BALANCING HEALTH NEEDS AND DRUG RESEARCH INCENTIVES

BY HANNAH E. KETTLER AND CHRIS COLLINS

Are there ways to improve access to essential drugs for people in developing countries while simultaneously retaining or creating the incentives for pharmaceutical companies to research and develop needed new drugs, especially for neglected infectious diseases? How will broader patent protection for drugs, as foreseen under the trade-related intellectual protection agreement (TRIPS) of the World Trade Organization (WTO), affect incentives to conduct research and development (R&D), drug access and pricing and domestic production of generic drugs in developing countries? Some possible new approaches to these issues are offered in this article, which is based on a report commissioned by the UK Commission on Intellectual Property Rights. It was written by Dr. Hannah E. Kettler, a Project Director at the Institute of Global Health, University of California, San Francisco, with assistance from Chris Collins, an independent consultant.

INTRODUCTION AND OVERVIEW

A key global health challenge is how to simultaneously encourage more innovation and R&D into new, more effective products and ensure that people needing these products can afford and have access to them. Intellectual property rights (IPR) sit at the center of this debate. 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. To the extent that it affects the price of patented drugs, IPR has a negative effect on poor patients' ability to afford and therefore access new drugs and vaccines. Other barriers to access, as shown by experience with HIV drug access in India, Brazil, and South Africa, include inadequate health care systems infrastructure and staff, poor government commitment to fighting the disease, and

the lack of sufficient financing to ensure access to HIV treatments.

To develop solutions within the current IPR system, new global norms for technology licensing agreements and pricing must be adopted. Considerable political discussion has been given to the establishment of differential pricing where the flow back of the cheaper priced products to the industrial countries is controlled. Second, in technology and research agreements, companies are making commitments, in exchange for their retaining the ownership of the IP, to help ensure that any approved product resulting from global health initiatives (and advanced with these initiatives' funds) will reach the patients who need them. At the same time, for substantive progress to be made, governments in developed countries must make substantive financial commitments to fund the development and purchase of new products. Governments in developing countries must also participate in global initiatives and help invest in the development of better health care infrastructure.

The R&D Problem

For at least 12 diseases, 99 to 100 per cent of all cases globally are located in developing countries. The 100 per cent category includes malaria with over 24 million sufferers (1996), chagas disease, dengue, encephalitis, lymphatic filariasis, onchocerciasis, schistosomiasis, tetanus, trachoma, and trypanosomiasis. In the 99+ per cent category are leishmaniasis, measles, polio, syphilis, diphtheria, leprosy and diarrhoeal diseases. For tuberculosis and HIV, the figures are 91 and 65 per cent, respectively (Lanjouw and Cockburn, 2001).

This group of "neglected diseases" is a low priority for both private and public investors in pharmaceutical R&D. Despite a large number of patients and significant need for products, the actual demand is small because of the targeted populations' inability to pay for new medicines. So companies see small markets and expect low returns from sales. The R&D process is long, risky and expensive, regardless of the indication or disease. At the same time, the marginal cost of producing pharmaceuticals, once tested, is low, which permits generics firms to manufacture and sell products at prices a fraction of that offered by innovator. Patent protection for the innovator, therefore, is considered an essential mechanism for securing economic returns on the innovation. For neglected diseases, however, that protection, and the market secured for the innovator, is insufficient to warrant the R&D investment.

Recent events in Canada point indicate the importance of patents as an incentive for investments in pharmaceutical innovation. Here, R&D investments rose significantly following the abolition of compulsory licensing (see terminology box), the strengthening of IPR, and adoption of tax incentives. World Bank-commissioned surveys of transnational corporations reveal that

BOX 1: SOME TERMINOLOGY

BOLAR PROVISION, sometimes called regulatory exception, allows manufacturers of generic drugs to use a patented invention, while still under patent, to develop the generic products that they can market as soon as the patent expires. The World Trade Organization (WTO) ruled that the provision is in accordance with TRIPS.

COMPULSORY LICENSING. Under TRIPS and the law of many individual countries, governments can, in the case of a national emergency, issue a license for production or purchase of a drug without approval of the patent holder. Patent holders are generally guaranteed some remuneration. Compulsory licensing has emerged as a primary issue of debate.

DIFFERENTIAL OR TIERED PRICING means pricing products differently in different markets where the segments ideally correspond with consumers' ability to pay. Some argue that the use of such policies has the potential to significantly lower the prices in developing countries of essential drugs that are still on patent, thereby expanding drug access without undermining the patent system.

DONATION PROGRAMS. A number of large pharmaceutical companies have initiated or participated in drug donation programs for HIV and other neglected diseases. In the case of HIV, companies tend to negotiate with countries on a case by case, or region by region basis.

LOCAL WORKING PROVISIONS require that a product be manufactured domestically within a certain time following its introduction in a country. For example, if a company does not manufacture and/or distribute a product in Brazil, within three years of its registration there, a Brazilian company is permitted to take a compulsory license and manufacture the product themselves. An opposing voice states that because of significant economies of scale in pharmaceutical manufacturing, local working requirements may actually make products more expensive. Another is that such provisions actually seek to protect local manufacturing capacity, not to benefit patients, and are therefore a violation of TRIPS.

PARALLEL IMPORTING involves the import of products from a third party rather than the patent-owning manufacturer to a second country. Parallel trade can undermine price differentials; if parallel trade makes a significantly lower price available internationally, it is difficult maintain higher prices in industrialized countries that are necessary for companies to recoup investment and seek profits.

