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BIO-PHARMACEUTICALS AND HEALTH

INTRODUCTION

The adoption of the agreement on trade-related aspects of intellectual property rights (TRIPs) by the World Trade Organization (WTO) on 1 January 1995 was a major step in the pharmaceutical industry's drive towards global patent rights. Since then, the goal of uniform and globally enforceable patent rights has given rise to numerous conflicts and to new initiatives, as efforts are made to bring the potential that patents offer as a stimulus to health-related research into line with the ability of those in developing countries to take advantage of these opportunities. The papers in this Technology Policy Brief discuss some of the controversies, what has been learned about the needs of developing countries vis-à-vis TRIPS and some ways that have emerged to deal with them.

S. Queiroz (page 2) analyses the Brazilian/American patent legislation dispute at the WTO and asks how the strategic retreat by the stronger opponent can be explained. Non-governmental organisations (NGOs) played a significant supporting role in mobilising public awareness, but this would not have happened if Brazil's policies to build the industrial and technological capabilities needed to produce anti-retroviral drugs at low cost and distribute these to AIDS patients had not been successful. This lent credibility to the introduction of a "working obligation" clause into Brazil's patent legislation, which was at the root of the controversy.

Compulsory licensing is also central to the process of aligning existing patent legislation in India with the TRIPS agreement. In his paper, *S. Chaudhuri* (page 3) notes that there is enough flexibility in the agreement regarding the grounds upon which a compulsory license may be granted, but the country itself must develop administrative procedures that do not turn the new rules into new restrictions.

Whether genes should be patented at all, *C. Correa* (page 5) argues, needs to be questioned, especially when it comes to gene-based research tools. Flexibility will be needed to avoid jeopardizing the success of international initiatives that are designed to strengthen developing country participation in bio-pharmaceutical research on neglected diseases and make use of such tools.

Access to current drug therapies in the developing world depends upon an adequate healthcare system to deliver the required drugs and their availability at affordable prices. *A. Arundel* (page 8) explores the pharmaceutical industry and NGO positions on these issues, notably the industry's preference for philanthropic solutions to these problems and the NGO preference for a competitive drug market to drive prices down. To stimulate additional research on neglected diseases, the paper suggests that we look towards new international initiatives that bring together stakeholders – such as the World Health Organisation (WHO), large pharmaceutical firms, local firms and research institutions – to develop such drugs.

K. ten Kate and *S. Laird* (page 10) relate this theme to the Convention on Biological Diversity and its Bonn Guidelines on Access and Benefit-Sharing. These, they argue, provide the basis for building partnerships that enable countries to use their untapped potential for research on genetic resources in order to produce low-cost botanical medicines directed at primary healthcare.

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BRAZILIAN/AMERICAN DISPUTE OVER PATENTS AT THE WTO

On 8 January 2001 the US asked the WTO to constitute a dispute panel in order to review Brazil's patent legislation. The establishment of the panel on 16 February made Brazil the first country to be questioned in the WTO for violating the TRIPS agreement since the beginning of 2000, the deadline for the adaptation of national legislations to meet the TRIPS requirements. A few months later, on 25 June, the US withdrew its complaint, ending the conflict.

What was at stake in this relatively short-lived dispute? What were the motivations on both sides? How might the unexpected outcome of this diplomatic struggle, in which the stronger opponent ultimately opted for a strategic retreat, be explained? To answer these questions a bit of history is needed. During the 1990s the Brazilian Ministry of Health put in place a successful anti-AIDS program which has, as an important component, the free distribution of a "cocktail" of drugs to patients. As part of its effort to lower the price of drugs, the government acted on two fronts. The first was investment in building technological and industrial capabilities – mainly in Far-Manguinhos, a division of the Oswaldo Cruz Foundation, the Rio de Janeiro-based institution with a long tradition of research in the health sector. This was required in order to be able to produce most anti-AIDS drugs. The second was the passing of legislation, on October 1999, which would permit the government to grant a compulsory license if the owner of a pharmaceutical patent did not begin to manufacture the drug locally after three years. This is known as the "working obligation" clause. The aim was very clear: the Brazilian government was seeking to increase its bargaining power in its price negotiations with large pharmaceutical companies. Eventually Brazil succeeded and the treatment of each AIDS patient now costs US $4,000 per year, in comparison with US $15,000 in the US.

The legal move, however, triggered a response from the American government. After several months of unfruitful negotiations between US trade officials and Brazilian diplomats, the Americans decided to consummate their threat and asked for a panel at the WTO. In Washington, the "working obligation" in Brazil's legislation was considered a violation of the TRIPS agreement as it discriminates between imports and local production and the Americans sought its elimination. In Brasilia, the section was seen as entirely consistent with international patent law. Moreover, Articles 204 and 209 of the American patent law made similar demands on firms in terms of "working the patent" locally. Brazil thus announced its intention to counter the American initiative with one of its own. This was the first time a developing country challenged the US over a patent issue at the WTO.

