052  | 1.2  |
| 1993              | 36.9                      | 10.1   | 53.2                                      | (12.6)  | 0.0046  | (12.6)   |
| 1994              | 41.3                      | 12.2   | 58.3                                      | 9.6   | 0.0049  | 7.7  |
| 1995              | 44.2                      | 15.2   | 62.6                                      | 7.3   | 0.0052  | 6.8  |
| 1996 <sup>b</sup> | \$90.4                    | \$18.1   | \$111.5                                   | -   | 0.0091  | -  |
| 1997              | 97.2                      | 16.9   | 114.1                                     | 2.3%  | 0.0089  | (2.2)%   |
| 1998              | 104.0                     | 17.9   | 118.0                                     | 3.4   | 0.0089  | 1.2  |
| 1999 <sup>c</sup> | 112.9                     | 19.2   | 124.2                                     | 5.3   | 0.0084  | (5.7)  |

<sup>1</sup> Other Institutions with spending on tropical diseases are: NCI, NIDR, NINDS, NICHD, NEI, NIEHS, NCRR, FIC.

<sup>b</sup>the definitions of “Tropical” changed in 1996 so the periods must be considered separately.

<sup>c</sup> Estimated values.

Source: Lanjouw and Cockburn, 2001,

**Table 3**

| Percent of Major German, Japanese, and U.S. Firms Reporting that Strength or Weakness of Intellectual Property Protection Has Strong Effects on Whether They Will Make Direct Investments of Various Kinds |                               |   |   |  |  |             |
|--|-------------------------------|---|---|--|--|-------------|
|  | <i>Sales and Distribution</i> | <i>Rudimentary production and assembly facilities</i> | <i>Facilities to manufacture Components</i> | <i>Facilities to manufacture complete products</i> | <i>Research and development facilities</i> | <i>Mean</i> |
| <i>Chemicals and Drugs</i>   |                               |   |   |  |  |             |
| Germany  | 0                             | 17  | 75  | 86   | 86   | 53          |
| Japan  | 44                            | 53  | 67  | 80   | 88   | 66          |
| United States  | 19                            | 46  | 71  | 87   | 100  | 65          |

Source: Mansfield, 1995, 4.

**Table 4 - The Impact of IPR on FDI Decisions**

| <b>IPR Too Weak to Permit Investment in JV with Local partners</b> |                         | <b>IPR Too Weak to Transfer Their Newest or Most Effective</b> |                         | <b>IPR Too Weak to Permit Their Newest of Most Effective Technology</b> |                         |
|--|-------------------------|--|-------------------------|---|-------------------------|
| <b>Country</b>   | <b>Percent of Firms</b> | <b>Country</b>   | <b>Percent of Firms</b> | <b>Country</b>  | <b>Percent of Firms</b> |
| India  | 74 (80 by US)           | India  | 72 (81 by US)           | India   | 89 (100 by G)           |
| Nigeria  | 51 (64 by US)           | Nigeria  | 44 (67 by US)           | Indonesia   | 61 (73 by US)           |
| Argentina  | 43 (57 by G)            | Chili  | 41 (47 by US)           | Thailand  | 60 (73 by US)           |
| Indonesia  | 40 (50 by US/G)         | Thailand   | 39 (60 by US)           | Nigeria   | 60 (73 by US)           |
| Brazil   | 39 (47 by US)           | Argentina  | 39 (44 by US)           | Argentina   | 54 (62 by US)           |
|  |                         |  |                         | Brazil  | 49 (69 by US)           |

Notes: German, US, and Japanese firms were surveyed.

This table presents the worst 5 of 14 countries considered in the survey.

The perceptions were based on the status of the IPR regimes in these countries in 1994.

Source: Mansfield, 1995, 6, 8, 10.

Table 5

**The “Standard” of Pharmaceutical Industry, by Country**

| Sophisticated Pharmaceutical Industry and Research Base   | Innovative Capabilities  | Reproductive Capabilities – Therapeutic Ingredients and Finished Products  | Reproductive Capabilities Finished Products Only  | No Pharmaceutical Industry   |
|---|--|--|---|--|
|   |  |  | 87 countries including  | 59 countries including   |
| <b>Belgium<sup>a</sup></b><br><b>France</b><br><b>Germany</b><br><b>Italy</b><br><b>Japan</b><br><b>Netherlands</b><br><b>Sweden</b><br><b>Switzerland</b><br><b>United Kingdom</b><br><b>United States</b> | <b>Argentina</b><br><b>Australia</b><br><b>Austria</b><br><b>Canada</b><br><b>China</b><br><b>Denmark</b><br><b>Finland</b><br><b>Hungary</b><br><b>India</b><br><b>Ireland</b><br><b>Israel</b><br><b>Mexico</b><br><b>Portugal</b><br><b>Korea</b><br><b>Spain</b><br><b>f. USSR<sup>c</sup></b><br><b>f. Yugoslavia<sup>c</sup></b> | Bahamas<br><b>Bolivia</b><br>Brazil<br>Bulgaria<br>Cuba<br>f. Czechoslovakia <sup>c</sup><br>Egypt<br><b>Indonesia</b><br><b>Norway</b><br><b>Poland</b><br>Puerto Rico<br>Romania<br>Turkey | Algeria<br><b>Bangladesh<sup>b</sup></b><br>Belize<br>Cambodia<br>Chile<br>Columbia<br><b>Costa Rica</b><br><b>Dominican Republic</b><br><b>Ecuador</b><br><b>El Salvador</b><br>Ethiopia<br>Gambia<br><b>Greece</b><br><b>Guatemala</b><br><b>Honduras</b><br><b>Hong Kong</b><br><b>Kenya</b><br>Lebanon<br><b>Malaysia</b><br><b>Morocco</b><br><b>New Zealand</b><br><b>Nicaragua</b><br><b>Peru</b><br>Philippines<br>Singapore<br>Somalia<br><b>South Africa</b><br><b>Taiwan</b><br><b>Uruguay</b><br><b>Venezuela</b><br>Zimbabwe | Botswana<br>Burundi<br>Central African Republic<br>Chad<br>Congo<br>Gabon<br>Guam<br>Guinea<br>Laos<br>Martinique<br>Nauru<br>Oman<br>Rwanda<br>Samoa<br>Senegal<br>Suriname<br>Togo |

- a. Countries in bold are members of the IFPMA as of 2000.
- b. Bangladesh is the only country that is both a member of the IFPMA and one of the 48 UN designated “least developed countries.”
- c. f. = former.

Source: Balance et al, 1992, [www.wto.org](http://www.wto.org); [www.ifpma.org](http://www.ifpma.org).

**Table 6: Incentives to Motivate Private Companies**

| <b>Push</b>  | <b>Pull</b>                          |
|--|--------------------------------------|
| Improve intellectual property protection for LDC medicines | Roaming market exclusivity*          |
| R&D tax credits*   | Purchase funds, price guarantees     |
| R&D grants*  | Tax credit on sales                  |
| Social venture capital funds                               | Creating functioning markets in LDCs |
| Investments in clinical trial infrastructure in LDCs       |                                      |
| Speed up the approval process                              |                                      |

Note: \*A modified Orphan Drug Legislation could combine R&D tax credits, R&D grants on the push side with roaming market exclusivity on the pull side.

