



Access to Medicines in Under-served Markets

What are the implications of changes in intellectual property rights, trade and drug registration policy?

A DFID HSRC overview paper, drawing on seven studies commissioned by DFID UK



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The DFID Health Systems Resource Centre (HSRC) provides technical assistance and information to the British Government's Department for International Development (DFID) and its partners in support of pro-poor health policies, financing and services. The HSRC is based at IHSD's London offices and managed by an international Consortium of seven organisations: Aga Khan Health Services Community Health Department, Kenya; CREDES-International, France; Curatio International Foundation, Georgia; IDS (Institute of Development Studies, University of Sussex, UK); IHSD Limited, UK; IHSG (International Health Systems Group, Harvard School of Public Health, USA); and the Institute of Policy Studies, Sri Lanka.

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This DFID HSRC overview summarises the key findings of seven studies commissioned by DFID's Access to Medicines Team in 2004. It was written by Nel Druce, with contributions from Professor Brook Baker, Elizabeth Gardiner, Cheri Grace and Dr Suzanne Hill.

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INDIA
Manual sorting of pills in a pharmaceutical company.



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1 Background and summary

1.1 Policy context and issues

Major changes in international trade, intellectual property (IP) protections and drug registration requirements are substantially affecting pharmaceutical markets, with significant implications for access to medicines by poor people. The UK government has set out its commitment to increase access to medicines, and to contribute to the efforts of other governments, the private sector, investors and wider stakeholders, in a comprehensive strategy, *Increasing access to essential medicines in the developing world: UK Government policy and plans*.¹

Within this framework, and drawing on legal, regulatory, economic and pharmaceutical industry expertise, the UK's Department for International Development (DFID) has commissioned a series of seven studies. The studies, summarised in this paper, examine the policy implications of these trends for emerging producers of generic medicines such as India and China, and for poor people in developing countries.² A key question is how strengthened intellectual property protections and heightened registration standards may or may not improve access to medicines in these currently under-served markets.

The changing IP environment is likely to affect the international market structure for existing and new drugs, and the incentives to invest in research and development (R&D) for new products. Similarly, efforts to harmonise drug registration standards will affect both the quality of generic medicines and the number of companies able to compete nationally, regionally, and internationally. Both markets and regulations are changing rapidly, posing challenges and opportunities to developing country governments, their development partners and to both research-based and generic pharmaceutical industries.

As World Trade Organization (WTO) member states, almost all countries are obliged to follow the 1994 WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Developed countries became TRIPS-compliant in the mid-1990s and most developing countries became so in 2000. Least developed countries will have until 2016 to comply fully with respect to patent protections for medicines. Transition periods for major producers of generic medicines, especially India, will expire on 1 January 2005. TRIPS is therefore already affecting the producers who supply under-served markets, particularly with newer medicines.

To address concerns over unmet public health needs and to expand access to medicines for all, in November 2001 WTO members unanimously adopted the Doha Declaration on the TRIPS Agreement and Public Health (the Doha Declaration). This clarified TRIPS-compliant flexibilities for accessing medicines. More recently, through the 30 August Decision (so called Paragraph 6 decision) in 2003, WTO members agreed a mechanism for supplying needed new medicines to non-producing countries that lacked sufficient capacity to produce such products domestically.

At the same time that international IP rules are both tightening and being clarified with respect to their flexibilities, there is increasing public health demand, and financing, for new and effective drugs of assured quality in under-served markets in Africa and Asia, especially for AIDS, TB and malaria. There is also growing demand for the widespread adoption of good practice in manufacturing standards. Major financiers require that medicines procured with their funds be approved for marketing by competent drug registration authorities or meet WHO's Good Manufacturing Practice (GMP) standards. Finally, there is growing acknowledgement of the need for public sector investment and market interventions to secure adequate R&D for sustainable access to newer and more costly medicines.

1.2 Key questions and findings

Use of TRIPS flexibilities

TRIPS flexibilities theoretically enable countries with public health needs and with insufficient manufacturing capacity to import lower-cost products from other countries. But what legislative and policy measures must importing countries and exporting countries implement to make these flexibilities more useable? What are the advantages and disadvantages of these flexibilities? What is the experience at country level, for example, Kenya and Malawi? What issues do developing countries face in ongoing trade negotiations? And what can and should donors do to expedite access to medicines? (See Baker 2004, Lewis-Lettington and Munyi 2004, Lewis-Lettington and Banda 2004, and Grace 2004a).

Enhanced IP protection affects access to medicines in both producing and importing countries by stimulating changes in market and industry structure. On the one hand, increased patent protections stimulate investment in R&D for new medicines, especially for products with demand in rich country markets. At the same time, enhanced patent protection limits price competition on new medicines by generic producers.

Overall, the reported findings suggest that TRIPS-related legislation is already having and will continue to have a negative effect on public health by increasing prices and decreasing availability of newer drugs. The prime example of this effect is India, which as of January 1 2005, will no longer be able to reverse-engineer pharmaceutical products and then sell the generic equivalents at much lower prices (where the product's

patent status and IP regime permits). In the short term, tightened IP protection may be contributing to a net decrease in pharmaceutical capacity in developing countries such as Chile.

However, not all of the study findings were negative. With appropriate public policy incentives, the stronger IP rights protection put in place with TRIPS could create incentives for R&D for drugs for the developing world, including neglected diseases. It may also create a secure environment for increased technology transfer and production capacity in emerging and under-served markets. Some developing country economies with growing innovative capacity, like India, may benefit from higher intellectual property protections. Some innovator pharmaceutical companies may register drugs in markets, such as China, previously deemed too risky from an IP protection perspective.

Analysts argue that TRIPS-related public health flexibilities can provide useful means for importing countries to gain legal access to new medicines, and for producing countries to manufacture less costly generics for export. These flexibilities include parallel importation, compulsory licences and government-use orders, and special import/export rules under the 30 August Decision (see Annex 1 for definitions).

Although some developing countries have already enacted legal provisions to take advantage of some TRIPS flexibilities, there are substantial legal and administrative obstacles to introducing and implementing these complex provisions in domestic law in sub-Saharan African countries, for example. These obstacles could reduce the availability of affordable new drugs.

An important finding is that existing IP protection in many least developed and developing countries, including Kenya and Malawi, is often already stronger than the minimum required by TRIPS – in other words, existing legislation is frequently TRIPS-plus. Such countries will be precluded from using important TRIPS-compliant flexibilities, unless domestic legislation is amended further.

Several least developed countries may need to legislate to take advantage of the 2016 extension for becoming TRIPS-compliant with respect to medicines but very few have done so. Accordingly, they risk legal challenges from patent holders if they import newer medicines without using TRIPS-related provisions. In addition, virtually all countries need to amend their national legislation to take advantage of the import/export mechanism sanctioned by the 30 August Decision.

There is widespread lack of clarity about the options available for importing generic medicines from lawful foreign producers. The lack of information about the patent status of products in both importing and exporting countries is a further barrier. For example, even if a drug is not under patent in its exporting country, it cannot be imported (without a licence or the patent holder's agreement) by another country where a patent has been granted and remains in force.

Within developing country governments, awareness of public health threats, and the political will to act, are often low. Experience in implementing TRIPS and its flexibilities is limited and requires effective cooperation between different government departments, including health, trade and industry, that may have limited experience in developing common policy.

Developing countries remain under economic pressure from more powerful countries to introduce so-called 'TRIPS-plus' legislation as part of regional and bilateral trading agreements. The experience to date of these agreements suggests that their effect on access to essential medicines is unlikely to be positive.