Supporting the American position was the powerful International Federation of Pharmaceutical Manufacturers Associations (IFPMA), which argued that the strengthening of patent laws was essential to assure the research commitments of pharmaceutical companies that ultimately would lead to the discovery of new products. Behind this, however, was the concern of drug producers that Brazil would create a precedent for other countries. The problem was not the developing countries, which accounted for only a small share of their profits, but rather their main markets, as consumers in Europe and in the US began to question the high prices of drugs.

NGOs, such as Oxfam, Médicins Sans Frontières and The Third World Network, gave vigorous support to Brazil's position in the debate. Refusing to accept the US attempt to treat intellectual property rights (IPRs) and public health policy as two separate issues, NGOs helped to mobilise public opinion in favour of a country that had been successful in its AIDS campaign and whose success was now threatened by the position of the American government and a number of large pharmaceutical companies.

As public awareness increased, there was a risk that the whole system of IPRs might unravel. The growing isolation of the US became apparent when on 23 April the UN Human Rights Commission approved – with 52 votes in favour, none against and one abstention (from the US) – a resolution introduced by Brazil that made specific reference to access to drugs at reasonable prices in situations of pandemic diseases like AIDS.

As a result of the mounting pressures and the failure of the two countries to agree on the names of three judges, the US chose not to exercise its right to request the WTO to proceed with the

selection of a panel. It thus abandoned its initiative. Reciprocally, Brazil gave up its intention to question the American patent code and offered to consult the US prior to the application of a compulsory license for any patent owned by an American firm.

What lessons can be learned from this episode, particularly for developing countries?

Clearly, the role played by the NGOs in mobilising public opinion was very significant. However, it is unlikely that this would have occurred if the Brazilian anti-AIDS program had not brought down the cost of treatment and triggered the legal measures that led to this international conflict. In this context, of critical importance were the Brazilian policies that strengthened domestic industrial and technological capabilities, contributed to its successful anti-AIDS programme and made credible its use of a compulsory license. Brazilian diplomacy was also a factor. The counter-attack directed at the US patent code, however ineffective it was, showed firmness and the intention to defend the needs of developing countries to put the health of their people first. Brazil also exercised a leadership role within the G-15* in defending the position of developing countries for a more flexible interpretation of the TRIPS agreement. The support garnered by this position, however, potentially put at risk some of the established pillars of the international patent system that the US had strongly supported.

Despite this outcome, it would be misleading to consider the strategic retreat of the US government as the end to conflicts over TRIPs. The pharmaceutical industry still has not fully understood how its uncompromising position undermines the effort of the developed nations to create a consensus on respect for IPRs – a position that Brazil shares.

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COMPULSORY LICENSING UNDER INDIA'S AMENDED PATENT ACT

In accordance with the TRIPS agreement, India is in the process of introducing product patents in pharmaceuticals. It is widely recognised that product patents tend to result in the creation of monopolies and hence high prices. One of the ways in which such adverse effects can be mitigated is through the grant of a compulsory licence to non-patentees. Compulsory licenses enable local firms to produce and sell the patented products. This note examines the extent to which India's Patent Act, as amended by the parliament in May 2002, takes advantage of all of the opportunities available under TRIPS to enable the granting of compulsory licenses.

Article 31 of the TRIPS agreement places no restrictions on the grounds upon which a compulsory licence may be granted. The Doha Declaration of November 2001 further affirmed that member countries have the right to grant compulsory licences and "the freedom to determine the grounds upon which such licenses are granted" (para 5(6)). Before a compulsory licence can be granted, however, certain conditions must be satisfied. These include:

- that authorization of such is considered on individual merits;
- that, except in cases of national emergency, extreme urgency or public non-commercial use, the proposed user will have made efforts over a reasonable period of time to secure a voluntary licence on reasonable commercial terms; and
- that the legal validity of the compulsory licence and the remuneration will be subject to judicial or other independent review.

As Jayashree Watal of the WTO and others have emphasized (Watal 2001), the procedure can be so specified that these conditions do not become restrictions.

Compulsory Licensing under Section 84

The general principles and the grounds for the grant of a compulsory licence in the amended Act sound very impressive. Under Section 84, an application for a compulsory licence can be made by any person three years after the sealing of the patent

on the grounds that the "reasonable requirements of the public" have not been satisfied, that the product is not available at a "reasonably affordable price", or that the patented invention is "not worked in the territory of India". The main problem is the interpretation of these terms and the procedure specified.