## **Appendix to Section B: Roaming Patent Exclusivity (draft)**

### Outline:

- a. Present idea of roaming patent exclusivity, explaining how it might work. In order to estimate its costs and potential success consider the case of the pediatric exclusivity provision.
- b. This comparison is important b/c: a. it demonstrates a federal agency's willingness to consider and support this kind of incentive for major companies; b. it suggests the potential for success – i.e. that companies respond to this kind of incentive; and c. the FDA's status report provides detailed calculations of the costs of such a program.
- c. The two provisions will involve different sets of drugs, but the types of payers will be similar so their approach could serve as a model for estimated the costs of the roaming patent policy.

The idea of a roaming patent or market exclusivity extension has been proposed as a possible incentive for pharmaceutical companies to allocate R&D resources towards the development of new drugs and vaccines for neglected diseases of the developing world. Under such a scheme, governments would award a company with extra months of exclusivity or patent life (exact time still to be determined) on a product of their choice in exchange for a product approved for launch for one of a pre-specified list of neglected diseases.

In particular, analyses of product availability and need identify the following diseases as priorities for new drug R&D: malaria, TB, African trypanosomiasis, Chagas disease, filarial infections, GI-nematode infestations, leishmaniasis, non-specific diarrhoeas, and schistosomiasis (WHO/IFPMA, 2001).

The success of the orphan drug legislation and the pediatric exclusivity provision, policies that are both based on extending market exclusivity or patent life (references), suggest that such a policy would prompt significant industry response. The primary obstacle to overcome is likely to be political. Under pressure to contain public health care budgets and, in the US, cut patients' drug costs, governments will resist implementing policies seen to be benefiting "innovative" pharma at the expense of generics producers and individual patients.

### **The Pediatric Exclusivity Provision Sets a Precedent**

The US Pediatric Exclusivity Provision, a part of the FDA Modernization Act of 1997, sets a precedent for using patent life or market exclusivity extensions as a policy tool to encourage specific kinds of industry development investments. Under this provision, the FDA awards a company an extra six months exclusivity to be attached to any existing exclusivity or patent protection on a drug that is on the FDA prepared list of products needing pediatric studies and for which the company has successfully completed these studies.

According to a status report the FDA drafted in late 2000, this program has proved highly effective for certain categories of drugs and age groups. For the 157 FDA issued Written Requests, sponsors have indicated that they have conducted or will conduct 80 % or more of the studies. In less than 3 years, 58 pediatric studies have been completed and exclusivity granted to 25 drugs. By contrast, in the six years prior to the enactment of the provision, drug sponsors promised to complete 71 post-marketing pediatric studies and only 11 were completed (FDA, 8). The provision does not specify to which of the sponsor's patents the additional six months to attach. The FDA has interpreted it broadly and added six months to any of the sponsor's listed patents or previous non-expired grants of exclusivity on drug products containing the active moiety that was studied (FDA, 7). This means that a company could earn added exclusivity on more than one of its drugs<sup>21</sup>.

However, the incentive does prove inadequate for certain categories of products and age groups. In particular, it provides no incentive for companies to conduct studies on products no longer on patent or with exclusivity. The exclusivity incentive is also inadequate for products that do not generate sufficient sales in either the adult or children populations to provide a large market return for conducting the studies.

In the long run, the pediatric studies by providing dosing, safety, and efficacy information for physicians, should lead to significant advances in pediatric medicine. This will mean reducing certain types of health care costs but increasing others. "Superior drug treatment information will permit quicker recoveries from childhood illnesses, with fewer attendant hospital stays and physician visits." (FDA, 14) The exclusivity extension will mean, however, the delay of the introduction of lower priced generic drugs.

Insufficient time has passed to measure the cost savings from health care improvements. The FDA has put the added cost of the six month extension for the set of targeted products at \$29.6 billion over 20 years (\$15.3 billion discounted at 7%). The payers are consumers facing higher drug prices (47% of total), generics firms losing sales revenue (36% of total), and pharmacies losing sales revenue from retail price mark-ups which tend to be higher for generic drugs than for on-patent ones (17% of total). That amount of money is transferred to the innovator pharmaceutical companies in the form of increased sales revenue<sup>22</sup>. In theory, this model can be used to calculate the costs of the roaming exclusivity provision. The set of actors is basically the same though, as is argued below, the set of affected consumers is likely to be narrower than in the pediatric provision.

## **Comparing the Two Policy Ideas**

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<sup>21</sup> The pediatric exclusivity attaches to all products with listed patents or exclusivity that contain the same active moiety as the product or products studied. An innovator may receive 6 months of exclusivity for several products by virtue of conducting studies on a single active moiety. (40)

<sup>22</sup> See Appendix C of the FDA report for information about how the figure was estimated and how the total is divided up across the three sets of payers.

There are important differences between the roaming patent provision and the pediatric provision, especially with regard to who benefits and who pays. In the latter case, the key beneficiaries of the pediatric studies are “our children”, probably with a focus on the US first, followed by other industrialized countries (depending on respective countries’ rules about approving products for pediatric use). In the roaming exclusivity plan, the key beneficiaries are the people of the developing world. Some recent work has been done (see CIA report for example) to emphasize the “borderless” nature of infectious disease, but clearly the primary market is the third world. This might pose difficult obstacles for advocates trying to rally support for the idea because it means convincing Americans (and policy makers), in this case, to pay more for drugs to help people in countries about which they know (care?) very little.

The composition of payers is also slightly different. In the case of the pediatric provision, the large number of products from a broad range of diseases means that the base of people paying more for drugs is also quite broad, with no segment feeling “picked on” (except, perhaps, for the generics industry as a whole). In the case of the roaming patent provision, there will, realistically speaking, probably only be a handful of winners (i.e. companies bringing drugs for neglected diseases). This produces a clear, small, set of patients who will be seen to be paying for the neglected disease drugs, i.e. those taking the product the company selects for the patent or exclusivity extension. This contrasts with tax credit policy options where the entire tax-paying population is paying for research.

Thus, difficult “fairness” issues might come up, above and beyond the predictable protest at the idea that major pharmaceutical companies would be the other key beneficiaries of the new drugs.

It is important to emphasize that all the “private” policy options seek ways to ensure a “reasonable” profit for private companies so as to encourage them to do the R&D. This is done either by reducing the costs so companies do not have to earn as much to make a profit or by ensuring enough sales revenue so companies are willing to put out the same resources they do for other diseases. So the advocate of the roaming patent idea needs to develop a persuasive argument for why private companies are the best organizations to be doing this research and that they are justified in their expectation of profit in exchange for successful work. The company does bare risks under the roaming patent provision. They are awarded the extension only upon production of a marketable product. If their R&D fails at some point along the way, they still loose the resources they sunk into the research, just as is the case with products in other disease areas.

Another important question in designing this provision is that of who is responsible for ensuring access. As companies are most likely not set up to ensure the delivery of products in developing countries, and to require proof of delivery as a prerequisite of the reward will only dilute the incentive for R&D, a separate organization(s) is needed to ensure that the approved products reach the patients who need them at a price they can afford. In this case, the company turns over the rights for that product markets, to a public access organization. In the event that there might be a small “paying market” (as in the

case of the travellers' market for malaria), the company might negotiate an arrangement whereby they maintain control over certain segments. But maybe not. Maybe to earn the patent extension they have to agree to turn over all rights. This would give the "access" organization the opportunity to use tiered pricing were there to be a range of income groups seeking the new product. Presumably companies would already be doing R&D in these diseases if there was a sizeable "paying" population and would thus have little ground for protest.