Much in TRIPS is open to a range of interpretations, and pro-access initiatives have historically been subjected to legal challenge. Examples include the pharmaceutical industry's 1998 lawsuit against the South African government's amendments to its Medicines and Related Substances Control Act and the USA's 2001 WTO complaint against Brazil.

Registration of drugs

Drug registration is the process by which a national or regional drug regulatory agency confirms a medicine's safety, quality and efficacy, in order to approve its use in the country. With growing demand for rapid registration of new and more complex drugs, how can drug regulation and capacity be developed in a way that also protects public health? Is regional harmonisation a viable option? What are the links between data protection, drug registration requirements, exclusive marketing rights and access to medicines? (See Baker 2004, and Hill and Johnson 2004).

Developing countries face an increasingly complex and challenging task to assess the quality, safety and efficacy of a new generation of medicines submitted for marketing approval, including therapeutically important drugs such as fixed-dose combination anti-malarial and anti-retroviral drugs for HIV (ARVs). Some of these new drugs have not previously been developed by the research-based pharmaceutical industry, so there is a lack of trial and other data to inform an assessment of a product's quality, efficacy and safety. National regulatory authorities and international agencies like the World Health Organization (WHO) are, of necessity, trying to fill the gap.

However, the processing and interpretation of newer, more complex data is greatly constrained by the organisational and scientific capacity of drug regulatory authorities in developing countries. Registration can take several years, and is vulnerable to a range of interest group lobbies. Regional harmonisation efforts have the potential to ease capacity bottlenecks, but are also technically complex. Lastly, marketing rights linked to patent protection and data exclusivity rules provided for in some trade agreements may prevent the use of originator data required for the registration of generic drugs, and further inhibit availability.

Impact of stronger patent protection in China and India

How is implementation of product patents in India and China affecting access to medicines both domestically and internationally? Will generic copies of patented medicines, such as second-line ARVs for treating HIV/AIDS, have to be withdrawn from the market? Will generic companies cease supplying products needed by poor consumers in developing countries to focus on developed country markets? (See Grace 2004a and b).

Most products on the WHO essential drugs list were patented before 1995 (before the effective date of the TRIPS Agreement) and are not protected by product-based patents in India. India can therefore continue to supply generic versions of these older drugs indefinitely.

However, stronger intellectual property rights will certainly affect patent status of newer and future drugs, and pharmaceutical production, in major supplying countries such as India and China. Beginning in 2005, there are major uncertainties concerning the status of drugs discovered between 1995 and 2005, which are being held in India's patent 'mailbox' pending review of their patentability after 1 January 2005. Drugs potentially affected by this retroactive review include newer ARVs for HIV and important anti-cancer drugs. Depending on decisions taken by the Indian patent authority, the existing legal production of generic versions may cease in 2005. Similarly, as of 1 January 2005, India will be required to grant patent protections for the newest pharmaceutical innovations.

Patents granted on mailbox applications and on post-2005 drugs could have major implications for cost and availability of the newest medicines, with few therapeutic competitors in both India and importing countries. The patent status of active pharmaceutical ingredients (APIs), and their legitimate export, is also of concern. Currently, other producing countries such as Brazil, Thailand and South Africa rely on API imports from India and China. The uncertainty that surrounds the patent status of 1995–2005 drugs in India also applies to APIs patented in the same time frame. Therefore, it is as yet unknown whether their production in China and India will continue. Production could take place under TRIPS-compliant compulsory licences, issued by both exporting and importing governments, and if sufficient incentives were in place for companies to manufacture the specific products.

Historically, generic industries in India and China have become major suppliers of high quality products to under-served markets. In India, these companies have provided credible competition for the research-based industry, and are thereby contributing to downward pressure on prices of newer drugs, such as ARVs. (For example, whereas the standard costs of triple-dose therapy in Europe and the US vary from US\$10,000 to US\$30,000 a year, Indian versions of first-line generic ARVs are currently being sold for as little as US\$140 per year.) China is a major supplier of APIs for antibiotics and ARVs,

whilst India supplies both APIs and finished products – notably vaccines and ARVs – to the developed and developing world.

However, from January 2005, when India implements TRIPS to incorporate patent protections for products (in addition to processes), Indian generic companies will no longer be able to legally reverse-engineer new drugs to produce generic copies unless compulsory licences or government-use orders are issued. Responding to the imminent changes in market access, the top generic companies are already gearing up alternative strategies, by becoming outsource partners for R&D industry, or by pursuing an increased generic share in mature markets.

Despite this trend, low-priced/high-volume markets are likely to remain relatively attractive to Indian and Chinese firms, given the lower cost structure of these firms and their existing expertise in under-served markets. Leading Indian companies are also likely to pursue their own R&D agenda, thereby increasing competition for the multinational research-based corporations, which could ultimately benefit consumers.

Pharmaceutical production, technology transfer and voluntary licences in developing countries

How feasible is it for a country like Ghana to have domestic production of pharmaceuticals? Does it promote better affordability for consumers? What role can voluntary licensing, public-private partnerships, and technology transfer arrangements play in furthering public health objectives? Will research-based multinational drug companies become more interested in working with firms in developing countries, including through technology transfer? (See Baker 2004, Guimer, Lee and Grupper 2004, and Grace 2004a and b.)

There are some prospects for expanding local production in under-served markets, possibly with a focus on regional markets, but not without substantially increased capacity; even then, there are no guarantees of competitive prices. Unfortunately, manufacturing capacity in most developing countries tends to be weak. Economies of scale, up-to-date technology and a skilled workforce are essential, but often lacking.

South-south generic company partnerships that include capacity building are beginning to develop. However, to compete internationally, these new partnerships will have to produce medicines of sufficient quality to meet international standards on GMP and to provide satisfactory evidence of safety and efficacy.

In addition to south-south cooperation, R&D companies are granting a growing number of voluntary licences (including technology transfer arrangements) to companies based in developing countries. These agreements may permit the production of on-patent products at affordable prices for local or regional markets.

There are TRIPS-compliant options by which governments can ensure that voluntary licensing agreements contribute to enhanced access – by expanding geographic scope, by requiring their application to multiple suppliers, and by prohibiting market segmentation between private and public sectors. Where unregulated, however, voluntary licences can protect nearly exclusive markets for licence holders, without contributing to access.

Prospects for R&D

Stronger IP protection, especially in larger and richer markets, provides theoretical incentives for R&D. However, there is a risk that any increased expenditures by companies in India and China will be targeted towards the more profitable treatments for conditions affecting richer populations rather than toward the so-called neglected diseases. Publicly financed incentives need to be provided through domestic policy measures and international public-private partnerships (See Grace 2004a).

1.3 Policy and research implications

Looking forward, several interventions are needed to shape the legal and regulatory environments, and to support market development for improved access to medicines. Action is needed in three broad areas, information, technical support and advocacy, to:

- Provide technical advice and capacity building inputs with developing country governments, and regional organisations, on the legislative changes and procedures required for the legal use of TRIPS flexibilities.
- Assist governments to understand the implications of free trade agreements; and discourage TRIPS-plus provisions that may be detrimental to public health goals.
- Strengthen regional collaboration in regulatory harmonisation – to maximise use and development of regulatory science capacity; to harmonise data requirements for new and generic products; and to develop new approaches for developing, evaluating and registering generic medicines, that provide TRIPS-compliant measures for protecting confidential data (but that simultaneously avoid data exclusivity and patent/registration linkages that delay or preclude marketing of generic products).
- Strengthen information about patent and drug registration status at country, regional and international levels, through patent banks and regional collaboration, for example.
- Support the World Health Organization's efforts for prequalifying high quality products and producers and other efforts to increase good manufacturing practice.