The procedure is open-ended without any time limit imposed at any stage. A copy of the compulsory licence application will have to be advertised in the official gazette. The patentee or any other person may oppose the application and will have to be given adequate time for doing so. A decision by the Controller of Patents will be made only after both parties have had the opportunity to be heard and the decision can be appealed. Such appeals will be considered by an Appellate Board before a compulsory licence is ultimately granted. Whether a patent is worked in India or not can perhaps be objectively assessed. But the grounds of "reasonable requirements of the public" or "reasonably affordable price" can be easily challenged by patentees. Arguments, counter-arguments and subsequent appeals, where these take place, may result in a process that takes years before a compulsory licence is granted, if at all. The huge expense involved in fighting the large pharmaceutical companies that hold the patents may dissuade non-patentees from applying for licences in the first place. These are not mere theoretical possibilities. This is precisely what happened in India under the Patents Act of 1911, which was in force until replaced by the Patents Act, 1970. The Act of 1911, which recognised product patents, also had elaborate provisions for compulsory licensing, as in the amended Act. Strange as it may appear, only five applications for compulsory licences were made under the Act of 1911, of which two were withdrawn, one was rejected and only two licences were granted (Chaudhuri 1994).

Compulsory Licensing under Section 92

In the case of an application for a compulsory licence made under Section 92, the procedure outlined above does not have to be followed by the Controller, if the emergency, extreme urgency or public non-commercial use is due to a public health crisis, including those relating to AIDS, tuberculosis, malaria, etc. This is a potentially important provision. But even here, any decision made by the Controller can be challenged and referred to the Appellate Board. Thus the benefits of this provision will very much depend on how it is used in actual practice.

What can still be done

If the bias in the Patents Act, 1970, which did not grant product patents in pharmaceuticals, tended to favour non-patentees, the bias in the amended Act is clearly in favour of the patentees. The wording of the grounds for a compulsory licence is not amenable to easy interpretation and is not operationally useful. The procedure is cumbersome and time consuming. In its attempt to be fair to the patentees and not allow others to use the patent except in very special cases, India has provided more extensive protection to patentees than is required by TRIPS. If the provisions of compulsory licencing are to be used to stimulate competition and check prices, then the presence of efficient non-patentees in the local market producing drugs at reasonable prices is needed. Hence there is enough justification for carrying out some amendments to tackle the bias against the non-patentees. But this may take time. What can be done immediately is to frame the "rules" for administrating the amended Act in such a way that granting a compulsory licence becomes easier and faster.

While framing the rules, a number of administrative steps might therefore be considered:

- Rather than adopting a case-by-case approach, the central government may notify the list of medicines eligible for a compulsory licence in public health crises. The list should be prepared in consultation with health experts and may be revised from time to time. The inclusion of any drug in the list would not be a ground for opposition and appeal. There is nothing in the TRIPS Agreement or the amended Act to suggest that it should be so.
- Following the examples of Japan and Germany, guidelines may be issued for the royalty to be paid to patent holders in the case of a compulsory licence.
- For any drug in the public health list, the Controller may, immediately after receiving an application, grant a compulsory licence, fixing a royalty rate using the royalty guidelines. Any opposition or appeal against the grant of such a compulsory licence would then only relate to the royalty rate fixed. While this is

being adjudicated, the non-patentee could begin to use the patent on the basis of an undertaking that the royalty rate finally decided will be paid in full. The case-by-case consideration of the royalty rates payable and the opportunity to oppose and appeal against the royalty rate fixed will satisfy the Article 31 clauses (a), (i) and (j) relating to consideration of individual merits and review of the compulsory licence decision.

- For other drugs, a simple time-bound procedure may be formulated for considering and deciding upon compulsory licence applications. The maximum time permissible at each stage may be specified. The royalty guidelines may be used to reduce uncertainty and speed-up decisions.
- The functioning of the Appellate Board may not be a time-consuming judicial one. Here too a simple time-bound administrative procedure may be formulated.

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PATENTS IN GENOMICS AND BIO-PHARMACEUTICALS

The use of genes for the development of new products (such as bio-pharmaceutical and transgenic seeds) posed an unprecedented challenge to the patent system in the 1980s. Patent offices and courts were called to decide on delicate legal and ethical issues concerning the granting of exclusive rights on DNA sequences, the building blocks of life. At the beginning of this process the main issues related to the patentability of processes and end products. With the development of genomics in the 1990s the problem became more complex: rights were claimed (and patents granted in some countries) over basic biomedical research tools, such as expressed sequence tags (ESTs), i.e. short sequences that are parts of genes being expressed in particular circumstances, and single nucleotide polymorphisms (SNPs), or receptors that lack therapeutic properties.

Policy and law makers had to face several thorny issues to address the demands of patent protection both by industry and academy. Can natural substances such as genes be patented, and if patentable, what should be the scope of protection? Is the identification of the function of a gene an invention or a pure scientific discovery? If the former, can patents be granted on genes even when the "inventor" has only unveiled one of its multiple functions? Do "isolation" (where DNA is synthesized/ copied and usually purified) and "purification" (where DNA is merely physically removed and then altered) amount to a patentable invention? (Warren-Jones 2001, 84) From a research perspective, can patents be granted on tools for research with no direct industrial application? More fundamentally, should the patent system protect investments rather than inventions? Should it provide rights for excluding anyone from using information in the gene sequences for research?