To estimate the economic impact of the roaming patent exclusivity on taxpayers and consumers we need to compare the sales revenue for each drug granted the additional exclusivity with sales revenues had the drug not had the extension.

Steps: 1. Estimate sales revenue during the year of patent/exclusivity expiration; 2. Estimate sales revenues following patent/exclusivity expiration, and 3. Compare the sales revenue of all products (containing the identified moiety) with and without a 6- month period of additional exclusivity added to the innovator's patent/exclusivity expiration.

In the case of the pediatric extension, the FDA has pre-identified products that qualify and so, at least for the products already on the market, they are able to estimate the sales revenues for the key years using available sales data and assumptions about the products' life cycle. In their calculation they use sales histories for 119 drug products (102 moieties) for which a sponsor has indicated, as of March 1, 2000, the intent to submit pediatric studies.

In the case of the roaming exclusivity, we do not know which companies are likely to bring new qualifying "neglected disease" products to market nor do we know which product, these successful companies will select for the patent extension. In order to do the cost calculations, we need to make "informed" guesses as the likely winners and the products they will select for the extension.

**(Need advice here – we could look at the companies w/ some R&D, even at a preliminary stage, underway, assuming they would be the first to respond. From these companies could then pick their best seller or their most important product soon to come off patent. I need advice from industry on what factors might go into the decision to select this product – is it as straightforward as which product will earn the most money w/ the extension?)**

Assumptions about the sales revenue life cycle:

1. Sales revenues increase once product commences marketing until generic competition enters (time period determined by date of patent expiration or expiration of any other exclusivity market rights such as those granted by the Orphan drug act). **These dates are available from FDA's Approved Drug Products w/ Therapeutic Equivalence Evaluations (the Orange book).**
2. Following generic entry, total drug sales revenue (innovator and generic sales totalled) gradually declines due to lower prices of generics and the entry of growing

number of generic competitors. FDA estimates assume that stabilization occurs 3 years after generic competition first enters.

In comparing the w/ and w/o exclusivity sales lines, the assumed difference is in the 3-year period post patent expiry (w/o additional exclusivity). “The two sales curves are identical, except that one includes an additional 6 months of innovator sales before generic competition enters the market. Beyond the 3-year period following patent/exclusivity expiration, the estimated difference disappears” (p. 78).

Data needed: sales revenue estimate for year of expiration and three years following it (estimate of the rate of entry of generic competition); depend on generic price as proportion of innovator price; discount rate. IMS Health data for sales history data (*Retail Perspective and Provider Prospective Combined Purchases*).

To estimate the costs of the patent extension:

Let:

Annual sales of innovator drug at exclusivity expiration = P

Discount on generic price in period I = d(I) {d(1), d(2)... d(n)}

Fraction of market captured by generics in period I = f(I) {f(1), f(2),...f(n)}

Then,

Innovator sales w/o AE =  $P + (1-f(n))*P + (1-f(2))*P + \dots(1-f(n))*P$  {1}

Innovator sales w/ AE =  $P + P + (1-f(n))*P + (1-f(2))*P + \dots(1-f(n-1))*P$  {2}

Generic sales w/o AE =  $P*f(1)*d(1) + P*f(2)d(2) + \dots P*f(n)d(n)$  {3}

Generic sales w/ AE =  $0+ P*f(1)*d(1) + P*f(2)d(2) + \dots P*f(n-1)d(n-1)$  {4}

So,

The difference in innovator sales = {2}-{1} =  $P-(1-f(n))*P = P*f(n)$  {5}

The difference in generic sales = {4}-{3} =  $-P*f(n)*d(n)$  {6}

Finally, the costs to consumers = {5}+{6} =  $P*f(n)-P*f(n)*d(n) = P*f(n)*(1-d(n))$

References:

Department of Health and Human Services – U.S. Food and Drug Administration (2000)  
 The Pediatric Exclusivity Provision, January 2001, Status Report to Congress  
<http://www.fda.gov/cder/pediatric/reportcong01.pdf>

## **C. The Impact of IPR on Access**

### **C.I. Introduction**

Pharmaceutical industry representatives often suggest that drug patents are not a significant constraint to access to essential therapeutic drugs in most low and middle income countries (LMICs). Take the case of India, where an absence of product patents and a flourishing generics industry has failed to secure broad based access to many drugs by the Indian population. Health care advocates point to Brazil and South Africa and find different lessons. In these countries, patents have been a significant factor in drug pricing, and government patent-related policies have had important, and very different, effects on the population's access to drugs.

Intellectual property (IP) is far from the only factor involved in access to medications. Financial resources, health care infrastructure, and political will are also pivotal. But patents clearly affect the price of newer therapeutic drugs, and in a resource-constrained world these higher prices have a direct impact on drug access. Generic versions of on-patent products play a central role in drug pricing and access for newer drugs, and have prompted multi-national drug companies to lower drug prices. To the extent that newer, on-patent treatments represent significant therapeutic advances over older off-patent drugs, the issue of early access to patentable products affects the personal health of millions.

A review of the literature on drug access and IP policies in three LMICs points to the significance of patent policy. It also indicates the importance of providing LMICs with flexibility in the use of a variety of policy options that can strengthen their hand in negotiating lower drug prices and further the importation or production of affordable medicines needed by their populations.

When and how does IP affect access to the most appropriate therapeutic drugs needed to treat disease? And in the face of stronger patent laws that will come with the introduction of TRIPS, what policies are needed to make newly developed on-patent drugs affordable in LMICs?

This section reviews current literature on the link between IP law, drug prices and product access. The chapter then looks at the interplay of IP and access in three countries, using access to AIDS therapies as case studies to demonstrate the importance of several country-specific conditions in determining the relative importance of patents. Comments from recent authors on several policy options are summarized in an Appendix.

The significance of IP to drug access depends on the status of several other factors in a country. For example, if there are extremely limited financial and health infrastructure resources, and minimal political will to make drugs available, patents will likely play a limited role in drug access. Similarly, if one imagines a fortunate nation where resources are limitless and there is solid commitment to drug access, patents also would not play a significant role. But if a country is not on one end of the financial extreme, if some

limited financial resources and infrastructure exist, combined with some political or private sector commitment to deliver essential drugs, patent law suddenly becomes crucial.

Specific diseases are yet another dimension of the relative importance of patents. The treatment of a disease for which effective, off-patent medications are already on the market is not likely to be affected by a country's patent policy. In fact, of the 300 drugs on the World Health Organization (WHO) model list of "essential drugs," fewer than 20 (5%) are under patent anywhere in the world.<sup>i</sup> But if some or all of the appropriate drugs used in therapy for a disease are on-patent, as in the case of AIDS, patents are likely to effect drug prices, and, by extension, access of the population to those therapies.

As stronger IP laws are introduced through TRIPS there is no doubt these laws will affect access to some drugs in many countries. TRIPS will have an effect upon LMICs as consumers of medicines, and, for some, as producers of drugs for export to other LMICs. Those countries that currently have active generic drug production industries, as well as nations that rely on importation of generic substitutes for on-patent medications, face serious challenges to securing drug access with the introduction of stronger patent laws.<sup>ii</sup>

## C.II. The Relationship of IP, Price and Access

Several researchers have documented the effect of IP laws on prices for therapeutic drugs. Borrell and Watal<sup>iii</sup> looked at private sector sales prices for AIDS antiretroviral medications (ARVs) in 34 LMICs between 1995 and 2000. They found that patents promote local availability of new drugs on the for-profit market in LMICs, but also result in higher prices overall for these drugs. In their study, market exclusivity increased average prices by \$US 808.41 (32%). The authors found that, "...Firms doubled mean prices when marketing exclusivity rights are available."