PRICE CONTROLS are another option available to countries seeking to extend drug access. One view is that price controls may be effective at reducing prices while leaving patent owners only negligibly worse off (Scherer and Watal, 2001). The opposing view is that price controls are contrary to the free market and threaten innovation by undermining the ability to make profits.

pharmaceutical companies rank patent policies high in their decision criteria for foreign direct investment.

It is still too early to judge the impact on developing countries' infant pharmaceutical industries of introducing IPR laws that comply with TRIPS of the WTO. Some predict, for example, that the introduction of product patent protection in India will put hundreds of small local generics companies out of business. At the same time, it will provide new opportunities for those companies able to invest in R&D capabilities and for larger generics companies which will be able to enter and compete for contracts in 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. Still, it will improve the prospects for cross-national joint ventures and for scientists trained in the US and Europe to return home and build their own companies.

There is less evidence that the introduction of TRIPS will encourage companies and scientists in endemic countries to invest in treatments for neglected diseases. One global study of "new research activity" in tropical diseases post-1980 found only slight developments in malaria patent and investment behavior, while all others were stagnant despite many new entrants to the R&D pharmaceutical industry (Cockburn and Lanjouw, 2000).

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.

To this end, some of the available policy options are:

Product development public private partnerships (PPPs) have been set up to develop drugs or vaccines for specific diseases. In exchange for funds and other support, the companies agree to contracts that include some mechanism for securing the development and delivery of any successful final product at affordable prices to developing world markets. In some cases, such as leishmaniasis, the PPP may be responsible for the market. In others, such as malaria, there is a paying travelers' market to which the industry partner may have first rights.

Incentives to invest in neglected diseases. Attempts to legislate effective national policies in the US and the UK for that purpose have been less successful. The goal is to combine cost-saving policies (push), such as grants and tax credits, and revenue-enhancing policies (pull), 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 to research-oriented companies, such a policy is unlikely to find favor with policymakers in developed countries who are

actively working to find ways to reduce the size of the publicly funded domestic drug bill. Generics companies whose strategies depend on predictable dates when product patents expire in large, profitable markets will also protest. An interesting but 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 diseases of concern to their own populations.

The Access Problem

Patents help determine access to new medicines in developing countries. Case studies of HIV drug access in India, South Africa, and Brazil show that the presence or absence of patent protection can affect drug prices and access, as well as the development of domestic industry. However, they also demonstrate that other, non-patent, factors cannot be ignored, factors such as the availability of international and domestic financial resources for health care, inadequate infrastructure and staffing needs, and political leadership. Even when companies offer to give away their products, the majority of the drugs can fail to reach the patients in need.

The move towards stronger IPR 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 per cent of the global pharmaceutical market (Attaran, 2001), it may seem difficult to see how lower prices in this market significantly impact MNCs' profits. But the real problem is that it is difficult to isolate policies to specific regions. Companies fear that the establishment of lower prices in the developing countries will undercut acceptance of higher prices elsewhere. A related concern is that the comparatively cheap products will not be made available to the domestic populations, but will instead be "reimported" back to rich markets.

Seeking a Coherent Policy

Examples from the way HIV drug access has been addressed (or not) in Brazil, India and South Africa provide useful lessons for those looking for a coherent policy that addresses the needs of developing countries. Each country demonstrates the critical importance of a combination of factors, including health funding, political commitment, and flexibility in implementation of IPR law. Of the three countries, Brazil has had the most success in extending drug access to its population. Its development of domestic public manufacturing capacity and its willingness to use options in trade law has turned the government into a powerful negotiator with patent-owning transnationals.

The Brazil model is less applicable to lower income countries that lack a domestic industry. In these countries, sig-

nificant injection of resources is absolutely necessary, combined with supplies of greatly reduced prices for pharmaceuticals. Political and economic incentives for *differential pricing* (particularly for essential medicines) must play an important role. For example, expanded efforts by industrialized and developing country governments will be needed to prevent re-importation of cheaper drugs to wealthier markets.

A crucial element in achieving reduced drug prices in developing countries has been *generic competition* or its threat. It would be irresponsible to constrain the ability of developing countries 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 imports was left unresolved at the WTO consultation in Doha, in November 2001. Developing countries without production capacity clearly need 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 developing country in the world to have its own production facility for every essential on-patent drug, particularly given the economies of scale in pharmaceutical production.

However, compulsory licenses should not be seen as a "magic wand" for obtaining affordable access to patented medicines in developing countries. Scherer and Watal (2001) have highlighted three limitations. First, compulsory licensees must have the capability to "reverse-engineer" or import the product without the cooperation of the patent owner. 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 the owner's competitors. 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 product areas with generic copies.

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

Third, compulsory licensees will only be attracted to large and profitable drug markets. Thus, essential medicines with small potential volumes or mostly poor patients will not attract many applicants, however important they are from the perspective of public health. Thus, existing and future drugs for most neglected diseases are not likely to be the focus of 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 developing countries. This is the difficult and urgent

challenge to policymakers. As developing countries increasingly demand funding and policy options to increase health care access, and policymakers begin to appreciate the role of health status in creating a more stable world, this challenge of balanced and equitable IPR policy becomes ever more important.

Anthrax and CIPRO — IPR Debates in a New Global Context

One could argue that, with the anthrax attack in October 2001, the US obtained first-hand experience with the complexities of the policy debates surrounding IP for global health. The US saw an immediate need for supplies of a product still on-patent that its owner, Bayer, was unable or unwilling to meet. The US government's first instinct was to consider compulsory licensing. Manufacturers, Cipla in India in particular, claimed they could meet the demand in less time and at a lower price. The US government, in the end, managed a deal with Bayer. By contrast, Canada's government immediately granted a compulsory license to a Canadian generics company (New York Times, October 19, 2001). This move did not follow legal requirements, however, and was withdrawn. Canada also eventually reached an agreement with Bayer.