After considerable controversy and hesitation, the patentability of gene-based inventions has been accepted in most countries, though treated differently under different patent law traditions. In the US, for instance, an isolated or purified form of a natural product is patentable when a use is disclosed.[1] (Grubb 1999, 213) Under US law a gene is considered a chemical entity, and patentable as such. By February 2001 there were patent applications in

the US covering 175,624 human gene sequences (Ho 2002,15). The European Directive on Biotechnological Inventions (98/44), essentially declaratory of long-standing law throughout much of Europe, established that "biological material" and substances isolated from nature are patentable.[2] Biotechnological inventions based on recombinant DNA can normally be protected under product-by-process claims. (Warren-Jones 2001, 80)

A similar approach has been followed in many other countries, including developing countries. There are some exceptions, however. The Brazilian patent law (1996), for instance, stipulates that no patents shall be granted with respect to living beings or "biological materials found in nature", even if isolated, including the "genome or germplasm" of any living being.

Patenting in bio-pharmaceuticals has been important in the last 20 years, despite the fact that the discovery of the DNA sequence today is routinely done with automatic sequencing devices, and no inventive step can be claimed in that process (Barton 2000, 805). Patent law responded to this problem in some countries by lowering the patentability requirements and introducing convenient legal fictions. In the US, for example, the doctrine established by a court in *re Deuel* (1995) paved the way for the patenting of DNA even when encoding known proteins, on the grounds that – due to the degeneracy of the genetic code – their structure could not have been predicted.[3] In addition, the US patent law was amended in 1995 (Public Law 104-41) in order to allow the patentability of non-patentable "biotechnological processes" using or resulting in a composition of matter that is novel and nonobvious. (Merges *et al.* 1997, 207.)

One of the major problems – beyond ethical and other legal considerations – with the patenting of genes is that since they perform different functions, the exploitation of all such functions, even if unknown to the patent owner, would be subject to the pantentee's authorisation. Thus, gene patents can grant rights to veto (or to charge license fees for) a vast number of potential downstream products, including applications that were not known when the patent was filed. Since the product obtained is equivalent to what exists in nature, inventing around is not possible. Control over the genetic information thus permits an effective monopoly in the final product market with obvious implications on pricing and access to health care. For this reason, many advocate today in Europe a more restrictive approach in drafting claims with regard to genes, so as to ensure that the scope of the patent is limited to the specific claimed use. Third parties which make use of the protected DNA sequence for any purpose other than the one claimed would not violate the patent.[4]

The patenting of DNA sequences, generally also covering the vectors used to insert them into cloning organisms, the cloning organisms themselves and the obtained proteins, has given rise to significant legal battles in the area of pharmaceuticals, such as in the case of interferon and erythropoietin EPO). Though these battles have proliferated in developed countries, they have also reached the developing world. For instance, although Genetics Institute was defeated by Amgen in the US and Europe after long litigation on the rights over the gene coding for EPO, the former has sued several local companies in Latin America, based on a process patent for the production of EPO.

The problem is further complicated when gene patents essentially cover research tools, such as ESTs used as a probe to identify an entire gene, or SNPs used to identify particular genetic conditions. For instance, there have been a number of patents covering the BRCA1 and BRCA2 mutations predisposing to breast cancer, leading to the monopolisation – deemed by many unacceptable on ethical and public health grounds – of testing based on such information. Patents can also be obtained on other tools, such as a receptor (a molecule on the surface of a cell) as a target for a drug, or a portion of a protein that triggers a receptor or an immune response.

Patents on research tools can significantly affect biomedical research. Access to patented research tools may only be obtained by approaching the patent holder directly, negotiating for a license and agreeing on a fee payment.[5] Potential users may find that the patent is not available for license, or that it has been exclusively licensed to somebody else. If licenses were available, the patent holder may seek "reach-through" royalties, that is, payments on sales of all commercial products developed with the use of the research tool, even if these products did not incorporate the patented invention. If the research tool could be incorporated into the product, the patent owner may request exclusive rights inthe product itself. Another problem is that potential users would have to disclose to possible competitors the directions of their research.

The situation is further complicated where different patents have been granted to different right-holders in relation to the same tool. In this case, it is necessary to obtain multiple licenses with the resulting escalation in time and effort needed for negotiation, as well as of license fees. (Heller and Eisenberg 1998, 698-699.)

The limitations imposed on research by the patenting of research tools is epitomized by the patent on the merozoite surface protein 1 ("MSP-1") of plasmodium, which provides one of the best candidates for the development of a malaria vaccine. The patent landscape of MSP-1 includes 39 patent families describing the antigen, processing fragments, constructs, production, delivery, etc. belonging to different title-holders. This complex landscape poses a serious challenge to the success of the Malaria Vaccine Initiative, as it requires the lengthy negotiation of multiple licenses, at an unpredictable cost.

