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CHAPTER 3

Intellectual property and access to medicines

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SUMMARY

In an era of increasingly globalized trade, pharmaceutical patents play a key role in the availability and affordability of medicines, as shown by the conflict over access to anti-retroviral medicines for people living with HIV/AIDS in resource-limited countries. Patent protection can also be a contentious issue in high-income countries, when high medicine prices impede access to effective treatment.

Governments grant intellectual property rights as an incentive to produce inventions that will benefit society as a whole. The varied extent of protection and enforcement of these around the world became a source of tension in international economic relations, leading to international negotiations within the World Trade Organization (WTO). These negotiations resulted in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which is a set of trade rules meant to introduce a global system to monitor and enforce the protection of intellectual property rights among WTO members.

TRIPS covers five essential issues—

- How to apply basic principles of the trading system and other international intellectual property agreements
- How to give adequate protection to intellectual property rights
- How to enforce such rights adequately in a country's own territories
- How to settle disputes on intellectual property among members of the WTO
- What special transitional arrangements to apply during the period when the new system is being introduced

Developing countries expressed concerns regarding the possible effect of TRIPS, including the following—

- TRIPS treats medicines like any other commodity, but medicines are not ordinary consumer products.
- Prices will likely be higher for new medicines in countries with no previous patent protection.
- Generic competition will be delayed in countries with a previous patent term less than twenty years.
- The local pharmaceutical industry could be weakened, and dependence on developed countries may increase.
- TRIPS may not improve research and development (R&D) decisions regarding treatments for the diseases common in poor countries.

The minimum standards required by TRIPS resulted in developing countries losing some capacity to regulate pharmaceutical patents and control the cost of medicines; however, the agreement left some flexibility for them to take measures to protect public health. Because the provisions relating to patents and pharmaceutical regulation are confusing and contentious, regulators must acquire the relevant technical expertise to use these flexibilities within TRIPS to improve access to medicines.

The international rules regarding intellectual property are evolving quickly. Developing countries must actively participate in discussions of the future of the intellectual property system to ensure its appropriateness for countries at very different levels of development. As the rules evolve, their impact must be properly understood if policies are to be based on relevant evidence.

3.1 The global pharmaceutical market

The international trade in pharmaceuticals has expanded dramatically since 1980. During the 1990s, trade grew substantially faster than production. High-income industrialized countries used to dominate international trade in pharmaceuticals. In 1999, they accounted for 93 percent of global exports by value. Between 1980 and 1999, middle-income countries' share of world exports fell, while the export share of some low-income countries, such as India, Pakistan, and Indonesia, more than doubled, from 1.1 percent to 2.9 percent. High-income countries also dominated imports. During the same period, their shares increased, and the shares of both low- and middle-income countries in world imports dropped significantly (WHO 2004).

With the exception of Japan, the countries that contribute most to world trade are also the world's major producers: the United States, the United Kingdom, Germany, and France. Japan, the world's second-largest producer, continues to produce primarily for its domestic market.

Sales figures by value from 2005 indicate that North America, Japan, and Europe accounted for almost 90 percent of the world's pharmaceutical purchases (IMS Health 2006). So although sub-Saharan Africa, for example, represents a huge proportion of the disease burden relative to the rest of the world, its global pharmaceutical market share is only 1 to 2 percent (Scheffler and Pathania 2005; CIPIH 2006), which generally makes it an unattractive target market for manufacturers. However, the number of emerging pharmaceutical markets increased from seven in 2006

to seventeen in 2010, with China expected to become the third-largest market by 2011—up from eighth-largest in 2006 (Campbell and Chui 2010).

Categories of pharmaceuticals

The world pharmaceutical market consists of several categories, characterized by different degrees of market competition. Innovative pharmaceutical products that are patented (*original brands*) are protected from competition for the life of the patent in the countries that recognize the patent. Legal competition is limited to medicines that are *therapeutically equivalent* (used to treat the same clinical indication) but that have either a different composition or a different manufacturing process from the original brand. At the other end of the spectrum are pharmaceuticals known as *generics*. Generally, generic pharmaceutical products are the chemical equivalent of the original brand product that are usually manufactured without a license from the originator company. This large category includes pharmaceuticals whose patents or other exclusivity rights have expired, pharmaceuticals that have never been patented, and copies of patented pharmaceuticals in countries where the drug is not patented or where a compulsory license has been granted (see Section 3.2). The legality of copying patented products depends on the manufacturing country's patent legislation.