In the light of the new (or newly perceived) bioterrorist threats, the US government also finds itself lacking effective tools to address specific threats and seeks to take steps to encourage rapid new product development and research. Most of the answers to bioterrorism are "in the hands of the biotech and pharmaceutical world" (*Contra Costa Times,* 10/24). During October 2001, US national headlines portrayed the pharmaceutical industry and the patent system as the key barriers to "national security," while also identifying them as the best opportunity for quick, innovative solutions to scientific problems that until then had no priority and little research. Public funds, infrastructure and support are essential, but not enough to meet the existing and future demands. Private company participation is essential.

What steps are needed to encourage private companies to participate? How can R&D be made affordable, especially for small biotech companies not able to pursue projects just out of patriotic duty? How, at the same time, can affordable supplies of products, new and existing, some on-patent, some not, some in stock, some not, be ensured? The US possesses the political and financial means to mobilize the resources needed in this national "emergency" — though, of course, results are not guaranteed given the uncertainties inherent in drug and vaccine development. At a global level, the exact same types of questions arise in the IPR debates over how to improve health in the developing world. Those countries in greatest need cannot mobilize the resources to solve their regional problems and depend on global solutions. To date, only incomplete answers have been found.

USING IPR TO SOLVE THE R&D PROBLEM

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 predominantly among the poorest segments of the peoples of the developing world.

The primary actors in pharmaceutical and vaccine R&D are public research institutions 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 development, production and commercialization processes. The division of labor has changed somewhat over the past 20 years though the relative comparative advantages have stayed the same.

Much evidence shows that diseases such as malaria, TB, leishmaniasis and others are a low priority. Only 5 to 10 per cent of health R&D goes to diseases prevalent in developing countries, and only 1 per cent of new products between 1975-1997 were developed specifically for tropical diseases (Troullier and Olliaro, 1999). In 1998 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). Of those DALYs lost, 68 per cent were linked to communicable diseases (World Bank 1999, WHO, 1999).

Private companies are not the only actors neglecting these diseases. In $41,887 million of research by the US National Institutes of Health in 2001, only 0.21 per cent went to TB and 1.13 per cent to AIDS vaccines, compared with 10 per cent to cancer, the disease with the largest budget. A joint study by WHO and the International Federation of Pharmaceutical Manufacturer Associations (IFPMA) shows that seven diseases do not have effective drugs on the market and have limited numbers of products, if any, in development: malaria, TB, lymphatic filariasis, onchocerciasis, leishmaniasis, schistosomiasis and African trypanosomiasis (WHO/IFPMA, 2001).

Africa has 10 per cent of the world's population but suffers 25 per cent of the disease burden.

A key factor that discourages private investment for R&D on these diseases is the poor expected return (Kettler, 2000, Kremer, 2001, PIU, 2001, Europe Economics, 2001). Despite high need — a large number of patients — these patients are unable to pay for medicines, and thus expected demand is very low.

Regarding malaria, estimates by Medicines for Malaria Venture (MMV) are that "at most $50 million in annual

returns" would be achieved by "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". This is "not enough for pharmaceutical companies seeking annual sales potential of $250 to $300 million for a new drug." The market for new TB drugs would be $700 million by the year 2010, according to a recent estimate by the Global Alliance for TB Drug Development (*New York Times*, November 15, 2001).

The public policy challenge is to construct incentives for 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, "local development work" is needed to make existing compounds more suitable for the specific circumstances of the country of focus, adjust dosages to local needs, and find combinations more appropriate for local medicine practices (Europe Economics, 2001, 8). Policy discussions have focused primarily on two alternative solutions.

- The first model — the commercial approach — strives to make neglected diseases as attractive as non-neglected diseases to private companies looking to make investment decisions. This requires a package of cost-reducing ("push") and market-enhancing ("pull") policies that provide incentives for more R&D into these diseases and improve its expected profitability;
- In the second model, public-private partnerships (PPPs) are set up to address R&D gaps for specific diseases.

Both models assume that private industry plays a critical role in the R&D process, and that strong IPR, especially patent protection, is required to give companies incentives to participate. This occurs within the current IPR environment where countries with pharmaceutical industries have, or are in the process of introducing, IPR legislation to comply with TRIPS. In both models, creative patent and licensing arrangements should be employed above and beyond the base protection rules to ensure success. Specific details of this are discussed below.

The challenge is to construct incentives for more aggressive R&D on new drugs for the neglected diseases of the poor.

Innovation through Patenting

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 hundreds of millions

of dollars per new product. The estimate includes the cost of failures and the opportunity cost of funds during the R&D process (Kettler, 1999). This amounts to more than 30 percent of the total cost of developing, producing, and marketing the typical product. Second, although the R&D process is lengthy and risky, most pharmaceutical products once tested and approved for patient use, 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 patents. 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 prices set at the marginal costs of manufacturing do not cover the fixed costs on R&D, the result would be a decrease in R&D, and hence a decrease in new products brought to market.

Although the R&D process is lengthy and risky, most pharmaceutical products once they exist are relatively cheap to produce.