In sum, though patents may encourage research and the development of new, inventive products and processes – at the price of restricting the use of the information so created – they may provide little service to society when they confer rights over materials existing in nature, held patentable only on the basis of artful legal fictions and a relaxation of patentability requirements. In specific, the patenting of research tools may slow down, if not block, the progress of biomedical research, particularly in public research institutions and in developing countries.

Developing countries can use the flexibility allowed by the TRIPS Agreement (which does not define what an "invention" is) to establish their own rules on the patentability of genetic materials. If granted, the scope of gene patents should be limited to the specific disclosed use. Patents should not be granted in the absence of demonstrable industrial applicability, thus excluding mere research tools. The flexibility to decide on these matters should not be limited by attempts to further harmonize patent law, as currently proposed in the framework of the WIPO Standing Committee on the Law of Patents.

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Endnotes

1 If a patent application discloses only nucleic acid molecular structures for a newly discovered gene, the claimed invention is not patentable. But when the inventor also discloses how to use the purified gene isolated from its natural state, the application satisfies the "utility" requirement *(USPTO: Utility Examination Guidelines, effective as of 5 January 2001).* Before issuance of these Guidelines, it was possible to get a patent on general claims such as using the sequence as a probe. These Guidelines are likely to reduce, but not to prevent, the patenting of ESTs and SNPs.

2 See, e.g., Grubb 1999, 213. Current EPO Guidelines specify that any natural substance which is isolated for the first time and which has 'no previously recognized existence', is patentable. In 1995 the EPO Opposition Division found, in the *Hormone Relaxin* case, that the isolation (synthesis and purification) of human H2-relaxin could be distinguished from relaxin as it is produced naturally in the body (Warren-Jones 2001, 85).

3 See, e.g., Baldock 1999, 21. However, the principle set out in *re Duel* does not apply in Europe. Gene sequences which code for a known protein are generally regarded as *prima facie* obvious, although such was not the case in the earliest days of molecular biology.

4 Jacobs and van Overwalle, 2001. Another option would be the use of compulsory licenses to remedy the possible negative effects on subsequent research that may result from the extension of patentability to simply isolated materials (Sena 1999, 736-738).

5 However, patents are unlikely to interfere significantly with access to research tools where they are readily available on the market at a reasonable price from a patent holder or licensee (such as in the case of some chemical reagents).

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PHARMACEUTICAL ACCESS AND RESEARCH INCENTIVES: STAYING TRUE TO TRIPS?

In searching for a solution to the continued struggle over TRIPs and the Doha Declaration, two problems need to be solved: first, how to provide poor countries with an adequate supply of current drugs, and second, how to ensure that new drugs are developed for the treatment of "neglected" tropical diseases that lack effective low-cost drug therapies. These include malaria, tuberculosis, sleeping sickness, Chagas disease, and leishmaniasis. There are two opposing perspectives on these two issues: the solutions proffered by the pharmaceutical industry and the approach taken by NGOs, such as Health Action International, Médicins Sans Frontières, Consumer Project on Technology and Oxfam. In resolving these issues, international organisations such as the WHO have become central.

Access to current drugs

Access to current drug therapies in developing countries depends on an adequate health infrastructure for delivering drugs and the cost of these drugs. Both NGOs and the industry agree on these two requirements, but they take different positions on their relative importance. The industry has argued, in respect to HIV/AIDS drugs in Sub-Saharan Africa, that prices and patents are not the problem. The IFPMA has stated that even free drugs would not go very far in solving the problem of HIV/AIDS due to poor health infrastructure. Similarly, the Pharmaceutical Research and Manufacturers of America (PhRMA) stressed that the "real barriers to access to medicines in developing countries" is not TRIPs but "poverty, too few trained doctors and adequately equipped facilities, high tariffs on medicines in many developing countries, the need for more developed country support, and political will in developing and developed countries alike".[1]

Clearly it is necessary to improve the health infrastructure in developing countries. Although largely a task for governments and international organisations, several pharmaceutical companies, such as Merck, Pfizer, and Bristol Myers Squibb, support HIV/AIDS education and clinics as part of their philanthropy programmes. These programs can also benefit the donors by developing an infrastructure for clinical trials of new drugs and vaccines.

Even where health care systems are adequate, affordable prices and the supply of drugs to meet the needs of developing countries remain at issue. Industry opposes the two methods to deal with these problems provided by TRIPs for national emergencies and which the Doha Declaration reconfirms: parallel imports and compulsory licensing. Either or both methods can be used by governments to lower drug costs and widen the supplier range. The industry argument against these two methods is that they will reduce the profit incentive for research into diseases that are widespread in developing countries, risk the introduction of substandard and counterfeit medicines, and somehow fail to improve access to essential drug care. Incomes in developing countries, however, are too low to provide much of an incentive for research into drugs that meet their health needs. The higher cost of patented drugs as compared with generics reduces access to essential drug care rather than expanding it. Why then does the industry argue against parallel inputs and compulsory licensing?