Generic medicines are usually sold under their generic names and may be manufactured and marketed by many companies. This market is highly price competitive because buyers can choose among several sources of chemically identical medicines. On the manufacturing side, the distinction between originator companies and generics manufacturers is often blurred. In some cases, major research-based international companies have generics manufacturing subsidiaries producing “branded generics.” For some medicines, these products account for a large share of the world's market in generics.

Another category comprises traditional or complementary medicine, which includes herbal medications. The use of herbal products has increased, especially in developed countries; however, regulation governing the quality, sale, and use of such medicines varies widely. Countries are recognizing the large role that traditional medicine plays in health care, and more countries are addressing the challenges of including traditional medicine in national health policy, including protecting indigenous knowledge and applying intellectual property rights. Chapter 5 discusses traditional and complementary medicines.

Role of patents in the pharmaceutical sector

In an era of increasingly globalized trade, pharmaceutical product patents play a key role in the availability and affordability of medicines, as shown by the conflict over access to

antiretroviral medicines for people living with HIV/AIDS in resource-limited countries. Patent protection can also be a contentious issue in high-income countries, when high prices for branded medicines impede access to effective treatment.

A *patent* is an exclusive right that a government gives to an inventor, preventing others from making, using, offering to sell, selling, or importing an invention or inventive process for a defined period. The patent does not give an inventor the right to make, use, or sell the invention. The inventor may have to comply with other laws and regulations to make use of the claimed invention. For example, a pharmaceutical company may obtain a patent on a new medicine, but it will be unable to market the medicine in a country without the government's regulatory approval.

The patent gives the inventor the opportunity to recoup his or her investment in R&D in exchange for publicly disclosing the underlying information about the invention. The concept behind patenting medicines is that the exclusive marketing rights provided by a patent allow high prices during the patent term, which generate profits that fund the R&D necessary to create and bring new pharmaceutical products to the market. Therefore, patients who buy patented pharmaceuticals (or their employers, their insurers, or their governments) pay a premium that is in theory designed to support the research process. When a patent expires, generic products enter the market and force prices down through competition.

One of the functions of a patent is to serve as a financial incentive for creators of inventions that benefit society (CIPIH 2006). However, people living in developing countries and their governments have little purchasing power, which removes real incentive to the global private sector to invest in developing medicines that treat diseases endemic in developing countries—also known as tropical and neglected diseases. Section 3.5 discusses R&D issues.

Developing countries and nongovernmental organizations have argued that patents on pharmaceuticals in the developing world raise prices and thereby reduce access to lifesaving treatment. In contrast, the research-based pharmaceutical industry and many developed countries have argued that the larger problem in resource-limited countries is an insufficient health service infrastructure.

3.2 Globalization of intellectual property standards and access to medicines

Ideas and knowledge are increasingly important parts of trade. Most of the value of new medicines and other high-technology products lies in the amount of invention, innovation, research, design, and testing involved. Creators can be given the right to prevent others from using their inventions, designs, or other creations—and to use that right to

negotiate payment in return from others using such intellectual property rights. These intellectual property rights, which include not only patents but also copyrights and trademarks, reward the results of innovation and creativity in many areas, including music, science, and authorship.

Governments give creators intellectual property rights as incentive to produce inventions that will benefit society as a whole. The extent of protection and enforcement of these rights varied widely around the world, and as the focus on intellectual property in trade intensified, these differences became a source of tension in international economic relations. New, internationally agreed-upon trade rules for intellectual property rights were viewed as a way to introduce more order and predictability and to settle disputes more systematically.

History and evolution of intellectual property rights for pharmaceuticals

Intellectual property rights were important to chemical firms in nineteenth-century Europe and to U.S. and European pharmaceutical companies in the twentieth century. Because these companies particularly wanted patent protection, they began lobbying governments on the design of such protection. Large companies focused more

and more on the use of intellectual property rights as part of their business strategy, which gave them an increasingly greater incentive to influence how such rights evolved.

World Trade Organization agreements. In the 1980s, this context gave rise to collaboration among U.S., European, and Japanese companies, including pharmaceutical and chemical companies, in campaigning for the inclusion of an agreement on intellectual property rights in the WTO's Uruguay Round of Multilateral Trade Negotiations. (See Box 3-1 for information on the WTO.) Those negotiations produced the Agreement on Trade-Related Aspects of Intellectual Property Rights and the Agreement on Technical Barriers to Trade. From its origin in 1989 until it was finalized in 1994, TRIPS evolved into a detailed international agreement containing industrialized-country standards of intellectual property protection, requiring multilateral trade negotiations among all WTO members. The Agreement on Technical Barriers to Trade seeks to ensure that technical standards, testing, and certification procedures do not create unnecessary obstacles to trade. This agreement can affect the development of production capabilities in developing countries by affecting their ability to export.