- Support the development of appropriate administrative structures and cultures to allow efficient, accurate and corruption-free drug regulation.
- Advocacy (together with appropriate incentives to focus on under-served markets) with pharmaceutical companies to explore further investment in low-cost production; further development of differential pricing schemes and non-registration of patents in poor countries; and research into neglected diseases and technology transfer to developing countries.
- Support civil society in coordination and advocacy for the use of TRIPS provisions to protect public health.



2 Implications of stronger IP for access

2.1 Using TRIPS-related flexibilities in producing countries

TRIPS-compliant IP standards are already affecting access to newer medicines in the two developing countries with significant manufacturing capacity, India and China. India's IP legislation is due to come into force in January 2005, and China implemented patent regulation in 2002.

India and China both have large but relatively poor domestic markets – together the two countries account for half the world's poorest people. Their growing pharmaceutical industries supply much of their domestic need and they are significant exporters to other developing country markets. In both countries, uncertainties concerning TRIPS implementation include how new legislation will be applied and how the changing competitive environment and market structure may affect prices, quality and availability of existing and future generic medicines. This affects the strategies of both domestic and multinational industry.

What is the likely impact of stronger IP in India?

Overall, in the Indian market, the impact of TRIPS-compliant legislation is likely to result in reduced access to affordable new products.

In India, typically there has only been a four to five year lag from the time that a new drug has been introduced to the market until a generic version is developed through reverse engineering. The introduction of product patents means that generic competitors for new drugs will not appear on the Indian market until up to 15 years after their introduction by the originator. If India incorporates a narrow view of TRIPS provisions on data exclusivity, in rare cases the originator's data could remain confidential for a further five years after patent expiry.

In January 2005, new drugs invented post-2005 will be eligible for patent protection. Drugs patented in regulated markets before 1995 (the majority on WHO's essential drugs list) will remain off patent, and therefore generic versions can be legally manufactured for domestic consumption, and for export (where the importing country's legislation permits). This category includes most first-line ARVs, most drugs on WHO's essential drugs list, and the large majority of products on the Indian market.



However, the status of important newer drugs patented between 1995 and 2005 (known as 'mailbox' drugs) is still very uncertain. About 5,000 applications are awaiting decisions on patent status, including some newer ARVs and important cancer drugs, which are already manufactured as generics in India.³ Applications will be approved on a case-by-case basis by the Indian patent authority. If approved, patents on these drugs will prevent their generic production in India, unless the Indian government invokes a TRIPS flexibility via compulsory licensing for domestic and/or export use.

The patent status of APIs, and their legitimate export, is also of concern. Currently, other producing countries such as Brazil, Thailand and South Africa rely on API imports from India and China. The uncertainty that surrounds the patent status of 1995–2005 drugs in India also applies to APIs patented in the same time frame. Therefore, it is as yet unknown whether their production in China and India will continue.

Analysts predict that the introduction of TRIPS-compliant product patent laws is also likely to result in the consolidation of the highly fragmented generics industry, which may lead to reduced competition and increased prices, as industry strategies change.

The prices of those drugs that are eligible for patent protection (about 11% of the Indian market) and have limited therapeutic competition are also likely to rise for the following reasons. Given that about 300 million people – nearly a third of India's population – can afford global prices, producers are most likely to simply skim this significant market by selling new drugs at a higher price to middle-class and elite consumers, rather than develop low-price access policies for poorer consumers.

The Indian government also has weak negotiating power to impose price controls on newer drugs. Should the government try to insist on lower prices, industry may simply withdraw from the market, providing fewer products to Indian consumers. India may also be reluctant to threaten its prospects for foreign direct investment by issuing compulsory licences to permit generic production.

How is stronger IP protection affecting access in China?

China, a producing country that introduced IP legislation in 2002, also provides some examples of how greater patent protections can directly or indirectly affect access to medicines. Despite heightened IP protections in domestic law, IP rights in China are widely viewed as weakly applied, with risks of data leakage and discrimination against overseas firms. For example, domestic firms have latitude to place generic copies of a patent-protected product on the market if a patent holder does not source APIs domestically. The state drug regulatory agency is responsible for both drug registration *and* the development of domestic industry. As a consequence of its divided mission, there have been reports of data leakage, notwithstanding domestic laws guaranteeing six years of data exclusivity. This may be discouraging innovator companies from registering their on-patent drugs available in China.

Despite this apparent protection of the domestic generics industry, there are few generic copies of therapeutically important ARVs currently on the market (some key WHO recommended drugs, for example, are missing). Reasons for this may include slow registration processes, lack of technological capacity amongst domestic generic producers, and unwillingness of innovator companies to engage in technology transfer in a weak IP enforcement environment.

2.2 Using TRIPS-related flexibilities in non-producing countries

IP rights on pharmaceutical products affect all developing countries, but their impact is most restrictive in non-producing countries – countries that lack sufficient and efficient capacity to manufacture particular medicines and which must therefore rely on foreign sources of supply, even when they lawfully grant exceptions to patent rights on a specific medicine. The negative impact on the ability to import medicines will be increased in 2005, when important generic suppliers, such as India, will no longer be able to produce and export post-1995 patented medicines. Accordingly, important sources of supply of low-cost newer medicines for non-producing countries will be seriously constrained.

Developing countries' sourcing options are affected by the interaction between four factors:

- The medicine's patent status in both the importing and exporting country;
- The date of discovery (flexibilities for importing medicines differ for older pre-1994/1995 drugs, newer 1994/1995–2005 mailbox drugs and post-2005 drugs);
- International guidelines contained in the TRIPS Agreement, the Doha Declaration and the August 30 Decision;
- Domestic legislation in both the importing and exporting country.

Key TRIPS-compliant flexibilities for importing lower-cost (usually generic) medicines include:

- Unrestricted importation where there are no competing patents in either the importing or exporting country (technically, this is not a TRIPS flexibility because no patent bar exists);
- Parallel importation of previously sold patented medicines from another country if the importing country has adopted the international exhaustion rule; a more liberal interpretation adopted in Kenya permits importation of medicines produced abroad pursuant to a compulsory licence or government-use order;
- Unlimited quantities of medicines produced pursuant to special competition-based compulsory licences or government-use orders issued in the exporting country;
- Unlimited quantities of medicines produced as a 'limited exception' under Article 30 (because of lack of support for this provision, few, if any, exporters may risk this currently untested option);
- Specified quantities of medicines pursuant to notifications and compulsory licences/government-use orders issued pursuant to the August 30 Decision – a procedurally cumbersome but potentially important mechanism for enabling importation.



However, the studies highlight the absence of key flexibilities in the existing IP law of many developing and least developed countries, including African countries such as Kenya and Malawi, which are the subject of detailed case studies. In order to make rational decisions about how to source needed medicines from abroad in a TRIPS-compliant manner, developing country decision-makers will need to address several important questions.

What national legislation is already in place in both the importing and exporting country? What needs to be amended to maximize TRIPS-compliant flexibilities?

Many developing countries, such as Kenya, Malawi, Ghana and South Africa, have existing IP legislation, enacted in response to the TRIPS Agreement, or dating back to patent laws introduced during the colonial period. As a result, many important medicines are under patent in developing countries, especially richer and larger ones like South Africa where, for example, the vast majority of ARVs are patent-protected.