Four industry concerns are important here:

1) setting precedents that could spread to middle income or even high income countries (particularly for parallel imports);
2) generics that might reveal the actual cost of drug manufacture, which could create problems in their domestic markets;
3) a preference for international aid organisations to pay for more expensive proprietary drugs; and
4) lower market growth for proprietary drugs in developing countries with rapidly growing incomes.

The industry thus provides two other solutions to drug access that would maintain TRIPs without resorting to finding "loopholes". The first consists of voluntary price reductions and, under some conditions, to offer drugs at not-for-profit prices. Since 15 April 2001 several pharmaceutical firms, including Pharmacia, Bristol Myers Squibb, Merck, Roche, Boehringer Ingelheim, and Abbot, have agreed to offer HIV/AIDS drugs to developing countries at prices far below the US $10,000-$15,000 per year charged in developed countries. GlaxoSmithKline (GSK) offers all its anti-retrovirals (ARVs) and anti-malarial drugs at not-for-profit prices to the least developed countries (LDCs) in Africa, such as Chad and Malawi, and at reduced prices for developing countries, including South Africa, Zimbabwe and Botswana.(GSK Annual Review. 2001) In April 2001, GSK charged US $730 per year for HIV/AIDS combination therapy in South

Africa for public patients and double that for private patients. Parallel imports would make such special contractual arrangements unnecessary.

Second, the industry donates some drugs for free for HIV/AIDS and other tropical diseases. The IFPMA estimates that industry donations to developing countries run at roughly US$ 500 million per year, which is equivalent to 0.14 per cent of global pharmaceutical sales.[2] Pfizer for example donates diflucan for opportunistic AIDS infections, Novartis donates multi-drug therapy for leprosy and GSK provides albendazole for lymphatic filariasis. Other large pharmaceutical firms have also "adopted" a tropical disease and have run programs to completely eliminate or control these diseases over a reasonable time frame. Aventis has a program to combat tuberculosis in South Africa, Pfizer runs a global drug donation program for Zithromax to treat trachoma, Merck donates Mectizan for river blindness, and Roche has a program to combat vitamin A deficiency.

These and other industry programs are welcomed by NGOs and the governments of developing countries. However, the industry offer of philanthropic donations and discriminatory pricing leaves discretionary control over supply and drug prices in their hands. The NGOs would prefer to have a competitive drug market to drive prices as low as possible. Both parallel imports and compulsory licensing have the potential to do this.

Generic firms offer ARV combination therapies at some of the lowest prices available. For example, Far-Manguinhos of Brazil offers a combination therapy of AZT, 3TC and Nivirapine at US$ 1.55 per day (US$ 565.75 per year). Cipla of India has offered to provide combination therapy for US$ 350 per year, although there are doubts about its ability to supply drugs at this price. Both the NGOs and the industry would likely agree that even the lowest cost generic ARVs are still too expensive for the majority of HIV/AIDS patients in Africa.

In addition to price, two other problems face generic production of ARVs or other drugs. One concerns quality guarantees. The pharmaceutical industry argues that generics are of poorer quality and may lack bio-equivalence. The WHO has acted to solve this problem by testing the quality of generic drugs. On 21 March 2002, the WHO released the first list of manufacturers of safe generic AIDS drugs.

Another issue that has not been resolved concerns access to drugs by developing countries that lack the capability to make drugs. Under TRIPs, countries can only offer compulsory licenses to domestic firms. Several countries, including the US, blocked a solution to this problem at Doha that would have permitted countries with generic manufacturers to export generic drugs. In the absence of imported generics, developing countries are obliged to rely on price reductions offered by the main pharmaceutical firms. A decision on exports of generics is expected by the end of 2002 and is likely to be hotly contested. In the meantime, large pharmaceutical firms have already signed agreements with Senegal, Uganda, Rwanda, Ivory Coast and Cameroun to provide steeply discounted HIV/AIDS drugs.

Developing New Drugs

The second problem is a lack of drugs to treat many diseases that are widespread in developing countries but rare in the developed world. These are referred to as "neglected diseases". Between 13 and 16 new drugs have been developed for tropical diseases in the last 25 years, compared to 1,380 drugs for diseases that also occur in developed countries (Pécoul *et al.* 2001). A study of patents and citations for tropical diseases between the 1970s and the mid-1990s found that these never exceeded more than 0.5 per cent of all pharmaceutical patents. (Lanjouw and Cockburn 2001).