The organization of R&D and the role of IPR in innovation have evolved over time in the pharmaceutical industry. The interplay between "policy regimes", of which IPR is a part, and "technological regimes" has been studied by Lacetera and Orsenigo (2001). They explore how these interactions have contributed to innovative performance and competitive success in the US and Europe during the industry's historical development since before World War II. Their account makes a number of key contributions to our IPR discussion:

- IPR, especially patents rules, are key factors in each stage. The structure of IPR and its influence as an incentive have varied and evolved as science, technological competencies and business strategies have evolved. For example, German companies tended to lead the industry in the first epoch, supported only by process patents that covered limited scientific and technological improvements rather than advanced innovations. In clear contrast, strong, targeted product patent protection in the modern era is one of the central contributors to the US' success in launching a vibrant biotech industry, and its absence is a factor for the Germans' problems in doing the same (Kettler and Casper, 2000).
- There is no one "best practice" in any one time period and 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 resources. This suggests that strong patent laws give an advantage to innovators, but are not enough to promote innovations where innovation capabilities and supporting institutions are low or absent. Similarly, achieving high economic returns on innovation is likely to be particularly important for sustaining innovation in highly innovative and competitive environments. There are countries where companies 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).

- There is not necessarily only one sustainable business model. Though not industry leaders in terms of R&D innovation or profits, companies in countries like France, for example, have, at least until recently, survived pursuing less innovative strategies based on domestic markets, me-too production, process imitation, inventing around, and the production and marketing of drugs under license or after patent expiration.

These findings raise important questions for the developing countries considering changes to their IPR system. Can we predict how companies in countries with emerging but relatively underdeveloped industries will respond to the introduction of the IPR standard of the globe's leading companies? In the absence of necessary competencies and institutional support, will IPR regulation in and of itself have any effect on developing countries' abilities to conduct R&D and innovation to a global standard? The extent to which countries can pursue "national company strategies" will vary with their dependence on global markets, resources, and competencies to survive. In addition, we know that the relative strength of patent protection influences foreign direct investment (FDI) decisions by US, German and Japanese firms in relatively high-technology industries like chemicals, pharmaceuticals, machinery, and electrical equipment (Mansfield, 1995). For drug and chemical companies, patent protection was important in both the manufacturing as well as the R&D stages.

Will globalization of patent protection affect the global level of pharmaceutical innovation, especially for neglected diseases?

IPR and R&D Capacity in the Developing World

Until recently, a limited number of countries and companies had a pharmaceutical industry, while the rest of the world was consumers. The situation is changing. Even before TRIPS, the production side of the industry had started to become more global. According to a 1991 UNESCO study, only Argentina, India, China, Mexico, and Republic of Korea among the developing countries had industries with innovative capabilities; eight others, including Brazil, Cuba, Indonesia and Egypt, could produce therapeutic ingredients and finished products that were competitive in regional export markets; and 59 countries had no industry at all and were totally reliant on imports to meet their pharmaceutical requirements.

Many proponents of TRIPS argue that a key benefit for developing countries is that it will improve the conditions necessary to attract foreign direct investment and technology transfer, inputs necessary to help develop local R&D capacity. Expected long-term benefits are that stronger IPR will:

- potentially globalize the effort to find cures for disease, bringing in core scientific skills from emerging economies that currently lack incentives to use them. In countries with emerging pharmaceutical industries such as India, Republic of Korea, Brazil, and China, it should encourage researchers to switch from molecule copying to innovative research of new drugs and developing-country versions of existing drugs;
- improve the transfer of, and access to, technology and information from established companies to developing country researchers;
- create jobs for skilled labor and perhaps limit the "brain drain" from developing to developed countries;
- improve international credibility for, and prospects for joint ventures and direct foreign investment in, developing country research.

Pharmaceutical companies refuse to bring products to market in countries where patents are not protected and domestic capacity exists for copying 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). Case studies of Canada, Mexico, and Republic of Korea suggest that pharmaceutical industry investors consistently located R&D and manufacturing in developing countries that respect IPR, according to Mossinghoff.

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. To test the incentive role of patent protection, a study was done on whether the trend in global research into

neglected diseases has changed significantly (and positively), as endemic countries implement strong IPR (Cockburn and Lanjouw, 2000). Given identifiable differences in drug demands in these countries, the authors surmised that changes in the pattern of research expenditures might be expected as a result of strengthening the patent system, and that those changes would be easier to detect and ascribe to policy reform than changes in overall levels of investment.

They find some evidence of new "research activity" in malaria in the 1980s/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 that patent protection on its own is not enough to provide incentives for new investment in these neglected diseases.

The Case of India

It seems unlikely that the potential cost advantage of doing R&D in the developing world would encourage emerging companies with R&D capabilities to focus on diseases neglected by the global players, as shown by the Indian example. There are several reasons for this (Kettler and Modi, 2001). In addition to the required fixed investments, companies need to move along a steep and rapidly evolving learning curve in order to achieve the predicted low 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, despite significant differences in cost structure between these categories.

In interviews, executives of India's leading companies revealed a global focus (Lanjouw and Cockburn, 2000). They seek to exploit their traditional experience and cost advantages in the generic drugs market, in improving the drug profile by modifying existing drugs, or in 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 per cent of R&D expenditure in India was targeted on tropical diseases or developing-country markets; about half was focused on developing suitable products for diseases of global incidence (Scherer and Watal, 2001).

In India, the Government has given priority to investment in new drug development for diseases of relevance to its population, including tuberculosis, malaria, and leishmaniasis. But without

explicit targeted incentives, such investment is unlikely to take place. A proposal to establish a support fund through a tax on formulations sold in India would help to fund research in areas of combined high cost and low return, e.g. neglected diseases (Lanjouw, 2000). It is unclear whether the estimated US$ 22 million generated annually by such a scheme would serve as an adequate incentive, and who would decide how to allocate funds.

Potentially large socioeconomic benefits could be gained by enabling private companies and research institutions in endemic regions to contribute to R&D on new treatments. Research facilities in these regions may be comparatively well placed to achieve quick solutions, relying on close contact with other parts of the health sector, on the local epidemiological environment, and on clinical, behavioral, and social sciences 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. The Indian companies most likely to survive the changes in patent laws are those that can exploit traditional strengths in 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 drug discovery are likely to target growing and potentially profitable global diseases.