Where a relevant patent has been granted and remains in force, competitors are ordinarily prevented from exporting a patent-infringing product for import into the patent-protected market. This means that cheaper generic versions of patented medicines can only be legally imported into these countries under certain conditions: if national legislation includes the relevant TRIPS public health flexibilities, and the government chooses to invoke them, or if the relevant patent is waived by the originator.

Pursuant to the Doha Declaration, least developed countries can legally postpone TRIPS compliance with respect to patent and data protections for medicines until 2016, but this authorisation must first be actualised in national law. Malawi, for example, has the right to suspend its patent protection laws concerning medicines until 2016. However, in common with some other least developed countries, it has not yet formally enacted national legislation to that effect. In such circumstances, sourcing medicines other than through TRIPS-compliant means may be illegal. Patent holders could contest importation of generic ARVs, unless compulsory licences, including government-use orders, are legally issued.

Non-producing countries are permitted under the August 30 Decision to issue a compulsory licence for the import of medicines, pursuant to a special compulsory licence for export issued in the exporting country. The case studies revealed that neither Kenya nor Malawi, in common with many other non-producing countries, has yet amended their legislation to enable importation in line with the August 30 system. Similarly, few exporting countries, other than Canada and Norway, have amended their laws to permit export under the new production-for-export system. The UK has indicated that it is planning to do so.

Furthermore, many developing countries have yet to adopt international exhaustion rules to permit parallel importation or even clear rules authorising ordinary compulsory licences to be satisfied by importation. Likewise, most countries have not so far developed robust

competition policy to deal with patent abuse and some that have, like Kenya, have failed to use it.

The credible threat of issuing a legal compulsory licence is an important tool in negotiations with research-based pharmaceutical companies. The patent owner may choose to lower prices, as was the case with suppliers of ARVs to the government of Brazil. Similarly, evidence suggests that GlaxoSmithKline (GSK) and Boehringer Ingelheim offered voluntary licences to various South African and Indian firms for supplying the region, after an adverse ruling by the South African Competition Commission.

What is the patent status of the product? What quantity is needed?

The ability of a non-producing country to import a drug depends on the product's patent status in both the importing and the producing country. For example, while a generic version of a pre-1995 ARV can be legally produced and exported by India, if a patent is in force in the importing country then the product cannot be legally imported unless a TRIPS-compliant means is used.

In addition to determining the patent status of the medicine, the importing country and the producer will need to assess the quantity that is needed, as that may affect the flexibility that can be used. For example, the quantity of medicines exported under an ordinary compulsory licence is limited by 'the predominantly for domestic use' rule in Article 31(f) of the TRIPS Agreement (in that the majority of product produced should not be exported). However, a licence issued to remedy an anti-competitive practice permits exportation (and thus importation) of unlimited quantities.

For newer medicines, most producer countries and most importing non-producing countries will need to rely on the import/export system outlined in the August 30 Decision. That system allows the exporter to bypass Article 31(f) quantity limitations, but it requires that the exporting country issue multiple compulsory licences, product-by-product and country-by-country. In addition, the new system requires the export compulsory licence to be for specific quantities only, so that additional licences may need to be issued as new quantity needs arise. An additional limitation under the August 30 Decision is that the importing country must also make required notifications to the WTO and demonstrate that it lacks sufficient manufacturing capacity to produce a needed medicine domestically.

What are the major information and capacity barriers?

The evidence above suggests that knowledge of TRIPS implications and flexibilities, and capacity for IP-related legislative reform and revised competition policy are weak in many developing and least developed countries. Countries with greater civil society capacity and expertise in IP law, such as South Africa and Kenya, have succeeded in introducing some public health-enhancing IP legislation. But regulators, courts, and administrative agencies remain vulnerable to lack of funding and political pressure.

Cross-governmental collaboration (across health, trade and the department responsible for legal affairs) also tends to be weak. It is not certain that governments in exporting and importing countries will be willing and able to organise and process the numerous compulsory licences required for each product and each quantity order. Whether the volumes of needed products will allow producers to reach efficient economies of scale, and will justify the risk of legal challenge, are further uncertainties that may deter generic producers from supplying needed medicines.

How do demands for enhanced IP protections in free trade agreements potentially affect access to medicines?

The US and other developed countries continue to seek enhanced IP protection for pharmaceuticals as part of regional and bilateral trade agreements. Standards found in US law are significantly stronger than those agreed by the WTO. The US continues to seek such protections in its bilateral trade negotiations.

The US has recently concluded trade negotiations with Chile, Central America and Singapore, and is in discussions with Thailand, Andean nations and the Southern Africa Customs Union. In most of these negotiations, the US has been seeking at least some of the following IP-related terms:

- limiting compulsory licences to national emergencies, to governmental, non-commercial use, to remedy anti-competitive practices and to preclude production for export;
- barring parallel trade if such trade is contractually restricted;
- enhancing protections for clinical trial data by providing at least five years of data exclusivity, thereby potentially delaying registration of medicines produced under compulsory licences and linking drug registration rights to patent status, thereby granting absolute marketing exclusivity.

Although these terms are not necessarily pursued with non-producing countries, inclusion of some in agreements with supplying countries such as Singapore could have a negative impact on generic production for domestic use and export.

The most troubling terms may be data exclusivity and patent/registration linkage. Once a country grants five years of data exclusivity, generic producers are precluded from relying on pre-existing data to establish safety and efficacy even when the producer has evidence that the two drugs are bioequivalent. Thus, in order to establish quality, safety and efficacy for purposes of drug registration, the generic company would have to duplicate time-consuming and expensive clinical trials, entailing substantial costs and risks.

Given this, data exclusivity could pose a threat to implementing an import/export compulsory licence scheme, at least for the first five years that a new drug is on the market. Similarly, a registration/patent linkage would require drug regulators to refuse to grant marketing rights to generic producers during the entire term of the patent. This term too

could prevent the registration and sale of a lawfully produced generic pursuant to a compulsory licence or government-use order.

The US Trade Representative has indicated that IP rules in free trade agreements will not limit effective utilisation of TRIPS and related flexibilities. However, until more explicit pro-health clarifications are formalized in agreements, it is likely that developing countries and compulsory licensees will be deterred from utilising the full range of TRIPS flexibilities.

Governments are understandably cautious about introducing or using TRIPS-related public health flexibilities, due to fear of loss of (or threat to potential) trade privileges. There is some anecdotal evidence of US government and industry pressures on developing country governments even outside the trade agreement context. The United Nations Development Programme's Human Development Report 2001 concluded that: 'pressure from Europe and the United States makes many developing countries fear that they will lose foreign direct investment if they legislate for or use compulsory licences'.

Will regional IP harmonisation help?

Regional IP organisations may offer support to their members. ARIPO (the Africa Regional Industrial Property Organization) and OAPI (Organisation Africaine de la Propriété Intellectuelle) are accepting and reviewing patent applications at the regional level and providing advice on legislative reform.

However, capacity is also weak at regional level. Regional organisations are not necessarily mandated to issue patents or develop legislation that applies regionally, and national legislation usually takes precedence. Some regional agreements, e.g. the Bangui Agreement in West Africa, override national patent law and are TRIPS-plus. Lastly, regional IP organisations such as ARIPO do not necessarily coincide with the same country groupings (such as the Southern Africa Development Community) that deal with harmonisation in drug regulation and with regional trade agreements.

2.3 Drug registration standards and procedures

What are the challenges in accessing high quality, safe and effective drugs?