One of the promises of TRIPs is that it would provide a stronger incentive for pharmaceutical firms to invest in research on drugs to treat neglected diseases. The steadfast position of the industry is that any dilution of TRIPs will substantially reduce these incentives. This position has also been articulated forcefully by the US, Australia, Canada, Japan and Switzerland.

The NGOs are in partial agreement, noting that stronger patent protection in developing countries would have benefits if it spurred large pharmaceutical firms to develop drugs for neglected diseases at a reasonable cost, and if it provided incentives for indigenous generic pharmaceutical firms, such as Cipla in India, to develop innovative drugs for both the domestic market and for export.

Lanjouw (2001) has proposed a simple change to patent rules within the Organisation for Economic Co-operation and Development (OECD) that might

resolve some of the problems noted above. Firms would be able to choose to patent drugs in either developed or developing countries, but not in both. Drugs for diseases that are prevalent in the developed world, such as HIV/AIDS, cancer, and cardiovascular diseases, would rarely if ever be patented in developing countries, leaving them open to generics. Even if this solution were to win the support of developed countries, it does not provide new incentives to overcome the lack of attention by large pharmaceutical firms to doing research on neglected diseases in developing countries.

NGOs thus support some form of international funding for not-for-profit research into drugs for neglected diseases, plus programs to develop the research and development capability of developing countries. The likelihood of success in these initiatives would increase if major pharmaceutical firms had incentives to participate, bringing with them their expertise in drug screening, genomics and biotechnology. New initiatives, such as the Drugs for Neglected Disease Initiative – launched by the Paris-based NGO Médecins Sans Frontières with the backing of the Pasteur Institute of France, Brazil's Oswaldo Cruz Institute, the Indian Council of Medical Research, the Science University of Malaysia and the WHO with support from GSK – may provide a model of how this could be done.

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Endnotes

1 PhRMA. 14 November 2001. WTO Doha Declaration reaffirms value of intellectual property protection. http://www.phrma.org/press/newsreleases/2001-11-14.310.phtml.

2 PhRMA. 14 November 2001. *op cit*. It is not clear from the press release if the total includes funding by partnership agencies such as the UN and governments.

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IMPLICATIONS OF THE CBD FOR HEALTH AND BIOPHARMA

Building local capacity for research on drugs based on natural products[1] provides a complementary avenue to meet local health care needs. Medicines derived from natural products still make a significant contribution to the medicine cabinet. Annual global sales of pharmaceuticals derived from genetic resources lie between US $75 and $150 billion and of botanical medicines between US $20 to $40 billion. (ten Kate and Laird 1999) A recent, striking example of a naturally-derived blockbuster drug is *Taxus baccata*, from which the anti-cancer drug taxol is manufactured. Marketed by Bristol-Myers Squibb, under the brand name Paclitaxel, worldwide sales from 1998 to the third quarter of 2001 were US $5.3 billion.[2]

A series of studies from the late 1990s confirm the continuing importance of biodiversity to health. Grifo *et al.* (1996) analysed the top 150 proprietary drugs from the US National Prescription Audit for the period January-September 1993. The audit is a compilation of virtually all prescriptions filled in the US during this time and the data are based on the number of times a prescription was filled. They found that 57 per cent of the prescriptions filled contained at least one major active compound "now or once derived or patterned after compounds from biological diversity". Cragg *et al.* (1997) analysed data on new drugs approved by either the US FDA or comparable entities in other countries between 1985-95, focusing on areas of cancer and infectious diseases. Of the 87 approved cancer drugs, 62 per cent are of natural origin or are modeled on natural product patents, and of the 299 anti-cancer drugs in pre-clinical or clinical development, the figure was 61 per cent. Newman and Laird (1999) demonstrated that the contribution of natural products to sales in the world's top pharmaceutical companies ranged from 10 to over 50 per cent.

Natural products may not maintain this market share in the future. During the 1990s, new technologies such as combinatorial chemistry, high-throughput screening and laboratories-on-a-chip provided unprecedented numbers of compounds to test and better ways to convert the resulting knowledge into synthetic molecules and those produced by biotechnology for testing. By comparison, natural products are often seen as too slow, costly

and problematic. Research dollars have been flowing out of natural products and into synthetic chemistry for rational drug design, combinatorial approaches and genetics that focus largely on human material. For example, GSK is increasingly focusing on drug discovery by screening synthetic chemical compounds, and states that it has limited interest in collecting and screening natural material. Collecting programs have drawn to an end and screening of existing collections is no longer conducted in-house, but by partners in countries such as Brazil and Singapore.[3]

However, natural products continue to hold key advantages: diversity and novelty resulting from years of evolution. Additionally, improvements in the technology associated with purifying and analysing compounds in complex mixtures have decreased the time involved in separating and analysing natural products. Although they may compete for research dollars, combinatorial chemistry and natural products are increasingly seen as complementary sources of new compounds for screening. (ten Kate and Laird 2000)