In the Borrell and Watal study, patents tended to benefit patients willing to pay high prices by promoting availability of drugs on the market, and hurt those who could not afford to pay higher prices. The authors write that the, "Patent option by itself does not have a significant fixed effect on prices, but the combined forces of market exclusivity and per capita income shift the price upwards." It appears that the presence of some consumers' with ability to pay, in combination with patent law that allows maintenance of higher prices, lead companies to place their products on the market. "Patents raise a difficult trade-off in poor countries," Borrell and Watal conclude, because, "patents could increase the odds of having new drug therapies locally available, but at the cost of higher prices."<sup>iv</sup>

The fact that many consumers in the countries studied by Borrell and Watal would not have been able to afford AIDS drugs, even at generic prices, demonstrates the importance of policies that provide adequate resources to purchase drugs. In fact, one response to the findings of Borrell and Watal is to argue that government policy should focus on controlling drug prices rather than considering actions that undermine the strength of patents. But the fact that IP is closely linked to price means that governments with limited resources may have to include consideration of IP law as they work to secure drug access for their populations.

The presence or absence of generic substitutes can also have a profound impact the cost of drugs. In a study of drug prices for ten essential AIDS drugs in eight countries, Perez-Casas of Medecins Sans Frontieres (MSF)<sup>v</sup> found that the price of AIDS drugs was 82% less than the US price in the developing countries with access to generic copies of on-patent drugs. According to Perez-Casas, "The presence or absence of generic competition in the market is a key determinant of pricing levels." Another study prepared by MSF in Fall 2001 provides an example of steep price reductions on the combination AIDS therapy d4T+3TC+nevirapine following introduction of low priced generic versions on the world market.<sup>vi</sup> Health groups have argued that it is generic competition, not voluntary drug company price reductions, that have lead to steep and sustained price reductions on AIDS therapies in Africa.

### *What will stronger IP laws mean?*

Several researchers have attempted to estimate the effects of stronger IP laws resulting from full implementation of the TRIPS agreement. In *Post-TRIPS Options for Access to Patented Medicines in Developing Countries*,<sup>vii</sup> Scherer and Watal note three studies that

predict price increases of 200% or more with the introduction of product patents, and the authors conclude that TRIPS will lead to “economic shock” in some LMICs because it will effectively outlaw generic copies of on-patent drugs. The authors argue that generics will have a crucial role to play in ensuring drug access in the future and that “vigorously competitive global markets for generics” are needed to ensure access to therapeutics.

The ultimate personal and social impact of stronger patent regimes will largely be determined by the degree to which new patented drugs represent significant therapeutic advances over off-patent products already available as generics at lower prices. Fink writes that, “if future drug discoveries are mainly new varieties of already existing therapeutic treatments, the impact [of stricter patents] is likely to be relatively small. If newly discovered drugs are medicinal breakthroughs, however, prices may be significantly above competitive levels and welfare losses will be relatively large.”<sup>viii</sup> If we find that the biotech revolution realizes the great promise of its promoters, it is fair to conclude that stronger patents, in the absence of other pro-access policy actions, will mean millions of people in LMICs will have very limited access to therapeutic advances in biotechnology.

#### *Calculating the effect of full TRIPS implementation in India*

Several authors have studied the potential effects of tighter patent laws in India. The effects of TRIPS in this country are particularly interesting. New patent laws will influence domestic access to drugs for that segment of the population that now purchase drugs. And strong patents will also affect India as a major international provider of generic drugs for other LMICs.

In her analysis of the potential effects of stronger patent protections in India, Lanjouw points out that for the 70% of Indians who do not have access to drugs now, expansion of IP protections is irrelevant.<sup>ix</sup> This may change, however, if average incomes and private purchase capacity in the country grow. Lanjouw finds that delays in the availability of patented medicines produced by multi-national corporations (MNCs) in India are not caused by the absence of product patents, but the concerns of MNCs regarding various administrative issues in the country, including potential impediments in winning marketing approval.

Lanjouw suggests that industry reluctance to market drugs may also result from the concern that lowering drug prices in India in order to make them accessible to a sizable market could undermine higher prices in wealthier countries. She warns that, “A tendency on the part of patent owning MNCs to delay the introduction of their innovative drugs in India could mean that, in the future, new drug therapies become available to Indian consumers more slowly than they would have if the current regime, which allows imitation, had been retained.”<sup>x</sup> According to Lanjouw, there is little reason to assume tiered pricing will make patented drugs available more rapidly in the future, since patent owning companies may, “set prices to maximize global profits, not profits in India.”

Watal has estimated<sup>xi</sup> there will be significant effects following from a move to stricter IP laws in India, with prices on patentable pharmaceuticals increasing from 26% to 242%, a

loss in consumer surplus of between \$11 million and \$67 million, and total “welfare losses” of from \$50 million to \$140 million. She finds that a large proportion of these losses will go to pre-tax foreign profits. Watal noted that the existence of substitute medications for on-patent products is a critical factor in estimates of price effects. Looking to TRIPS implementation in India, Fink also predicts<sup>xii</sup> significant effects, noting that large losses to consumers are possible, but pointing out that in India patented products represented only 10.9% of pharmaceutical sales in 1993. Fink argues compulsory licensing or continued use of price controls may be useful in controlling prices for Indian consumers.

### **C.III. AIDS as a Case Study**

AIDS is the most deadly infectious disease in the world, claiming 8,000 lives each day, over 95% of them in the developing world.<sup>xiii</sup> An analysis of the availability of AIDS medications in LMICs well illustrates the complex issues of IP and access. A variety of drugs, typically combined in a “cocktail,” have been shown to improve and prolong the lives of people living with HIV disease. Some of the drugs commonly used in AIDS treatment were developed years ago, and are not widely subject to patent protection. Others, including most protease inhibitors that have revolutionized the treatment of HIV disease, were launched recently and remain on-patent in most industrialized countries. Unlike malaria and TB treatments, there is a large market for AIDS drugs in industrialized countries, so discussions concerning price tiering or weakening of IP for these drugs raises deep concerns with patent holders of AIDS drugs.

Case studies from India, South Africa and Brazil show that IP, financial and infrastructure resources and political will all play key roles in determining access to AIDS drugs. In some countries, patents are not recognized or industry has failed to file patents for AIDS drugs, but each of the countries studied here has its own patent law and has signed the TRIPS agreement. Each country has also used or is considering policy approaches to promote increased drug access for its population. (The Appendix to this section provides a brief review of policy options and commentary from articles reviewed for this chapter.)