While the role of drug regulation is above all to protect public health, national regulatory authorities are subject to numerous, and often conflicting, pressures from local and international industrial interests and health policy makers. Regulatory authorities tend to be poorly resourced, with limited capacity. Registration processes can be slow and unnecessarily complex, and may be a major barrier to access. Kenya, for example, has no reliable fast-track procedure for registering new essential medicines, such as ARVs. Local clinical trials are required which might deter and delay registration.

There are strong arguments for regional collaboration among national agencies in carrying

out drug registration review processes. In the EU, assessment processes are shared among member states and decisions are made at regional level for national consideration. Efforts to agree common international standards through the International Conference on Harmonization (ICH), for the US, Europe and Japan began in the 1990s. Several regional trading organisations in Southern Africa and Latin America (with the Pan-American Health Organization) are developing common approaches, but harmonising drug regulation across countries or regions is a slow and complex process. Developing a shared technical framework is an important first step, especially for new drugs. The critical challenges are to generate the political will and legislative capacity to reform national drug legislation, to ensure that it is in line with national IP law, and to ensure that staff capable of implementing what is required are in place.

The WHO is playing a critical role in generating consensus on quality standards, and in building capacity for the International Standards in Good Manufacturing Practice and Good Laboratory Practice, and in regulatory competence. New WHO technical services include the prequalification of products for HIV/AIDS, malaria and TB. Countries may be able to use these standards as a benchmark for their registration procedures. A major current challenge is agreeing standards for the assessment of new fixed-dose ARV combinations where there is, as yet, no innovator equivalent and very limited data.

As briefly discussed above, drug registration processes as well as IP legislation influence the availability of medicines. Although patent protection is governed under separate legislation, drug regulatory frameworks may need reform to ensure compatibility with TRIPS requirements to ensure maximum utilization of TRIPS flexibilities.

How does TRIPS affect access to drug registration data?

Although the TRIPS Agreement authorises a wide range of practices with respect to protecting registration data, the US and Europe interpret the relevant provision quite rigidly. Article 39 of the TRIPS Agreement prevents only 'unfair commercial use' of confidential data submitted to a drug regulatory agency as a condition of approving the marketing of pharmaceutical products, if the collection of that data required considerable effort.

Many developing countries have interpreted this provision to permit a drug regulatory agency to rely on previously submitted data to assess the safety and efficacy of follow-on products. However, the US and Europe interpret the provision to require 'data exclusivity', an exclusivity that categorically bars access to the innovator's drug dossier for five years in the US and eight to eleven years in the EU.

This restricted access to a drug dossier on US/EU terms can result in market exclusivity for the originator drug because it prevents the use of the innovator company's comparative data by regulatory authorities at country or regional level for assessment of generic substitutes. Such data restrictions could effectively prevent registration of drugs in a country even if TRIPS flexibilities are in use to enable importation.



3 Prospects for supply in emerging and under-served markets

3.1 Trends in major producing countries

India and China are major suppliers of APIs and generics to domestic and export markets, including newer medicines for developing countries. Companies in these countries have also provided credible competition for the research-based industry, and are thereby contributing to downward pressure on prices of newer drugs. Major questions concern how the prospects for these industries, in the context of changing IP, may affect the availability of existing and future drugs in developing country markets and incentives to invest in R&D for new products.

What will be the impact on India and China's pharmaceutical industries?

Traditionally, Indian companies have focused on supplying the domestic and other developing country markets with generic products. As of 1999, India was one of the few countries achieving self-sufficiency in drugs, supplying over 70% of domestic needs. The large domestic market has also enabled economic viability in producing APIs, which require economies of scale as well as technical expertise. Fierce competition, combined with a highly efficient cost structure, has kept prices low.

Companies have developed substantial expertise, especially in chemical synthesis, and are highly competitive in terms of capital, R&D and marketing costs. Manufacturing quality standards are also improving. Over 60 manufacturing plants in India have US Food and Drugs Administration approval, second in number only to the US itself. In 2003, India was the source of one-third of all applications (mainly for new formulations or dosages of existing drugs, as opposed to more novel entities), allowing firms to gain access to highly regulated (and profitable) markets. In 2003, already 40% of revenues came from export markets and the Indian industry supplied 20% of the world's drugs, in volume terms.

From January 2005, Indian generic companies will no longer legally be able to reverse engineer new drugs as generic copies. One of the outcomes of strengthened IP in India is therefore likely to be increased competition for multinational research-based and generic companies in the major markets, as Indian firms look for new markets for their high quality and lower cost products. They are developing three main strategies:

- manufacturing generic API or final product to meet quality standards in the regulated markets of the US and Europe;
- producing 'difficult to manufacture' generic products such as injectables (including vaccines), and biogenerics (insulin), and innovative reformulations of older molecules;
- developing R&D capacity for new chemical entities (a few advanced firms such as Ranbaxy and Dr Reddy's aim to bring R&D expenditure to 10%).

Whilst some Indian firms are implementing these strategies independently, others are working in collaboration with western multinational corporations. For instance, since the 1990s, Indian manufacturers have been supplying quality APIs to branded and generic corporations serving the wealthier, highly regulated markets. Contract manufacturing of final product is a more recent phenomenon. Wyeth Lederle has contracted with Bharat Biotech for production of the HibTITER vaccine, and this is the first example of an Indian company contract-manufacturing a vaccine for a major research-based company. Research partnerships are taking off as well. Pfizer, Bristol-Myers Squibb and AstraZeneca have all contracted research to Biocon in Bangalore, whilst Divi's Laboratories does custom chemical synthesis for Merck, Abbott Laboratories and GSK.

Ranbaxy and Dr Reddy's are mixing cooperative and competitive strategies. For example, Ranbaxy is establishing an R&D partnership with GSK while at the same time marketing generic versions of two GSK products that are on-patent in regulated markets.

While the evidence base is weaker, it is clear that, as the world's tenth largest market, the Chinese industry has substantial growth potential as a supplier of generic and branded drugs. It is already a major supplier of APIs to India, to other developing country producers and to some multinational corporations (usually through owned affiliates or subsidiaries). However, there is a higher level of government involvement than in India, lower technological capacity in chemical synthesis, and lower ability to commercialise innovations. Relative to India, China's market is less conducive to strategic partnerships and inward investors in the pharmaceutical sector, in part due to the threat of IP violations, slow product approval processes, and discrimination in favour of local suppliers.

Despite these barriers, China does have some comparative advantages, for example in large molecule (bio-tech, traditional medicines) R&D, and in low-cost primary ingredient manufacture. New Indo-Chinese partnerships have potential for further expanding into the low-cost generics market, as GMP becomes further mainstreamed. There is a case for strengthening IPR management in China, both to encourage investment and to

enable the Chinese industry to manage and to protect its own, potentially very significant innovations.

Some have voiced concerns that Indian and Chinese pharmaceutical firms will move away from serving their traditional low-priced/high-volume markets as they increasingly focus on more lucrative markets. However, a more likely scenario is that Indian firms' supply to their traditional markets will continue alongside the increased emphasis on wealthy markets. This is due to their lower cost structure, existing capacity to serve these markets, and their need for a 'cash cow' with which to fund and diversify their more risky forays into the major markets.

Theoretically, increased IP protection should also encourage more R&D in India and China. However this expenditure is likely to be directed towards developing drugs with higher profitability potential, rather than towards drugs for neglected diseases. For example, as of 1999, only 16% of India's R&D expenditure was targeted to neglected diseases. Indian public sector research partnerships are primarily focused on non-communicable diseases, which are already of epidemiological importance within India and China, and which also happen to be the more profitable categories.