The Convention on Biological Diversity (CBD) and the regulation of access to genetic resources

The CBD and the Bonn Guidelines on Access and Benefit-Sharing adopted by the parties to the CBD in April 2002 provide the basis for building partnerships that enable countries to use the untapped potential for research on genetic resources to meet domestic needs. The CBD reflects a commitment by governments to facilitate access to genetic resources in return for a fair and equitable sharing of benefits such as technology transfer (CBD Article 1). It recognises the sovereign right of states over their biological resources and the consequent authority of national governments to determine access to genetic resources (Article 15(1)). Some 100 countries have introduced, or are developing, laws and other policy measures to regulate access to genetic resources so as to ensure prior informed consent and benefit-sharing.[4] These laws typically govern access by nationals and foreigners alike to genetic resources, biochemicals and associated traditional knowledge. They require the sharing of benefits, such as royalties, technology, joint research and information, on mutually-agreed terms.

In 1996, for example, following an exclusive licensing agreement granted by the US National Cancer Institute, the US pharmaceutical company Medichem Research entered into a joint venture, called Sarawak Medichem Pharmaceuticals (SMP), with the Sarawak State Government (Malaysia), where a sample containing a promising anti-AIDS compound had been collected. SMP has the right to file patents (to be owned jointly by Medichem Research and the Sarawak Government) on all subsequent innovations arising out of this work. The State Government of Sarawak is sharing the risks as well as the rewards of the joint venture by providing funding up to the completion of Phase I clinical development of one of the compounds. Another facet of the partnership is its flexibility: the benefit-sharing arrangements can be shaped over time to reflect the partners' respective contributions. Through this partnership Sarawak scientists have been trained in screening and isolation at the National Cancer Institute and Medichem Research and are to participate in clinical work. For example, a Malaysian PhD chemist is treasurer of the joint venture and worked in the SMP offices in Illinois, observing clinical trials and conducting pre-clinical studies and toxicological work on two back-up compounds.

Implications for developing countries

ABS partnerships can be a source of sustainable economic development, providing developing countries and their stakeholders with benefits such as improved capacity for conservation, new products and income to meet basic needs such as healthcare, as well as support for value-added scientific research. They can also enable developing countries to conduct research on neglected diseases while their foreign commercial partner focuses on the therapeutic areas of interest to the company. However, ABS embraces a complex, varied and unpredictable set of issues, linked to policy-making in many areas of government, as well as to domestic and global markets. The uses of genetic resources are diverse and the stakeholders involved range from multinational companies to indigenous communities, each with different priorities. In addition, demand for access to genetic resources fluctuates significantly and can be difficult to predict in the medium- to long-term. There are no simple ways to put a finite price on the value of genetic resources and associated knowledge, to assess how ABS policy can contribute to national sustainable development or to judge whether individual partnerships involving access are fair and equitable.

The most beneficial ABS partnerships are likely to be achieved when they are integrated into a national strategy on ABS, closely linked to national strategies

in related areas, such as health, science and technology and industrial competitiveness. (ten Kate and Wells 2001) A clear strategy on ABS can help define informed and realistic policy that meets stakeholders' priority needs, and enables a country to remain competitive in the face of uncertainty and rapid changes in the scientific, technological, economic and legal context. Countries might do well to use the untapped potential for research on genetic resources to meet domestic needs, for example, through low-cost botanical medicines directed at primary healthcare, rather than seeking only to supply fickle international markets for industrial research abroad, driven by others' priorities.

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Endnotes

1 *Biologicals or bio-pharmaceuticals:* an entity that is a protein or polypeptide either isolated directly from the natural source or more usually made by recombinant DNA techniques followed by production using fermentation. *Natural Product Drugs:* drugs of natural origin classified as original natural products, products derived from natural products or synthetic products based on natural product models.

2 http://www.bms.com/ and http://www.sec.gov/.

3 GSK Policy Position on the Convention on Biological Diversity, February 2002. Personal communication, Tod Hannum, GSK, 28 February 2002.

4 These include: the Andean Pact (Bolivia, Colombia, Ecuador, Peru, Venezuela); Australia (the States of Western Australia and Queensland); Brazil (at the Federal level and the States of Acre and Amapa); Cameroon; Costa Rica; the Republic of Korea; Malaysia (the State of Sarawak); Mexico; Nicaragua; the US (within Yellowstone and other national parks), Thailand and the Philippines.

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Future Technology Policy Briefs will address issues in energy and environment; information and communication technologies; and transnational corporations and innovation.

The next TPB will focus on energy and environment and the three main forces driving the sector: innovation, market liberalisation and the role of institutions. The objective will be to track the ways in which these issues impact on developing countries and how a balance can be maintained between energy needs and environmental concerns.

Comments, criticisms, and suggestions on this Brief are welcome. Please contact Lynn Mytelka at: mytelka@intech.unu.edu

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