#### **India**

India has a set of policies that have nurtured a generic drug industry in the country. The Patent Act of 1970 made pharmaceutical products unpatentable, engendering a large pharmaceutical industry focused on making copies of on- and off-patent medications. It is estimated that 200 pharmaceutical companies now operate on the national level in India, and approximately 23,000 compete at the regional level.<sup>xiv</sup> India has taken the option to delay full implementation of TRIPS until January 1, 2005, allowing domestic drug companies to continue producing generic versions of drugs that are on-patent elsewhere until that date.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that in 2000 there were 3.7 million people living with HIV or AIDS in India, or 0.7% of the adult population. The case of AIDS treatment in India emphasizes the importance of dedicating adequate financial resources to fighting domestic disease. India’s generic pharmaceutical companies make several drugs used in AIDS therapy, and these companies have offered to sell AIDS drugs in developing countries at prices far below those charged by the patent-holding MNC pharmaceuticals. Yet the production of lower priced products has not translated into widespread drug access to therapeutic drugs for AIDS and other diseases among India’s poor.<sup>xv</sup>

The international pharmaceutical industry has used the example of limited access to drugs in India as a way to question the importance of generics in assuring drug access. The Pharmaceutical Research and Manufacturers of America (PhRMA) has argued that, “generics now provide no benefit for the vast majority of the Indian population.” As the

International Federation of Pharmaceutical Manufacturers Associations (IFPMA) has noted, “If patents were indeed the problem, large populations within India and similar countries should have easy access to...copied, generic versions of AZT and other medications.”<sup>xvi</sup>

### **South Africa**

South Africa provides a dramatically different example. That country is in the midst of an horrific AIDS epidemic. As of 2000, UNAIDS estimated that 4.2 million people (or 20% of the adult population) in the country were infected with HIV. The vast majority of people living with HIV do not have access to AIDS medications and the government has been widely criticized for its failure to act more aggressively to make AIDS drugs, including drugs to prevent mother-to-child transmission, available.

Like India, the example of South Africa points out the importance of adequate financial and infrastructure resources in meeting the needs of people living with HIV. Yet in the extremely resource-constrained environment of South Africa, the interaction of IP policy and pharmaceutical prices clearly impacts drug access. South Africa has traditionally had a strong intellectual property regime relative to other developing countries,<sup>xvii</sup> and patented versions of many drugs produced by MNCs are available for sale there. South Africa is also known for its high prices for patented drugs as compared with other LMICs. The *South African Health Review 2000* notes that the costs of drugs in South Africa has long been contested, but are thought to be among the highest in the world.<sup>xviii</sup> A survey of AIDS drug prices by MSF found that a one gram vial of Ceftriaxone is US \$10.90 in South Africa, and US \$1.8 in India where it is sold as a generic. Fluconazole is 14 times more expensive in South Africa than in Thailand, where the drug is sold as a generic.<sup>xix xx</sup>

In addition to strong IP laws, high distribution chain costs, including mark ups between initial sale and retail price, are blamed for high consumer drug prices.<sup>xxi</sup> South Africa is currently reviewing implementation of a new *Medicines and Related Substances Control Amendment Act* that will impose controls on drug mark ups, encourage sale of generics when generic substitutes are available, and allow parallel importing under some circumstances. (Compulsory licensing is not addressed in the draft guidelines for the Act, although it is apparently allowable under the existing Patents Law.)

In *Patent Protection and Access to HIV/AIDS Pharmaceuticals in Sub-Saharan Africa*<sup>xxii</sup> the International Intellectual Property Institute (IPI) argues that infrastructure and financial resources are the most pressing issues with regard to AIDS drug access in South Africa. The IPI paper suggests that patents need not be a major problem in drug access in South Africa because TRIPS permits flexibility to expand access using such tools as compulsory licensing and parallel importation.

The South Africa-based advocacy organization Treatment Action Campaign (TAC) has responded to the IPI paper by arguing that ARVs are not available in the public sector medical system largely because of cost, which is closely related to the strong patent system in their country. Responding to IPI’s claim that TRIPS allows countries

flexibility to maximize drug access, TAC has argued that, “the scope of TRIPS is sufficiently complex to allow pharmaceutical companies to pursue time consuming, costly legal action...” with the goal of delaying implementation of alternatives.<sup>xxiii</sup>

A widely debated analysis by Amir Attaran of Harvard University and colleagues, published in October 2001, concluded that patents do not appear to be the primary factor restricting access to ARV treatments in most African nations. Attaran studied the patent status of 15 ARVs in 53 African countries and found these drugs were not covered by patents in most countries. Attaran also found that geographically, patent coverage is not correlated with ARV treatment access on the African continent. Attaran and colleagues conclude that, “a variety of de facto barriers are more responsible for impeding access to antiretroviral treatment, including but not limited to the poverty of African countries, the high cost of antiretroviral treatment, national regulatory requirements for medicines, tariffs and sales taxes, and, above all, a lack of sufficient international financial aid to fund antiretroviral treatment.”<sup>xxiv</sup> While each of these factors is critically important, the analysis fails to adequately acknowledge the relationship between patents and “the high cost” of ARVs.

Five health advocacy groups, including the Consumer Project on Technology, Essential Action, Oxfam, Treatment Access Campaign, and Health Gap, responded to the Attaran article with a statement claiming that several combinations of AIDS treatments were not adequately included in the published survey. The joint health group statement also emphasizes the special circumstance of patents in South Africa, and the role of that country in the region:

In South Africa every three drug ARV cocktail is blocked by patents...The South Africa market is important for several reasons. First, there are 4 to 5 million HIV+ persons in South Africa. Second, the South Africa economy has more than 40 percent of the GDP for sub-Saharan Africa, a per capita income of more than \$3 thousand and a relatively good health care infrastructure, making ARV treatment feasible, if drug prices are low enough. Third, entry into the South Africa market is necessary for generic suppliers to reach the economies of scale (volume) needed for the most efficient production, particularly for those products with post 1996 patents that are patented in Brazil, such as efavirenz or nelfinavir, and currently lack a significant generic market outside of Africa.<sup>xxv</sup>

In 2000 and 2001, MNCs made a string of price reduction offers on sale of AIDS drugs in Africa. Many health advocates argued these price cuts were motivated by earlier offers from generic companies, including Cipla and Aurobindo. Oxfam noted that even with the new drug company price cuts, AIDS triple combination therapy would cost African governments \$1000 per person annually, still more than three times higher than the cheapest offer from Indian generic company Aurobindo.<sup>xxvi xxvii</sup>

## **Brazil**

Brazil is rightly held up as an example of how LMICs can both respect patent law and expand access to new drugs. In 1996, Brazil passed strong patent laws to comply with international agreements, and these laws were largely praised by industry observers. But the Brazilian patent law stipulated that patents for drugs commercialized before May 14, 1997 would remain off-patent in the country.

In 2000, UNAIDS estimated that 530,000 Brazilians, or 0.57% of the adult population, were living with HIV. There has been an official government commitment to providing AIDS treatment to all citizens since 1996 and Brazil has implemented a broad based AIDS treatment program. To make pharmaceuticals affordable, the government uses its public manufacturing plant, Far-Manguinhos, to produce drugs that are off-patent in the country. Brazilian public health officials have also shown willingness to threaten compulsory licensing and domestic production of on-patent drugs in their negotiations with pharmaceutical companies.