However, there are indications of some prospects for R&D for products for smaller markets including neglected diseases, since the lower cost structure of Indian and Chinese firms makes such niche strategies more feasible. Nonetheless, public sector financed incentives will still be necessary for Indian and Chinese firms to invest in R&D for neglected diseases, just as they are necessary for western-based companies. The Indian public sector and international institutions are already offering such incentives to some degree, sometimes in collaboration with multinational corporations contributing through technology transfer.

3.2 Production and technology transfer in under-served markets

When is it feasible to increase domestic production capacity?

In response to the potential impact of TRIPS on the availability of low-cost generics of newer drugs, and sometimes combined with industrial development objectives, some developing countries are exploring prospects for local production of drugs. ARVs have been of particular interest, including the manufacture of patented products under voluntary or compulsory licences. Increased affordability is the key component of access most likely to benefit through local production, but equal attention is also needed for developing appropriate and quality products.

These efforts need to be assessed from a business perspective, on a case-by-case basis, to determine whether production of high quality drugs in sub-Saharan Africa can be both price-competitive and sufficiently profitable to justify investment in expanding



local capacity. A preliminary study of a hypothetical generic company producing medicines under three different scenarios suggested that the imaginary enterprise could be profitable as well as price competitive. However, there are multiple constraining factors and some unavoidable risks, including the need to produce at an international-quality standard, uncertainty in achieving a meaningful market share in a larger regional market, and dependence on imported APIs, the cost of which may fluctuate.

Unfortunately, manufacturing capacity in most developing countries tends to be weak. Significant capacity is limited, except in India, China, South Africa, Thailand and Brazil. The costs of local production, including energy and transportation, also need to be considered. In the highly competitive drugs market, local companies may have higher cost bases than Indian counterparts, for example. Economies of scale, up-to-date technology and a skilled workforce are essential, as is access to financial capital.

Because most sub-Saharan African national markets are too small to support a fully operational plant focusing on medicines for AIDS, TB, and malaria, the producer would need to develop capacity to operate efficiently within a regional market. Doing so is complicated by the need to register the products with multiple regulatory authorities and by the need to address the patent status of the drug in the importing markets, the latter possibly requiring voluntary or compulsory licences.

In addition, in order to sustain local/regional production, there would need to be appropriate capacity for meeting international production standards according to recognised GMP. Domestic producers will also need to meet the quality standards set by major international commodity financier, all of whom currently require adherence to international quality standards. (These same donors often require proof of bioequivalence as well, especially for ARVs.) Working with the WHO prequalification project is one strategy that should be explored, but with regard to drugs not subject to WHO prequalification, the local producer may well need to work with stringent regulatory agencies in the US and Europe.

If the business case can be satisfied, there is an emerging role for domestic industry policy whereby governments can provide incentives across the value chain, from R&D to finished product. This would be particularly justified where public health objectives can be furthered in conjunction with industrial development objectives.

There are also technology transfer obligations in TRIPS through which governments can encourage research-based pharmaceutical companies to enter into voluntary agreements with developing country producers. Competition regulations can also be called upon to ensure that voluntary licensing agreements between research-based corporations and developing country firms contribute to enhanced access. Where unregulated, voluntary licences can protect nearly exclusive markets for licence holders, without contributing to access. But a pro-competition policy that encourages voluntary licences and that proactively regulates their terms could be helpful.

However, governments also face a policy dilemma – a strategy that depends on use of TRIPS safeguards, such as compulsory licensing for domestic firms, may mean that multinational corporations are more reluctant to invest in subsidiaries or voluntary licensing partnerships. Increased local capacity also decreases a country's ability to use the August 30 Decision to import under compulsory licence, which is dependent upon a demonstrable lack of manufacturing capacity.

Further research is needed in relation to a number of aspects of local production. These areas include: operational research to define human resource needs and costs that would be incurred by manufacturers attempting to meet GMP standards; preparing comprehensive regulatory dossiers for products for local markets; how best to reinforce drug regulatory authorities' control of distribution systems; and at the same time, how to make distribution systems efficient. These areas need to be included in consideration of how best to use legislation to exploit the provisions in TRIPS.

How can technology transfer be encouraged?

Technology transfers and exchanges involve knowledge sharing/transfer between developed and developing country firms. The transfer of technology is potentially an important source of technological catch-up and growth in developing countries, as encouraged by TRIPS (see Box 1).

Technology transfer experience so far has been dominated by research-based company agreements with firms in countries with existing capacity. These companies are increasingly engaging in partnerships to produce a limited number of licensed drugs for under-served markets, where there is both significant demand *and* ability to pay (through increased international development assistance for priority diseases).

In all of these partnerships, both the research-based company and the developing country firm stand to benefit. Sometimes the commercial benefit is more immediate whilst at other times the benefit might be longer term and less obviously attributable to the engagement. For example, response to public pressure and the company's own commitments to corporate social responsibility objectives often contribute to the business case. More immediate and directly attributable benefits to partners include access to scientific excellence, technology and skills, new products for new markets, and help, for example, in developing the registration dossier to international standards.

The following observations relate to technology transfer experiences documented to date.

- For highly proprietary or profitable products, companies are likely to supply the market from their centralised plants or via wholly-owned subsidiaries, and technology transfer may be limited.

- Where the product or technology has lower market potential, terms of engagement tend to be looser, and the protection of intellectual property rights less emphasised. Under pressure to optimise their R&D portfolios, companies are commonly motivated to participate in this situation by the prospect of freeing up management and production time for more commercially interesting products. A third party – a public sector or philanthropic body – is often involved as a broker for the partnerships and to provide technical and financial assistance. The product is usually donated or offered at reduced prices. Examples include the WHO's involvement with Aventis and Eli Lilly's partnerships with companies in emerging markets for producing (respectively) drugs for sleeping sickness and for multi-drug resistant TB.
- Technology transfer experiences that occur more spontaneously between research-based companies and Indian and Chinese firms might be more

Box 1 TRIPS and technology transfer

The TRIPS Agreement recognises that: 'the protection and enforcement of IPRs should contribute to the promotion of technological innovation and to the transfer and dissemination of technology', and suggests that developed country members introduce incentives to encourage technology transfer by private companies. However, TRIPS does not require developed country governments to encourage such agreements.

Although there is a WTO working group on technology transfer, government initiatives in developed countries (e.g. the UK, Canada and Japan) have so far been modest, and include tax incentives and public finance for research and development partnerships, as well as wider efforts to support an enabling environment for foreign direct investment. The South African government is planning to launch the Initiative on Pharmaceutical Technology Transfer to promote the production of off-patent pharmaceuticals, where the public sector would negotiate technology transfer arrangements and encourage participation of local companies.

UN agencies, such as the UN Conference on Trade and Development, and the UN Industrial Development Organization, have been active in the wider technology transfer field, promoting, documenting and analysing over 80 multilateral, bilateral and regional instruments.

Increasingly, technology transfer is a component in non-profit initiatives and public-private partnerships for increasing access to existing but underused technologies or new product development, often involving developing country government partners as well as the private sector. For example, several R&D companies are linking with industry partners in India, China and elsewhere in order to facilitate quality supply of patented drugs. The WHO, international philanthropic bodies, and NGOs are playing brokering roles in partnerships between R&D and generic companies.

appropriately termed technology ‘exchange’ since the partners are relatively more equal contributors to the relationship. Examples include the partnership between GSK and Ranbaxy for the latter to ‘research molecules that may become the building blocks for drugs’ and the contract R&D partnership between Dr Reddy’s and Novartis.