Local solutions to local disease problems seem a long-term prospect at best, and will 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, companies from developing countries can be expected to focus on diseases where they too can earn profit. To increase the R&D investments committed towards neglected diseases, additional incentives and explicit policies and projects focused on specific diseases are needed.

Large benefits could be gained by enabling private companies and research institutions in endemic regions to contribute to R&D work on new treatments.

Policy thinking has focused on two different R&D models: the commercial model, which provides incentives for "traditional actors" to replicate the R&D process applied to global diseases to neglected ones; and the public private partnership model, which involves 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 give private companies incentives 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. 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 (see detailed discussion in Kettler, 2000).

With our focus here on IPR, we focus only on roaming patent exclusivity as part of a modified orphan drug act. An attractive feature of typical orphan drug acts is that they combine push incentives (tax credits, grants, fast-track approval) and pull incentives (guaranteed market exclusivity for 7–10 years) to encourage companies to invest in rare diseases for which there are limited numbers of patients in the respective market. A roaming patent exclusivity clause would allow companies to extend the patent life of a product of their choice for a limited, prespecified period of time in exchange for bringing a neglected diseases product to market and making it affordable to patients in need (Kettler, 2000, WHO-IFPMA, 2001).

In a hypothetical scenario, an international team of experts, perhaps housed at WHO, would prepare and update a list of qualifying disease categories and approve applications for special orphan designation. Individual countries would provide the research grants, tax credits to support the cost of the research and special exclusivity rights as a reward for any effective, affordable product approved for market. A cap could be set on the additional funds companies could earn from the granted patent extension for their other product.

The main problem is that the burden of financing the roaming exclusivity measure falls predominately on the users of the existing drug. Developed country governments would likely face opposition from strong domestic patient groups, as well as the generics industry. A second problem is that this proposal will only be valuable to companies that already have approved products and would exclude small biotechnology companies, for example, that have no products to receive exclusivity rights.

Under any incentive policy, developed countries would subsidize the R&D costs for developing countries to benefit. Two key issues are, first, whether the work is done by public or private organizations, and, second, whether the subsidy will be "hidden" as extra costs to payers and patients using the products with the extra months of exclusivity, or "open" with a grant paid out of general taxation to, say, a purchase fund set up in WHO.

Another question is whether the types of push and pull incentives created in rich countries for transnational corporations would also work in India or other countries with emerging industries. To be most effective, incentives should probably take

explicit account of the distinct cost structures, skills, and strategic capabilities of companies in the developing countries. Also, different policies are needed to encourage the participation of small, often loss-making biotechnology companies, as opposed to transnational corporations. How global incentive packages should be designed and executed are topics for important research in the future.

Policies on Public Private Partnerships (PPPs)

IPR plays a critical role in these new disease-specific initiatives (see Kettler and Towse, 2001). Many PPPs choose to pursue an IP strategy designed to maximize the social value of product and process patents. Arguably one of the most important strategic tools is the partnership research contract, and in particular the IP ownership conditions. Evidence suggests that the PPPs are pursuing some combination of the following strategies:

- 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 target markets in developing countries;
- ensuring there are incentives to deliver to these markets — e.g. requiring simultaneous launch in rich and poor countries;
- providing incentives to supply sufficient volume to developing country markets; and
- retaining reversion rights, should commercial partners not deliver on their commitments.

IP is a key tool for pharmaceutical companies in the pursuit of products and profits. PPPs must be as assertive in the way they use IP as any commercial unit, but for a different purpose — the 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.

PPPs are breaking into completely new territory with their IP negotiations. The conditions PPPs place on IP negotiations — price guarantees, volume guarantees, and market specifications — are new and risky, and the challenge is how to make it attractive for major companies to do deals. (For details, see Kettler and Towse, 2001.)

THE IMPACT OF IPR ON ACCESS

Studies, most notably the Commission on Macroeconomics and Health and Attaran (2001), suggest that drug patents are not a significant barrier to access to essential therapeutic drugs in the least developed countries. Of the 300 products on the WHO designated Essential Drug List, 95 per cent are off-patent worldwide. Furthermore, cases such as India and HIV drugs demonstrate that even in situations where product patents are not recognized and a flourishing generics industry exists,

patients are not able to access the therapeutics that they need. Health care advocates point to events in Brazil and South Africa, where governments are trying to address the HIV crisis with a package of policies — including taking or threatening to take a compulsory license — to show that patent policies can have an observable impact on product prices and thus, presumably, patient access.

IP is far from the only factor involved in access to medications. The lack of financial resources, health care infrastructure, and political will are also pivotal. Price is, of course, linked to how many resources are available to buy all health care products, including drugs. To the extent that the presence of generic competition brings down the prices set for on-patented products, the introduction of that competition (or its threat) arguably would affect that piece of the equation. Where newer, on-patent treatments are significant therapeutic advances over older off-patent drugs, early access to patentable products affects the health of millions, and thus the seeming conflict between encouraging the development of those new products and ensuring their affordability must be addressed.

When and how does IP affect access to the most appropriate therapeutic drugs needed to treat disease? And what policies are needed to help ensure affordability in view of the harmonization of stronger IP laws of the next few years?

The significance of IP to drug access depends on several country-specific factors. For example, if there are extremely limited financial and health infrastructure resources, and minimal political will to make drugs available, the existence or not of patents will have little effect on access to existing drugs. If a country has some, albeit limited financial resources and infrastructure and a political or private sector commitment to deliver essential drugs, the patent status of those drugs becomes more critical.