The Brazilian Ministry of Health estimates that because of the expanded availability of ARVs, 146,000 hospitalizations were avoided from 1997-1999, saving \$422 million. According to the Ministry, price reductions in AIDS drugs are due to establishment national manufacturing labs and effective negotiation of prices with companies. AIDS drugs made in Brazil fell 72.5% in price from 1996 to 2000. Imported drugs fell 9.6% during the same period.<sup>xxviii</sup>

The country's budget for AIDS drugs is evidence of the price differentials between off-patent domestically manufactured therapies and imported on-patent drugs. AIDS therapies produced in the country represent 47% of ARVs used, but consume only 19% of total AIDS drug spending. AIDS drugs purchased from MNCs represent 53% of ARVs used, and consume 81% of expenditures.<sup>xxix xxx</sup> In its analysis of drug prices, MSF found that locally produced ARVs in Brazil are sold at fraction of the global price. Combination ARV therapy is produced locally in Brazil but in Thailand the same ARVs are not available as generics.

As a result, according to MSF, it costs the same in Brazil to treat 1000 people with HIV/AIDS as it does the Thai government to treat 552 people with the disease.<sup>xxxi</sup>

Price controls and the threat of compulsory licensing have been effectively used by Brazil as bargaining chips to negotiate with MNCs for lower prices on AIDS drugs. (A Brazilian Presidential decree on compulsory licensing enables the government to override market exclusivity of patents and authorize third party production on the grounds of public interest or national emergency.) A recent example of successful negotiation was the agreement with the pharmaceutical company Roche to provide 40% price cut on the ARV nelfinavir after Brazil threatened to break the patent and produce the drug itself. As a *New York Times Sunday Magazine* article on AIDS in Brazil reported, "Just the credible threat of generic competition is enough to get manufacturers to lower their prices."<sup>xxxii</sup>

## **C.V. Conclusion**

Patents are one of several important factors that help determine access to medicines in LMICs. The current literature and lessons from India, South Africa and Brazil demonstrate that the presence or absence of patent protection has affected drug prices and access, as well as development of domestic industry. But though patents are important, it is possible to overemphasize their effect on drug access and ignore other important factors such as the availability of international and domestic financial resources for health care, infrastructure needs, and political leadership.

The move towards stronger IP protections through the TRIPS agreement presents complex issues. There is evidence that strong patents have had a negative effect on affordable prices. Industry continually raises concerns that the erosion of patent protections will undermine incentives for product development. Since Africa represents only 1.1% of the global pharmaceutical market,<sup>xxxiii</sup> it is difficult to see how lower prices in this market significantly impact MNC profits. The real fear is that lower prices will undercut acceptance of higher prices elsewhere, and could lead to flow-back of cheap drugs to richer markets. Political and legal actions are needed to address both concerns.

LMICs clearly have a stake in product development, particularly for diseases affecting their populations. By themselves, stronger patents in LMICs are unlikely to provide adequate incentives to encourage the private sector to significantly expand research on treatment and vaccines for tropical diseases. Yet patents may well represent one important part of a comprehensive package of incentives necessary to increase industry work on diseases of the poor.

In looking for a balanced policy that addresses the needs of LMICs, examples from the three countries discussed above can be useful. They each demonstrate the critical importance of a combination of factors, including health funding, political commitment, and flexibility in implementation of IP law. Of the three countries, Brazil has shown the most impressive successes at extending drug access to its population. In that country, development of domestic public manufacturing capacity and willingness to use options in trade law have allowed the government to be a powerful negotiator with patent-owning MNCs. One goal of a balanced IP policy might be to encourage flexible policies that acknowledge patent rights, but also provide options that strengthen the negotiating hand of LMICs with MNCs. To achieve this balance, LMICs will need the ability to implement policy options including compulsory licensing (for import as well as domestic production), parallel importing, and other options without undue legal challenge or risk of trade sanctions for industrialized nations.

The Brazil model is less applicable to lower income countries without domestic industry. In these countries, significant injection of resources is absolutely necessary, combined with greatly reduced pharmaceutical prices. Political and economic incentives for tiered pricing (particularly for essential medicines) can play an important role here, and there is evidence (noted above and in the Appendix) that interventions will be needed to encourage greater use of tiered pricing. The evidence tells us that generic competition, or its threat, has been a crucial element in achieving reduced drug prices in LMICs and it

would be irresponsible to significantly constrain this as an option, especially if other approaches, such as price tiering, are not fully successful.

The AIDS pandemic demonstrates the desperate need for policies that foster early and broad access to life saving drugs, as well as the promotion of research on future technologies. This is the difficult and urgent challenge to policy makers. Yet there is little justice in demanding populations in LMICs forego access to today's AIDS drugs in order to promote future R&D on products that would also be inaccessible to many in these countries.

TRIPS and other international trade agreements will remain a priority for industrialized countries, yet they are not ultimately sustainable unless greater equity in the delivery of health care technology is achieved. As LMICs increasingly demand funding and policy options to increase health care access, and policy makers begin to appreciate the role of health status in creating a more stable world, this challenge of balanced and equitable IP policy becomes ever more important.

## **Appendix to Section C: Policy issues and options**

The international community is now faced with making numerous decisions on regulations that will guide implementation of TRIPS, in particular the options available to LMICs in designing their own patent laws. Following is a brief review of points on policy issues made in articles reviewed for this chapter.

**Compulsory licensing** is a provision in the TRIPS agreement and in the law of several countries that allows governments to issue a license for production or purchase of a drug without the approval of the patent holder in the case of national emergency or other necessity. Patent holders are generally guaranteed some remuneration when a compulsory license is issued. Compulsory licensing has emerged as a primary issue of debate.

Barton has pointed out that compulsory licensing that is limited to domestic use will be feasible only for countries that have a market large enough to support drug manufacture. Scherer and Watal write that LMICs without manufacturing capacity will need to be able to use compulsory licensing for importation, rather than production, of therapeutic drugs. A competitive world market supply of generic products will be required to encourage generic manufacturers to offer their drugs at lower prices. The authors note that a determination from WTO is needed on what percentage of domestically produced drug using a compulsory license is allowable for export.<sup>xxxiv</sup> In *Pharmaceutical Price, Patents and Welfare Losses*, Watal identifies compulsory licensing as the superior option to price controls, observing that it is possible to achieve comparable levels of price reduction and higher levels of welfare with lower administrative costs.<sup>xxxv</sup>

Bermudez of the National School of Public Health in Rio and his colleagues<sup>xxxvi</sup> have endorsed a range of policy measures to reduce the perceived negative impact of patents in Brazil, including government manufacturing capacity, centralized procurement, and they urge consideration of a broader list of remedies, including compulsory licensing.

**Parallel imports** refers to the practice of importing products from a third party rather than the patent-owning manufacturer. In *Differential Pricing for Pharmaceuticals: Reconciling Access, R&D, and IP*, Danzon writes that parallel trade should be avoided because it breaks down the feasibility of maintaining price differentials.<sup>xxxvii</sup> In other words, it may be difficult to maintain higher prices in industrialized countries that are necessary for companies to recoup investment and seek profit if parallel trade makes a significantly lower price available internationally. Danzon argues there are often quality concerns with drugs acquired through parallel importation. Instead, she urges a policy that fosters patent rights and differential pricing. Companies should be encouraged to enter into contracts with payers that include confidential rebates and price cuts. Danzon notes that this system will not provide sufficient incentives for research on neglected diseases, or fully address the challenge of access to current drugs. Additional resources for drug purchases will be needed, since many countries will not be able to purchase drugs even at marginal prices.<sup>xxxviii</sup>

In a paper for IFPMA, Europe Economics is also critical of parallel importation, arguing that it, “causes the replacement of (socially preferable) differentiated pricing based on ability to pay by an (economically inefficient) uniform monopoly price which is not affordable in poorer countries, and which generates lower returns for the IPR [intellectual property rights] holder.”<sup>xxxix</sup> IFPMA suggests that, as a result, parallel importation undermines both access to current drugs and creates a “barrier to innovation.”