WTO agreements, including TRIPS, are treaties that create international obligations among the members. TRIPS

Box 3-1 World Trade Organization

The World Trade Organization (WTO) is the international organization that deals with the rules of trade between nations at a global or near-global level. At the center of the organization are the agreements that the members comprising the majority of the world's trading countries or customs unions (158 members as of July 2008) negotiate and sign. These agreements provide the legal ground rules for international commerce. WTO membership requires nations to adopt the terms of the twenty-six existing agreements and mandates that members' national laws conform to the global standards. The content of the WTO's twenty-six agreements covers many aspects of national law related to trade in goods, services, and intellectual property.

The majority of the WTO's current agreements come from the 1986–94 negotiations called the Uruguay Round and earlier negotiations under the General Agreement on Tariffs and Trade. Although difficult to achieve with so many diverging points of view, the WTO generally makes decisions based on member consensus. The highest decision-making authority within the WTO is the Ministerial Conference, composed of members'

ministers of trade, who meet at least once every two years to negotiate any matter under any of the multilateral trade agreements. Other meetings involving various committees, working groups, and special sessions occur between full meetings. The Council for Trade-Related Aspects of Intellectual Property Rights, which deals with TRIPS-related issues, reports directly to the WTO General Council. The World Health Organization (WHO) has an observer-status seat on the TRIPS council.

The WTO is unique as an international organization in that it has a dispute settlement body, the decisions of which are final and binding on members. This capacity gives the WTO the power to enforce trade rules.

Because many of the agreements have important implications for public health, WHO has established a new department called Trade, Foreign Policy, Diplomacy, and Health to promote greater policy coherence between trade and health policy, so that international trade and trade rules maximize health benefits and minimize health risks, especially for poor and vulnerable populations.

introduced intellectual property rules into the multilateral trading system for the first time and attempted to narrow the gaps in the way these rights are protected around the world and to bring them under common international rules. Consequently, TRIPS globalizes a set of intellectual property principles and harmonizes intellectual property regulation by establishing minimum levels of protection that each government has to give to the intellectual property of other WTO members. To the chemical and pharmaceutical companies that had been promoting it, TRIPS was a major step in the globalization of standards of protection for patents, copyrights, trade secrets, and trademarks.

Previously, patenting essential public goods such as medicines and food was considered contrary to the public interest. When the WTO launched the Uruguay Round of trade negotiations in 1986, more than fifty countries were not granting product patents on pharmaceuticals. After TRIPS, all WTO member countries had to reform their domestic intellectual property laws to conform to the new obligations of the agreement.

Many questions arose regarding the (mainly developing) countries that seemingly had little to gain by agreeing to these terms of trade. Lacking intellectual property experts in their WTO delegations, most developing states did not have a clear understanding of the ramifications of the TRIPS negotiations. Some countries were interested in agreeing to TRIPS in exchange for concessions that would expand their exports of agricultural or textile products. However, because TRIPS required countries to recognize patents on pharmaceutical products—often for the first time—it had implications for both the cost of patented medicines and the long-term outlook of the generics industries in those countries. In addition, TRIPS covers many more issues relevant to public health, including traditional medicines, biotechnology, genetic materials, medical devices, and technology transfer.

The Doha Declaration. Although one of TRIPS' stated goals was to reduce tensions arising from intellectual property protection, patent protection for pharmaceuticals and its effects on public health—and particularly access to medicines—has remained a highly controversial issue. Debate in developing countries reflected growing concerns about the implications of TRIPS regarding access to medicines, which were seen as signs of the conflict between the recognition of intellectual property rights and essential public health objectives.

Developing countries expressed concerns regarding TRIPS' possible effect that included the following—

- TRIPS treats medicines like any other commodity, but medicines are not ordinary consumer products.
- Prices will likely be higher for new medicines in countries with no previous patent protection.

- Generic competition will be delayed in countries with previous patent terms less than twenty years.
- The local pharmaceutical industry could be weakened, and dependence on developed countries may increase.
- TRIPS may not improve R&D decisions regarding treatments for the diseases common in poor countries.