- There is evidence of increasing south-south collaboration between generic companies in emerging and under-served markets, which has the potential to improve regional access to lower priced products. Generic companies have subsidiaries or partnerships in South Africa, China, Brazil, Thailand and Nigeria. Such collaborations offer opportunities for capacity building and developing local markets, especially at regional level, and could contribute to supplying regional markets with use of appropriate TRIPS provisions.
- A choice to engage in technology transfer may also be in response to an obligation. For example, technology partners in US National Institutes of Health programmes, who have licensed compounds made from natural materials, are required to go back to the originating country and reach an agreement with government authorities to share benefits arising from the compound. Similarly, GSK and Boehringer Ingelheim made their ARV licences available to multiple companies in response to the South African Competition Commission, which recommended that generics companies be allowed to make copies of the drugs, otherwise the two companies would be fined for charging excessive prices for AIDS drugs in the country.

As for the future of technology transfer, theoretically, incentives for the recipient to seek and for donors to enter into transfer arrangements are enhanced under increased IP conditions, at least in countries with existing production capacity. As prospects for IP are perceived to increase, research-based companies may also be more likely to develop arm’s-length contractual relationships, such as voluntary licensing, as opposed to owning subsidiaries or affiliates in countries with weaker IP regimes.



4 Action to increase access

4.1 Market interventions to promote access to existing and new products

1 A strong pro-public health IP policy would support India's key role in supplying drugs to under-served markets. Such a policy might include:

- taking an approach to granting patent applications in the 1995-2005 'mailbox' that supports access in domestic and under-served markets to newer essential drugs;
- enabling Indian companies to continue supplying APIs and finished products to under-served markets (e.g. show willingness to issue compulsory licences for exporting drugs);
- continuing to ensure that public investment in R&D funding is linked to agreements to retain IP rights for domestic and under-served markets.

Similar policies may also be considered by middle-income producer countries, such as Thailand, Singapore, South Africa and Brazil. Stronger IPR management in China may be needed to increase the likelihood of private sector investment. Exporting countries in the developed world also need to support the implementation of TRIPS-compliant flexibilities, such as by amending their legislation to permit production for export under the August 30 Decision.

2 Stronger regional capacity for generic production and enhanced incentives for technology transfer in sub-Saharan Africa are needed to support a competitive pharmaceutical industry. Support is also needed for efficient systems for procurement, supply and delivery, including regional procurement models that deliver economies of scale.

3 Measures for effective segmentation between developing and developed country markets are needed to bolster confidence among research-based companies to introduce widespread and sustainable discounted pricing arrangements and regulated voluntary licences for production and technology transfer in developing country markets. Differential branding by some companies and regulatory anti-diversion measures, such as those strongly pursued by the EU, are important supportive measures.

4 Long-term policy and financing signals are needed to secure a sustainable and affordable supply of key drugs. For example, some development partners are considering longer-term commitments for The Global Fund to Fight AIDS, TB and

Malaria, which is a major financier of commodities. WHO's 3 by 5 ARV treatment targets, and The Clinton Foundation's efforts to secure API supply, are further examples of such signals to the market.

5 R&D incentives for products of public health importance need to be tailored to the specific comparative advantages, strategies and cost structures of firms (which will differ between western and developing country firms), as well as to the product and market characteristics.

6 There may be a role for increased investment in brokerage mechanisms between research-based companies needing to divest products and technology recipients. Given the importance of knowing a product's patent status in both producing and importing countries, consideration should be given to developing a centralised, searchable patent information bank by the World Intellectual Property Organization (WIPO).

7 Donors and international organisations should increase their consideration of low-cost, high-quality suppliers, particularly in India, as legitimate partners in researching, developing and manufacturing products that address public health needs, as the lower cost structure of these firms make them more natural partners for publicly-funded programmes concerned with cost.

4.2 Investing in and implementing pro-access IP regimes

8 The WHO (or WIPO) should develop a model TRIPS-compliant law that makes maximum use of TRIPS flexibilities to achieve public health goals. Systems for monitoring the public health impact of TRIPS, as well as the impact of regional and bilateral trade agreements, also need strengthening.

9 Although regional compulsory licences may not be legally feasible, regional approaches to timing of compulsory licences would help streamline negotiation with the patent holder, and enable a joint request to the export country. Consolidating demand for one product would also help economics of scale and therefore lower prices.

10 Support to non-producing countries, possibly provided through regional groups such as ARIPO, is needed to facilitate the introduction of appropriate legislation, as well as impact assessment of TRIPS implementation, and negotiation of trade agreements. Technical assistance at both national and regional levels needs to be provided by 'honest brokers' to assist countries in developing TRIPS-compliant, but not TRIPS-plus, legislation.

11 Cooperation among regional drug registration authorities could help to ensure manufacture and marketing of drugs of assured quality, with preferential and fast-track



registration of medicines prequalified by the WHO. Legislative harmonisation in IP and drug regulation may be a longer-term objective, but such efforts should always be assessed from a public health perspective. Such harmonisation may be necessary for regional procurement to succeed.

12 International procurement and financing agencies need clear policies and expert technical competence on IP issues, especially if they are providing IP advisory functions or managing procurement at country level. Support is also needed for civil society groups to lobby and provide qualified assistance at country level.

13 Efforts are also needed to encourage more patent holders to waive patent rights for new products in least developed and low-income countries.



Annex 1

KEY DATES AFFECTING PATENT STATUS OF MEDICINES IN DEVELOPING COUNTRIES

Pre-1995 drugs (older drugs, including first-line ARVs)	TRIPS is not retroactive – drugs not patented in a WTO Member State before 1995 do not need to be patented by that Member State. However, these ‘older’ medicines may be on patent in developing countries that had adopted more restrictive national patent legislation before TRIPS.
1995 – 2005 ‘mailbox’ drugs TRIPS Article 70 (newer drugs including some second-line ARVs and cancer drugs)	<p>WTO members which did not recognise patents on pharmaceutical products before 1995 were granted transition periods within which to become TRIPS-compliant. These countries, like India, were required to accept patent applications on post-1995 innovations and to hold them in a so-called ‘mailbox’ for processing until that country became TRIPS-compliant. Most developing countries started processing these in 2000, but countries such as India (which had legislation granting process patents, not product patents) were given until 2005 to become TRIPS-compliant.</p> <p>In addition to holding the applications in a patent ‘mailbox’, transitional countries were required to grant patent applicants five years of exclusive marketing rights once the drug was in the mailbox and had been registered with the national drug regulatory authority, if that drug had also been patented and registered by another Member State.</p> <p>Least developed countries (LDCs) are exempted from accepting patent applications if they have passed legislation to extend their transition period until 2016.</p>
2005 drugs (the newest drugs)	Except for LDCs, all WTO members must grant patent protection for pharmaceutical products as well as processes patented from 2005.
Transition periods for Least Developed Countries (LDCs) 2006 2016	Least developed countries must become TRIPS-compliant by 2006 unless they obtain further extensions. Transition periods for patents on medicines, however, were automatically extended until 2016 pursuant to Para. 7 of the Doha Declaration, meaning that LDCs are not obligated by TRIPS to enact patent protections or to enforce existing patent rights until Jan 1 2016. Despite this new flexibility, national laws may still apply with respect to previously granted patents and thus even LDCs may need to issue compulsory licences or government-use orders with respect to previously granted patents.