To facilitate parallel importation that does not undercut prices in industrialized countries, Scherer and Watal argue for an international agreement to bar re-export of drugs to a rich country brought into a LMIC through parallel importation. Price controls and drug donation tax credits can also play a valuable role, according to the authors.<sup>xl</sup>

Extensive use of **tiered (or differential) pricing** refers to the practice of pricing products differently in different markets, ideally linked on the consumers’ ability to pay. In the case of therapeutic drugs, tiered pricing that provides much lower prices for drugs in LMICs is often pointed to as an approach that could greatly expand drug access without undermining the patent system. To significantly increase access to drugs, use of tiered pricing would need to be greatly expanded. As noted above, MNCs may continue to have reasons to price their products in lower income countries at global market levels rather than a lower price to maximize sales in resource poor countries.

In *Differentiated Pricing of Patented Products*,<sup>xli</sup> Barton references two studies that suggest only a limited relationship between average income in a country and its drug prices. Data from MSF reveal wide diversity in prices between countries but little correlation between price and national per capita income. The MSF study found that the lowest prices (on average) were in India and Brazil (the first is a low income and the second a middle income country, both with flexible IP laws). Scherer and Watal studied AIDS drug prices in several countries and found a slight income effect that is increasing over time as MNCs reduce prices of AIDS drugs in LMICs. The authors suggest that prices are likely to be higher in nations with maldistributed income.

**Local working** provisions require that products be manufactured domestically within a certain time following introduction of the product in the country. Brazil’s Article 68 permits compulsory licensing unless products are manufactured in Brazil within three years of market introduction. In *Drug Companies vs. Brazil*, Oxfam argues that Brazil’s local working requirement is justified and that, “there are strong development grounds for a local working requirement... By encouraging local manufacture and thus greater self-reliance, a developing country enhances its long-term health security.”<sup>xlii</sup> Peg Willingham of PhRMA responds<sup>xliii</sup> that the country’s local working policy “is not tenable,” and argues that in the pharmaceutical industry there are significant economies of scale which mean local working requirements may actually make products more expensive. IFPMA has argued that Brazil’s Article 68 is a clear violation of TRIPS. The real intent of the law, according to IFPMA, is to protect local manufacturing capacity, not to benefit patients. “This is clearly an industrial policy that seeks to protect national business interests, not improve access to medicines,” they write.<sup>xliiv</sup> And the organization argues

that if many other countries required local production, it would lead to reduced drug access around the world.

**Price controls** are another option available to countries seeking to extend drug access. PhRMA has argued that price controls in Brazil are “contrary to the free market,” and threaten innovation by undermining the ability to make profits.<sup>xlv</sup> PhRMA has also accused India of practicing “discriminatory differential pricing that favors the local product.” Scherer and Watal find that there has been a “poor” experience in India with enforced pricing of drugs. Still, they note that price controls may be effective at reducing prices while leaving patent owners only negligibly worse off.<sup>xlvi</sup> **[confirm]**

In her study on strengthened patents in India, Watal<sup>xlvii</sup> writes that price controls now cover 50% of country’s pharmaceutical market, and all patented pharmaceuticals in the future will likely be subject to price controls. Watal argues that reference pricing may be more effective than price controls, but she also sees a role for selective use of price controls. The author notes that for many widely used patentable pharmaceuticals there are few substitutes, suggesting that the price of these products needs to be addressed if access is to be extended to a larger share of the population.

**Bolar provisions** allow for research and development of generic products before the product goes off-patent. The WTO recently ruled that Bolar provisions in Canadian law (allowing product development and submission of information required for marketing approval) are not inconsistent with TRIPS requirements. India has been interested in inclusion of Bolar provisions as amendments to its Patents Act.<sup>xlviii</sup>

Several MNCs have initiated **donation programs** for AIDS drugs. Oxfam has argued that drug donations leave countries dependent on charity, are not sustainable, and often come with conditions that are difficult to accept. For example, the pharmaceutical company Abbott wanted to make its offer of reduced-price AIDS drugs conditional on an agreement that South Africa forego the import of generic medicines.<sup>xlix</sup>

## D. Report Conclusions

The R&D and the access sections of this report have addressed two different though clearly related aspects of the broader set of factors affecting health in the developing world. A critical challenge, well recognized by all involved, is that of finding a balance between IPR rules that allows for affordable access to new, on-patent technologies while continuing to protect companies and other institutions who have invested in a risky and lengthy research effort and demand return on that investment. Steps to cut prices for existing products now may jeopardize prospects for new products in the future. Patients suffering from one of the neglected diseases can only hope for new products as effective treatments currently do not exist.

As a group, infectious diseases constitute 25 percent of all deaths in developing countries and a slightly broader set of diseases (communicable, perinatal and maternal) 70 percent of the region's total disease burden. Each disease, however, has distinct "R&D" and "Access" characteristics, implying that no single policy package will solve all problems for all diseases. As a way to design policy proposals and evaluate their effectiveness to "cover" the range of problems, it is useful to categorize diseases according to the size and location of their markets. The Working Group 2 of the CMH has undertaken such an exercise (Working Group 2, forthcoming).

### Categories of "Neglected Diseases"

**Category 1** – Potential Markets are Truly Global (acute respiratory, measles, HIV drugs).

- Private returns are not so low as to impede private sector although social returns are also high. So main concern is not lack of R&D pipeline but:
  1. speed at which new products are developed
  2. applicability of products for developing world (different delivery systems; different biological combinations)
  3. regulatory hurdles that respond to risk/benefit criteria of the Rich country (eg. HIV vaccine)
  4. financial constraints on poor countries that limit ability to access (also all other access issues)

**Category 2** - Potential Markets are Predominately in Developing Countries, but also in the Developed Countries (e.g. TB, Malaria, GI nematode infestations, HIV/AIDS vaccines).

- Social returns will clearly outweigh private returns on investment, and expected private return may be insufficient to incentivize R&D. Pharmaceutical firms and biotech are more likely to invest in Category 1 diseases and/or diseases for which the potential markets are exclusively in the developed countries.
- Furthermore, since the social returns on investment will more directly accrue to poor countries, rich countries have been slow to organize to correct the market failure—in other words, the public sector failures are notable.

**Category III** – Potential market are exclusively in the developing countries (African sleeping sickness (trypanosomiasis), Chagas disease, and schistosomiasis)

- These diseases are nearly all caused by tropical parasites with complex life cycles that require warm temperatures for successful transmission. There is almost no market for products in these diseases (and as a result little R&D) because their constituencies are fewer in number than the higher-burden diseases of Category II, and they are also extremely poor.
- When new technologies are developed, they are usually serendipitous, as when a veterinary medicine developed by Merck (ivermectin) proved to be effective in control of onchocerciasis in humans.

Only a few of the priority “disease of the poor” fall into Category I, most importantly HIV, where there are global markets, true threats of compulsory licensing, and real opportunities for differential pricing. That said, populations are rightly demanding access to products in other disease categories as well, to treat cardiovascular problems, cancer, depression and so on. That means it is essential to get the balance “right” for the case of HIV. Everyone’s health depends on it.