The relative importance of patents varies in significance across diseases as well. 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. But if some or all of the appropriate drugs for a disease are on-patent, as is the case of AIDS at the moment, the link between patents, price, and access becomes central to the treatment debates.

The Relationship of IP, Price and Access

Several researchers have documented the effect of IP laws on prices for therapeutic drugs. Borrell and Watal looked at private sector sales prices for AIDS antiretroviral medications (ARVs) in 34 developing countries between 1995 and 2000. They found that patents promote local availability of new drugs on the for-profit market, but also result in higher prices. Their study found that "firms doubled mean prices when marketing exclusivity rights are available" and average prices increased by 32 per cent,

raising "a difficult trade-off in poor countries." One response to these findings is that government policy should focus on control of drug prices rather than on 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 on the cost of drugs. In a study for Médecins sans Frontières (MSF) of ten essential AIDS drugs in eight countries, Perez-Casas (2000) found that their prices were 82 per cent less than the US price in developing countries with access to generic copies of on-patent drugs. "The presence or absence of generic competition in the market is a key determinant of pricing levels," he wrote. For the combination AIDS therapy d4T+3TC+nevirapine, his 2001 study showed steep price reductions following introduction of low-priced generic versions on the world market. Health groups have argued that it is generic competition, not voluntary drug company price reductions, that have led 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. Scherer and Watal (2001) refer to three studies that predict price increases of 200 per cent or more with the introduction of product patents. The authors conclude that TRIPS will lead to "economic shock" in some developing countries 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. In this specific case, prices may be significantly above competitive levels. In the absence of other pro-access policy actions, millions of people in developing countries will have very limited access to therapeutic advances in biotechnology. It is important to keep in perspective, however, the fact that the majority of these people do not now have access to off-patented, generic products either.

Potential effect of full TRIPS implementation in India

Within the literature on the impact of stronger patent laws on pharmaceutical access, many authors focus on the case of India. New patent laws would arguably

influence domestic access to cheap generic copies of new drugs, and will also affect India's ability to serve as an important exporter of generic drugs to other developing countries. But for the 70 per cent of Indians without access to drugs now, expansion of IP protections is irrelevant (Lanjouw, 1998). Delays in availability of patented medicines produced by transnational corporations in India are not caused by the absence of product patents, but by the transnationals' concerns regarding administrative issues in the country, including potential impediments in winning marketing approval.

Industry reluctance to market drugs in India may also result from concern that lowering drug prices here to make them accessible to a sizable market could undermine higher prices in wealthier countries (*ibid.*). Patent-owning companies may "set prices to maximize global profits, not profits in India."

Watal (2000) has estimated that following the introduction of product IP, prices on patentable pharmaceuticals could increase from 26 to 242 per cent, with a loss in consumer surplus of between $11 million and $67 million, and total "welfare losses" of from $50 million to $140 million. Watal notes that a large proportion of these losses will go to pre-tax foreign profits, and that the existence of substitute medications for on-patent products is a critical factor in price effects. Fink also predicts significant effects, noting that large losses to consumers are possible, but pointing out that in India patented products represented only 10.9 per cent of pharmaceutical sales in 1993.

AIDS as a Case Study

AIDS is the most deadly infectious disease in the world, claiming 8,000 lives each day, over 95 per cent of them in the developing world (UNAIDS, 2000). An analysis of the availability of AIDS medications in developing countries 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 treatment, 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 raise deep concerns with patent holders of AIDS drugs.

A mix of lessons can be learned from a look at three case studies: India, South Africa, and Brazil. In general, these cases show that IP, financial resources, infrastructure and political will all play key roles in determining access to AIDS drugs.

India

India's Patent Act of 1970 made pharmaceutical products unpatentable,

engendering a large generic drug industry focused on copying on- and off-patent medications. An estimated 200 pharmaceutical companies now operate on the national level, and approximately 23,000 compete at the regional level, according to de Souza. India has taken the option to delay full implementation of TRIPS until January 1, 2005, so domestic drug companies can produce 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 per cent of the adult population. Indian companies making generic drugs used in AIDS therapy have offered to sell them to patients in other developing countries at prices far below those charged by patent-holding transnational companies. Yet these lower-priced products have not resulted in widespread drug access to therapeutic drugs for AIDS and other diseases among India's poor.

The international pharmaceutical industry points to this evidence to support their position that the mere presence of a strong generics industry ensures access to drugs. The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) has noted that "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."

South Africa

In the midst of a horrific AIDS epidemic, South Africa provides a dramatically different example. As of 2000, UNAIDS estimated that 4.2 million people (or 20 per cent 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 available, including drugs to prevent mother-to-child transmission.

The South Africa case demonstrates 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 drug prices clearly impacts drug access. South Africa has traditionally had a strong IP regime relative to other developing countries, and patented versions of many drugs produced by transnationals are available for sale there. South Africa is also known for its high prices for patented drugs — long thought to be among the highest in the world as compared with other developing countries (Gray, 2000). 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$1.80 in India as a generic. Fluconazole is 14 times more expensive in South Africa than in Thailand, where it is sold as a generic (Perez-Casas, 2000).

High consumer drug prices are blamed on strong IP laws, but also high distribu-

tion chain costs, including mark-ups between initial sale and retail price. South Africa has considered the introduction of controls on drug mark-ups, of taking steps to encourage sale of generic substitutes where available, and of allowing parallel importing under some circumstances. Compulsory licensing is technically already permitted within the existing Patents Law.