The medicine access issue and related advocacy resulted in the Declaration on TRIPS and Public Health at the WTO Ministerial Conference in Doha in November 2001. The Doha Declaration, as it is known, affirms the right of developing countries to protect the health of their populations, declaring that TRIPS “can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all.” The right to health is embedded in international, regional, and national human rights instruments, including the constitution of WHO, the United Nations Universal Declaration of Human Rights, and various national constitutions.

Despite initial resistance by some developed countries, the Doha Declaration was adopted by consensus. It is one of the important benchmarks in trade history, because it is regarded as elevating public health above trade with respect to national intellectual property law. In addition, the Doha Declaration resulted from the success of civil society in focusing attention on these issues and from developing countries' solidarity in standing up collectively for their concerns about the intellectual property regime under TRIPS.

The Doha Declaration was not intended to amend TRIPS. Rather, it aims to clarify the relationship between TRIPS and public health policies of WTO member countries and to confirm the rights retained under the agreement, particularly by defining the flexibility allowed in certain key policy areas. The declaration can make it easier for developing countries to adopt measures necessary to ensure access to health care without the fear of legal consequences. However, the Doha Declaration is not self-executing, and countries therefore need to make the legal amendments necessary to implement it. Developing countries in particular should be encouraged (and provided the relevant technical assistance) to review their legislation to ensure that they incorporate into national laws any flexibilities allowed by TRIPS to address public health concerns.

Key concepts related to TRIPS

TRIPS covers five essential issues—

- How to apply basic principles of the trading system and other international intellectual property agreements
- How to give adequate protection to intellectual property rights

- How to enforce those rights adequately in a country's own territories
- How to settle disputes on intellectual property among members of the WTO
- What special transitional arrangements to apply during the period when the new system is being introduced

TRIPS includes an enforcement mechanism through economic sanctions for countries that fail to comply with the minimum standards for protecting intellectual property rights. When intellectual property disputes between countries arise because of differences in the interpretation of TRIPS, the WTO provides a dispute settlement process that includes negotiation, dispute settlement decision making, and an appeal process. Trade sanctions may be imposed only if the dispute settlement process has run its course and the losing country has failed to comply with the decision.

As mentioned, TRIPS introduced minimum standards for protecting and enforcing nearly all forms of intellectual property rights, including those for pharmaceuticals. As a minimum-standards agreement, however, TRIPS allows members to protect intellectual property more extensively if they choose. Members are free to determine how best to implement the provisions of the agreement within their own legal system and practice (see Correa 2000). The key concepts for pharmaceuticals are described in the following subsections.

Patent protection. Under TRIPS, member countries must provide patent protection for a minimum of twenty years from the filing date of a patent application for any pharmaceutical product or process that fulfills the criteria of novelty, inventiveness, and usefulness. National legislation and practices define what can be patented, and countries must establish their own criteria for what constitutes a “new” and “inventive” product.

Countries should recognize that patentability standards that are too broad can contribute to extending the patent life of a new medicine through designating new or inventive uses as described above or different dosages. This practice is called *evergreening*. To limit this extension of rights to original patent holders, national patent legislation needs to ensure that public health needs are taken into account. Similarly, incremental innovation, or “me-too” drugs, is within the same chemical class as one or more other pharmaceutical products already on the market; however, the pharmaceutical industry feels that me-too drugs advance safety and efficacy and support the development of novel products (Wertheimer and Santella 2009).

Transitional arrangements. TRIPS provides transitional periods during which countries must bring their national legislation and practices into conformity with its provisions. The compliance dates for WTO members were 1996 for developed countries; 2000 for developing countries;

2005 for developing countries that had not introduced patents for pharmaceuticals before joining the WTO, such as India; and 2016 (for medicines only) and July 2013 for least-developed countries (LDCs) in recognition of these countries' economic, financial, administrative, and technological constraints to conforming.

Generic medicines. After a patent expires (or a license is issued), copies of a medicine can legally be made. These are called multisource medicines—or generics—and should be chemically equivalent to the original brand medicine. Promoting generic medicines within a country requires appropriate legislation and regulations, reliable quality-assurance capacity, professional and public acceptance of generic medicines, and economic incentives and information for both prescribers and consumers.

Under the TRIPS regime, a different manufacturing process for a chemically equivalent pharmaceutical product would be blocked if the originator company still held a product patent on the chemical entity. Currently, a different chemical entity may pose therapeutic competition to an existing medicine, and a different company may hold such a patent. In some cases, however, an originator company will place a patent not only on the chemical entities in the ingredients, but also on the resulting metabolite that produces the desirable therapeutic effect (Correa 2000). Such metabolite patents may block pharmaceuticals in the same therapeutic category if they share a common metabolic pathway.