KEY TERMS AND DEFINITIONS

Patent	A time-limited, territorially-based right to exclude others from making, using, offering for sale, selling or importing an invented product or from using an inventive process for 20 years after the patent is granted by a nation state (resulting in about 10–15 years of market exclusivity). A country's patent law, and the specific patent status of a product, determine whether a drug's production, export and import are legal.
Exclusive marketing rights (EMRs)	A time-limited, territorially-based right to market a product without competition. Patents themselves grant a form of EMRs, but EMRs may also be awarded to 'mailbox' patent applicants, in India for example, before a patent is granted so long as the medicine has been registered for distribution, assuming it has previously been patented and registered by another WTO Member State.
Drug registration	Process by which drug regulatory authorities assess and confirm the safety, quality and efficacy of medicines in order to approve their use in the country. Innovator products, based on new chemical entities, require more complex assessment than their generic equivalents. Most countries therefore carry out a partial review based on approval provided by US or European Union regulatory agencies, the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA). Assessment of generic drugs tends to take place at national level, where there is a comparable innovator product already in the market. However, access to, and the evaluation of, bioequivalence data can present a particular challenge for under-resourced national agencies.
TRIPS 1994	WTO Agreement on the Trade-Related Aspects of Intellectual Property Rights (1994) created an integrated framework for the protection of IPRs worldwide.
Doha Declaration 2001	Clarifies TRIPS flexibilities and asserts the primacy of public health and access to medicines for all.
Para 6 Decision August 30 2003	Permits non-producing countries to issue a compulsory licence to import medicines pursuant to a special compulsory licence for export issued in the exporting country. Countries include all LDCs and developing countries that can demonstrate insufficient capacity to manufacture a particular medicine. Widely viewed as a complex and unwieldy solution. Requires negotiation with patent holder for voluntary licence first (unless for government use etc as below), applies to a specific drug in needed quantities only, and product differentiation to reduce diversion. Both importing and exporting countries will need to pass enabling legislation. So far, Canada and Norway have introduced general legislation to permit production-for-export, and it is in the UK pipeline.

<p>Compulsory licence (including for government-use order, emergency-based licence and licence based on competition grounds) (TRIPS Article 31)</p>	<p>Government authorisation permitting production of a patented product or use of a patented process (or importation by a non-producer) without the patent holder's consent. Issuance ordinarily requires prior negotiation with the patent holder for a voluntary licence, and payment of a royalty. An ordinary compulsory licence must be primarily for domestic use (over 51%), but could enable export of 49% to a non-producer, without invoking Para 6 Decision (if an Article 31 ordinary compulsory licence is in place in the importing country).</p> <p>Licences issued to permit governmental, non-commercial use, or in order to address extreme urgencies or remedy anti-competitive practices, do not require prior negotiation.</p> <p>A competition-based compulsory licence is not limited to the domestic market. A generic producer operating under a competition-based compulsory licence could produce unlimited quantities for export, including for LDCs with a legal extension to 2016, or a developing country with an ordinary compulsory licence or where there is no conflicting patent. Issuing such licences is a very complex process because of rights of appeal. The US has used anti-trust enforcement to limit market exclusivity of pharmaceutical companies, and required increased access to confidential data and manufacturing know-how.</p>
<p>Voluntary licence (TRIPS Article 40)</p>	<p>Agreement negotiated between patent holder and another company for manufacture and marketing. The regulation of anti-competitive features of voluntary licences is authorised by TRIPS Article 40. Regulation could favour export and regional production, non-exclusivity, technology transfer requirements, access to confidential test data access, and disclosure of reasonable royalty rates.</p>
<p>Parallel importation (TRIPS Article 6)</p>	<p>The importation of a patented medicine (at a cheaper price) where the patent holder's rights have been exhausted through the first sale (by the patent holder or licensee in another country). TRIPS permits countries to determine their own exhaustion regimes – international exhaustion permits parallel trade, and may permit importation of a drug produced under compulsory licence in another country. Pre-existing or new 'TRIPS-plus' legislation often specifies national exhaustion. Here the patent holder has exclusive marketing rights, and resale is permitted only within the country after first sale. If no patent is on file, product can be parallel imported, irrespective of national legislation. Discount or preferential pricing offers are frequently linked to the prevention of parallel importation between developing and developed markets (see EU anti-diversion regulation and recent ruling).</p>

Limited exception (including Bolar exception)	Limited and reasonable exceptions to patent holders' exclusive rights are permitted under Article 30, which could be justified if they do not conflict unreasonably with normal exploitation of the patent holder, taking legitimate third party interests into account. This could possibly be used to justify production for export and importation, using an ordinary compulsory licence or in the absence of a patent. The best-known limited exception is the Bolar exception, which was first recognized in the US, and permits a generic company to formulate a generic product and to prepare its registration application before the patent expires. Data exclusivity rules (see below) may delay the date of final marketing approval if such approval is based on use of the innovator's registration data.
(TRIPS Article 30) Data exclusivity (TRIPS Article 39) and TRIPS-plus sections of free trade agreements	In addition to protecting patent rights, TRIPS provides for protection of confidential drug registration data against unfair commercial use (for new chemical entities only). The US and Europe have legislated even greater data protections restricting access for 5–10 years to the confidential drug registration dossier submitted to secure regulatory approval for innovator drugs. This could prevent lawful registration of generics (because it prevents access to data for comparative assessment) and therefore can result in market exclusivity. The US in particular is seeking data exclusivity clauses in bilateral and regional free trade agreements.

Notes

1 For DFID publications and other information, see:

<http://www.dfid.gov.uk/aboutdfid/organisation/accessmedicines.asp>

2 Access the studies using the following links:

Baker B, 2004. Processes and issues for improving access to medicines: willingness and ability to utilise TRIPS flexibilities in non-producing countries, DFID HSRC

http://www.dfidhealthrc.org/Shared/publications/Issues_papers/ATM/Baker.pdf

Guimier JM, Lee E and Grupper M, 2004. Process and issues for improving access to medicines: the evidence base for domestic production and greater access to medicines, DFID HSRC

http://www.dfidhealthrc.org/Shared/publications/Issues_papers/ATM/Guimier.pdf

Grace C, 2004a. The effect of changing intellectual property on pharmaceutical industry prospects in India and China: considerations for access to medicines, DFID HSRC

http://www.dfidhealthrc.org/Shared/publications/Issues_papers/ATM/Grace2.pdf

Grace C, 2004b. Leveraging the private sector for public health objectives: a briefing paper for DFID on technology transfer in the pharmaceuticals sector, DFID HSRC

http://www.dfidhealthrc.org/Shared/publications/Issues_papers/ATM/Grace.pdf

Hill S and Johnson K, 2004. Emerging challenges and opportunities in drug registration and regulation in developing countries, DFID HSRC

http://www.dfidhealthrc.org/Shared/publications/Issues_papers/ATM/Hill.pdf

Lewis-Lettington R and Banda C, 2004. A survey of policy and practice on the use of access to medicines-related TRIPS flexibilities in Malawi, DFID HSRC

http://www.dfidhealthrc.org/Shared/publications/Issues_papers/ATM/Lettington.pdf

Lewis-Lettington R and Munyi P, 2004. Willingness and ability to use TRIPS flexibilities: Kenya case study, DFID HSRC

http://www.dfidhealthrc.org/Shared/publications/Issues_papers/ATM/Lettington2.pdf

For further references on international issues in access to medicines, see the Eldis/DFID Health Systems Resource Guide: <http://www.eldis.org/healthsystems/access/index.htm>

3 Note that it is estimated that only a maximum of 50 new molecules per year would properly qualify as genuine new chemical entities and thus be eligible for patent recognition under narrow patent eligibility standards.