Debates continue about the relative importance of patents on South African drug access. Infrastructure and financial resources are the most pressing issues with regard to AIDS drug access in South Africa, according to an International Intellectual Property Institute (IIPI) paper. IIPI argue that in South Africa TRIPS compliance already permits expanded access by means of compulsory licensing and parallel imports. In response, South African's Treatment Action Campaign (TAC) has argued that ARVs are not available in the public sector medical system largely because of cost, which they claim is closely related to the strong patent system in their country. TAC has also claimed 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 (Geffen, 2001).

In an attempt to introduce more evidence into this debate, Attaran and colleagues at Harvard University conducted a controversial study of the patent status of 15 ARVs in 53 countries. They concluded that patents do not appear to be the primary factor restricting access to ARV treatments in most African nations. They found that patents in most countries did not cover these drugs and that patent coverage is not correlated geographically with ARV treatment access. Attaran and colleagues conclude that "a variety of de facto barriers are more responsible for impeding access to antiretroviral treatment." Their list includes but is 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."

Five health advocacy groups (the Consumer Project on Technology, Essential Action, Oxfam, Treatment Access Campaign, and Health Gap) responded to the Attaran article with a joint statement (2001) claiming that several combinations of AIDS treatments were not adequately included in the published survey. Their 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 $3,000 and a rel-*

atively 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. This is particularly true for those products with post-1996 patents, such as efavirenz or nelfinavir, that currently lack a significant generic market outside of Africa.

In 2000 and 2001, transnational corporations reduced the price on a number of Aids drugs sold in Africa. Many health advocates argued these price cuts were motivated by earlier offers from generic companies, including Cipla and Aurobindo. Oxfam (2001) noted that even with the new drug company price cuts, AIDS triple combination therapy would cost African governments $1,000 per person annually, still more than three times higher than the cheapest offer from the Indian generic company Aurobindo.

Brazil

Brazil is often held up as an example of how developing countries can both respect patent law and expand access to new drugs. In 1996, to comply with international agreements, Brazil passed strong patent laws, steps highly 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 per cent of the adult population, were living with HIV. Since 1996, the government has been officially committed to provide AIDS treatment to all citizens and 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.

Local manufacture of generic AIDS drugs in Brazil reduced their prices by 72.5 per cent from 1996-2000. Their use avoided 146,000 hospitalizations and saved $422 million from 1997-1999.

The Brazilian Ministry of Health (2001) estimates that, because of expanded availability of ARVs, 146,000 hospitalizations were avoided from 1997-1999, saving $422 million. It claims that price reductions in AIDS drugs are due to the establishment of national manufacturing labs and effective negotiation of prices with companies. AIDS drugs made in Brazil fell 72.5 per cent in price from

1996 to 2000. Imported drugs fell 9.6 per cent during the same period.

Brazil's AIDS drugs budget shows the price differentials between off-patent domestically manufactured therapies and imported on-patent drugs. AIDS therapies produced in the country represent 47 per cent of ARVs used, but consume only 19 per cent of total AIDS drug spending. AIDS drugs purchased from transnational corporations represent 53 per cent of ARVs used, and consume 81 per cent of expenditures (Ministry of Health, 2001). In its analysis of drug prices, MSF (2000) 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 1,000 people with HIV/AIDS as it does for the Thai government to treat 552 people.

Brazil has effectively used price controls and threats of compulsory licensing as bargaining chips to negotiate with transnationals for lower AIDS drug prices. A 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 successful negotiation was the agreement with the pharmaceutical company Roche on a 40 per cent price cut for the ARV nelfinavir after Brazil threatened to break the patent and produce the drug itself. "Just the credible threat of generic competition is enough to get manufacturers to lower their prices" (*New York Times*, January 28, 2001).

Toward balanced policies

Current literature and lessons from India, South Africa and Brazil demonstrate that the presence or absence of patent protection is one of several important factors that have affected drug prices and access, as well as development of domestic industry. 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 per cent of the global pharmaceutical market, it is difficult to see how lower prices in this market significantly impact transnationals' profits. The real fear is that lower prices will undercut acceptance of higher prices elsewhere, and could lead to a flowback of cheap drugs to richer markets. Political and legal actions are needed to address both concerns.

Developing countries have a clear stake in product development for diseases

affecting their populations. By themselves, stronger patents in developing countries are unlikely to provide adequate incentives for the private sector to significantly expand research on treatment and vaccines for tropical diseases. Yet patents may well be an 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 developing countries, the examples from the three countries above 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 this case, the 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 transnationals. 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 developing countries with transnationals. However, the price that the company charges to a country distributor is often a fraction of the final price charged to the patient.

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 can play an important role here, particularly for essential medicines, and there is evidence that interventions will be needed to encourage greater use of tiered pricing.

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 policymakers. Yet there is little justice in demanding that populations in developing countries forgo 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 developing countries increasingly demand funding and

There is little justice in demanding that developing countries forgo access to today's drugs so as to promote future R&D on products that would also be inaccessible to many in these countries.

policy options to increase health care access, and policymakers 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.

CONCLUSIONS

The R&D and access issues discussed above are among the broad set of factors affecting health in the developing world. A critical challenge, well recognized by all involved, is to find a balance between IPR rules that allow for affordable access to new, on-patent technologies, while continuing to protect companies and other institutions that have invested in a risky and lengthy research effort and demand a return on that investment. Steps to cut prices for existing products now may jeopardize incentives for companies to develop new products for the future. And patients suffering from one of the neglected diseases can only hope for new products, as effective treatments currently do not exist.

Only a few of the priority "diseases of the poor" fall into the category of diseases with truly global markets and where differential pricing (or the threat of compulsory licenses) are part of the access debate. The most important example is HIV.