For diseases in Categories II and III, affordability and access are legitimate concerns but for the moment the primary issue is how to realize new products through R&D. Here creative ways to attain the often referred to “dynamic innovative” opportunities of IPR are needed. Whatever the incentives package is chosen, it might include access conditions to help insure eventual product delivery should any of the research efforts product marketable products.

Governments in both the north and the south working to design effective IPR policies for global health must consider the role IPR plays in other separate yet related issues. IPR policies are critical in shaping the path of domestic industry development. Ironically governments may feel pressured to choose between an IPR policy that helps support its domestic industry (and arguably further economic development) and an IPR policy that others have argued is essential for supporting global health. Equally complicated are decisions about how to both further scientific research and ensure access to research tools. We have teased out and discussed in detail the role IPR plays in the global health debates. In the end, policy makers need clearly identified goals, an understanding of what motivates the necessary participants, and a willingness to accept that IPR is only one of a necessary package of instruments they need to consider.

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## Endnotes For Section C

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- <sup>xiv</sup> de, Souza, NJ, Overview of the Indian Pharmaceutical Industry: Imperatives for the Next Millennium, [www.gbhap-us.com/magazines/pharmanews/5-6-article.htm](http://www.gbhap-us.com/magazines/pharmanews/5-6-article.htm)
- <sup>xv</sup> Europe Economics, Medicines Access and Innovation in Low Income Countries, a Draft Report by Europe Economics to IFPMA, May 25 2001, [www.europe-economics.com](http://www.europe-economics.com)
- <sup>xvi</sup> International Federation of Pharmaceutical Manufacturer Associations, TRIPS, Pharmaceuticals, and Developing Countries: Implications for Health Care Access, Drug Quality, and Drug Development, Geneva, 2000
- <sup>xvii</sup> The United States initially opposed the implementation of the new Medicines law. But responding to public pressure, in 1999 President Bill Clinton pledged that the US would, "implement its health care and trade policies in a manner that ensures that people in the poorest countries won't have to go without medicine they so desperately need." This Executive Order was extended by the Bush Administration. In Spring 2001, a lawsuit filed by the Pharmaceutical Manufacturers Association of South Africa against the government was withdrawn, with the government agreeing to consult industry on Medicines Act implementation. (Case study from the Commission on Intellectual Property Rights, UK)
- <sup>xviii</sup> Gray, A, Matsebula, T, Drug Pricing, Chapter 9 in South African Health Review 2000, Health Systems Trust, South Africa, <http://www.hst.org.za/sahr/2000/>
- <sup>xix</sup> Perez-Casas, C., et al, HIV/AIDS Medicines Pricing Report. Setting Objectives: is there a Political Will?, *Medecins Sans Frontieres*, July 6, 2000
- <sup>xx</sup> Representing the Government of South Africa at an April 2001 WHO/WTO Workshop on tiered pricing, Desmond Johns noted that competition within classes of drugs is often held up as the means to reduce drug prices in LMICs. Yet, according to Johns, this has not been South Africa's experience. "Newer and therefore patent protected products of the same therapeutic class, have always tended to clustered in the same price range," said Johns, "and this relationship was maintained even as prices increased." (Johns, D., WHO-WTO Workshop: Differential Pricing and Financing of Essential Drugs, A Developing Country Perspective, 2001) In other words, substitution or price tiering are not bringing the costs of therapeutic drugs down sufficiently to be widely accessible in the public health system.
- <sup>xxi</sup> Gray, A, Matsebula, T
- <sup>xxii</sup> International Intellectual Property Institute, Patent Protection and Access to HIV/AIDS Pharmaceuticals in Sub-Saharan Africa, Washington, D.C., 2000
- <sup>xxiii</sup> Nathan Geffen of Treatment Action Campaign has written<sup>xxiii</sup> that IFPMA's Harvey Bale is wrong when he claims that people in South Africa do not have access even to off-patent drugs. Many do get TB drugs, Geffen writes, but health clinics strain to afford patented TB medications. He also argues that

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compulsory licensing would lead to development of a stronger generic industry in South Africa. According to Geffen, local generic production gives some protection against exchange rate fluctuations, an important fact in South Africa where the currency has steadily declined over two decades. (Geffen, N., Pharmaceutical Patents, Human Rights and the HIV/AIDS Epidemic, presentation to the World Business Council for Sustainable Development Project on Innovation and Technology, May 31 2001)

<sup>xxiv</sup> Attaran, A, Gillespie-White, L, "Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?," *Journal of the American Medical Association*, vol. 286, no. 15, October 17, 2001

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<sup>xxvi</sup> Oxfam, WTO Patent Rules and Access to Medicines: The Pressure Mounts, [www.oxfam.org.uk/policy/papers/wtorules.htm](http://www.oxfam.org.uk/policy/papers/wtorules.htm), accessed 9/19/01

<sup>xxvii</sup> Price reductions have not been the only industry response to pressure for expanded drug access in Africa. In October 2001, GlaxoSmithKline said it would allow South African generic drug maker Aspen Pharmacare Ltd. to produce three on-patent GSK AIDS medications. In its article on the agreement, the *Wall Street Journal* noted that "with the threat of competition from generic-drug makers such as India-based Cipla Ltd., several major pharmaceutical companies have slowly cut the prices of AIDS drugs..." Glaxo conceded that because the government of South Africa has so far chosen not to purchase ARVs, even at cut rate, the company is, "not giving away a substantial amount of the business." (Zimmerman, R., Glaxo Licenses AIDS Drug to Generics Firm, *Wall Street Journal*, October 8, 2001)

<sup>xxviii</sup> Ministry of Health of Brazil, AIDS Drugs Policy, [www.aids.gov.br/assistencia/aids\\_durgs\\_policy.htm](http://www.aids.gov.br/assistencia/aids_durgs_policy.htm), accessed 9/19/01

<sup>xxix</sup> Ministry of Health of Brazil

<sup>xxx</sup> Sudo and colleagues, in an abstract presented at the XIII International Conference on AIDS, attributed the significant (over 65%) decrease in prices of some AIDS drugs to local manufacture of therapies. The authors observed that, "despite the increasing quantities acquired, there was no correspondingly significant reduction in the prices of non-locally produce ARVs." (Sudo, E., et al, The Costs of Anti-Retroviral Medicines in Brazil from 1996 to 1999; abstract presented at the XIII International AIDS Conference, Durban, South Africa)

<sup>xxxi</sup> Perez-Casas, C., et al, HIV/AIDS Medicines Pricing Report. Setting Objectives: is there a Political Will?, *Medecins Sans Frontieres*, July 6, 2000

<sup>xxxii</sup> Rosenberg, T, Look at Brazil, *New York Times Sunday Magazine*, January 28, 2001

<sup>xxxiii</sup> Attaran, A, et al

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<sup>xxxvi</sup> Bermudez, JAZ, Access to Drugs, the WTO TRIPS Agreement, and Patent Protection in Brazil: Trends, Perspectives and Recommendations to Find Our Way, 2000, <http://www.neglecteddiseases.org/04.pdf>, accessed 9/19/01

<sup>xxxvii</sup> Danzon, PM, Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and IP, Draft August 2001

<sup>xxxviii</sup> Danzon, PM

<sup>xxxix</sup> Europe Economics

<sup>xl</sup> Scherer, FM, Watal, J

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