For diseases which predominate in developing countries, and for which no effective treatments currently exist, affordability and access are legitimate concerns, but for now the primary issue is how to realize new products through R&D. Creative ways to attain the "dynamic innovative" opportunities of IPR are needed. Regardless of the incentive package, it must include explicit conditions to help ensure that any approved product of the research be affordable to the patients in need.

TRIPS and other international trade agreements are not ultimately sustainable unless greater equity in the delivery of health care technology is achieved.

Governments in both the north and the south working to design effective IPR policies for global health must consider the short and longer-term impacts of IPR policies. IPR policies are critical in shaping the path of domestic industry development. Ironically, governments of developing countries may feel pressured to choose between an IPR policy that could help promote domestic-based research industries and investment (and arguably long-term economic development) and one that some argue will help improve immediate access to products now, and thus the health of their population. Looking closely at the role IPR plays in the global health debates, policymakers need clearly identified goals, an understanding of what motivates the necessary partici-

pants, and a willingness to accept that IPR is only one of a necessary package of instruments they need to consider.

REFERENCES

- Attaran, A. and L. Gillespie-White (2001). "Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?" *Journal of the American Medical Association*, vol. 286, No. 15
- Borrell, J. and J. Watal. "Access to HIV/AIDS Drugs in Developing Countries: Assessing the Impact of Patents" (preliminary version).
- Chaudhry, P.E and M.G Walsh (1995) "Intellectual Property Rights: Changing Levels of Protection under GATT, NAFTA, and EU", *Columbia Journal of World Business*, 30 (2): 80-92.
- Consumer Project on Technology, Essential Action, Oxfam, Treatment Access Campaign, Health Gap (2001). "Comment on the Attaran/Gillespie-White and PhRMA Surveys of Patents on Antiretroviral Drugs in Africa." www.cptech.org/ip/health/africa/dopatents-matterinafrica.html
- DeSouza, N.J. "Overview of the Indian Pharmaceutical Industry: Imperatives for the Next Millennium." www.gbhap-us.com/magazines/pharmanews/5-6-article.htm
- Europe Economics (2001). "Medicines Access and Innovation in Low Income Countries", draft report to IFPMA, London. www.europe-economics.com
- Fink, C. "How Stronger Patent Protection in India Might Affect the Behavior of Transnational Pharmaceutical Industries." Washington, D.C.: Development Research Group, The World Bank.
- Geffen, N. (2001). "Pharmaceutical Patents, Human Rights and the HIV/AIDS Epidemic." Presentation to the World Business Council for Sustainable Development Project on Innovation and Technology.
- Gray, A. and T. Matesebula (2000). "Drug Pricing," in *South African Health Review*. Health Systems Trust, South Africa. http://www.hst.org.za/sahr/2000.
- International Federation of Pharmaceutical Manufacturer Associations (2000). "TRIPS, Pharmaceuticals, and Developing Countries: Implications for Health Care Access, Drug Quality, and Drug Development."
- Kettler, H. (2000). *Narrowing the gap between provision and need for medicines in developing countries*, Office of Health Economics, London.
- Kettler, H. and S. Casper (2000). *The Road to Sustainability in the UK and German Biotechnology Industries*, Office of Health Economics, London.
- Kettler, H. and R. Modi (2001). "Building local research and development capacity for the prevention and cure of neglected diseases: the case of India", *Bulletin of the World Health Organization*, Vol. 79, No. 8, 742-747.
- Kettler, H. and A. Towse (2001). "Public Private Partnerships — A Report for Working Group 2 of the WHO Commission for Macroeconomics and Health", unpublished draft.
- Lacetera N. and Orsenigo L. (2001). "Political regimes, technological regimes and innovation in the evolution of the pharmaceutical industry in the USA and in Europe", paper presented at Conference on Evolutionary Economics, Johns Hopkins University; Baltimore, MD, USA, 30–31 March 2001.

- Lanjouw, J. (1998). "The Introduction of Pharmaceutical Product Patents in India: Heartless Exploitation of the Poor and Suffering?", NBER Working Paper No. 6366.
- Lanjouw, J. and I. Cockburn (2000). "Do Patents Matter?: Empirical Evidence After Gatt", NBER Working Paper 7495.
- Mansfield E. (1995). *Intellectual property protection, direct investment and technology transfer — Germany, Japan, and the United States*. Washington, DC, World Bank, (International Finance Corporation Discussion Paper No. 27).
- Ministry of Health of Brazil (2001). "AIDS Drugs Policy." www.aids.gov.br/assistencia/aidsdrugspolicy.htm
- Mossinghoff, G. J. and T. Bombelles (1996). "The Importance of IP Protection to the American Research-intensive Pharmaceutical Industry", *Columbia Journal of World Business*, 31 (1): 38-49.
- Oxfam (2001). "WTO Patent Rules and Access to Medecines: the Pressure Mounts. www.oxfam.org.uk/policy/papers/wtorules.htm.
- Perez-Casas, C., *et al.* (2000). "Setting Objectives: Is There a Political Will?" HIV/AIDS Medicines Pricing Report. Médecins sans Frontières.
- Perez-Casas, C., *et al.* (2001). "Accessing ARVs: Untangling the Web of Price Reductions for Developing Countries." Campaign for Access to Essential Medicines, Medecins Sans Frontiers.
- UNAIDS (Joint United Nations Program on HIV/AIDS). "AIDS Epidemic Update," December 2000.
- Watal, J. (2000). *Pharmaceutical Patents, Prices and Welfare Losses: Policy Options for India under the WTO TRIPS Agreement*. Oxford: Blackwell Publishers.
- WHO-IFPMA (2001). "Priority infectious diseases requiring additional R&D", April draft.