Trade liberalization can increase competition and reduce prices for generic medicines that are already on the market. But inappropriately implementing TRIPS-compliant national legislation can delay new generic products, which can result in large economic costs. The prompt introduction of generic medicines can be facilitated by drafting appropriate legislation and regulations on patentability, such as using exceptions to permit early testing and approval of generics and compulsory licensing (see following subsections).

As an alternative to promoting generics, some brand-name pharmaceutical manufacturers have volunteered to lower their prices in certain markets (for example, selling certain medicines in developing countries at greatly reduced prices compared to prices in major markets); however, such programs usually feature multiple restrictions. Some companies have gone further by donating medicines for particular programs (see Chapter 15).

Compulsory licensing (TRIPS Article 31). As a provision of TRIPS, compulsory licensing occurs when a government authorizes the production of a patented product or the use of a patented process without the patent holder's consent as long as certain conditions are met, such as the license being used predominantly (that is, 51 percent) for the domestic market. The patent holder, however, retains intellectual property rights and “shall be paid adequate

remuneration” according to the circumstances. In other words, compulsory licensing allows local manufacturers in resource-limited countries to make close-to-marginal-cost versions of patented medicines to address public health needs, if they give a royalty payment to the patent holder. Generally, the grant of a compulsory license requires prior negotiation with the patent holder. However, grounds for governments to grant compulsory licenses without any previous negotiation may include public interest, national emergencies such as epidemics, public noncommercial use, or remedying anticompetitive practices.

In the pharmaceutical sector, compulsory licenses have been used to stimulate price-lowering competition and to ensure the availability of needed medicines. For example, if a new product introduced to the market were to play an important role in public health, such as a vaccine against HIV/AIDS or malaria, a country’s national law could grant a compulsory license under Article 31 of TRIPS. Compulsory licensing, however, is not always a solution for resource-limited countries. For instance, when prior authorization from the patent owner is required, as is the normal case, negotiations can be lengthy and complicated, and a country may not have the necessary legal expertise. In addition, the manufacturing process for a pharmaceutical product may be protected under a separate patent or as a trade secret. Finally, countries may lack the technical expertise or facilities necessary to copy and manufacture the product or to attain the economies of scale that make such a decision feasible (see Chapter 7 on production policy).

Despite the constraints, a country’s comprehensive patent legislation should adequately provide for granting compulsory licenses to strengthen its position, even if the country rarely uses the provision. Now, most developed countries and many developing countries include compulsory licensing in their national legislation; for example, in 2010, Colombia successfully used the threat of compulsory licensing to reduce by two-thirds the price of Kaletra, an antiretroviral, while the United States has used the threat to mitigate anticompetitive situations.

Figure 3-1 shows the exact text from a compulsory license granted in Zambia in 2004.

Voluntary licensing (TRIPS Article 40). A voluntary license is an agreement negotiated between the patent holder and another company for manufacturing and marketing. TRIPS Article 40 authorizes the regulation of anticompetitive features of voluntary licenses. Regulation could favor export and regional production, nonexclusivity, technology-transfer requirements, access to confidential test data, and disclosure of reasonable royalty rates. Usually, efforts must first be made to obtain a voluntary license on reasonable terms and conditions before a party obtains a compulsory license (see Country Study 3-1).

Parallel importation (TRIPS Article 6). Parallel importation occurs when a third party, without the consent of the

patent holder, imports a medicine that has already been put on the market abroad more cheaply by the patent holder or a licensee. The practice is based on the principle that the patent holder has been compensated through the first sale of the product and that further control over the resale of the product would unreasonably restrain trade and competition. In other words, having been paid, the patent holders are said to have “exhausted” their rights. If the importing country’s patent system provides that the patent holder’s right has been exhausted when the patented product has been placed on the market in another country, the patent holder cannot prevent parallel importation into the importing country. TRIPS permits WTO members to determine their own rules regarding exhaustion—international exhaustion permits parallel trade and may permit importation of a medicine produced under compulsory license in another country.

Because most pharmaceutical companies set prices for the same products at different levels in different countries, parallel importation promotes competition for the patented product by allowing the importation of equivalent patented products marketed at lower prices in other countries. However, companies have been pressuring governments not to import medicines from countries that produce generic versions, claiming that the practice is a breach of the TRIPS agreement. Article 6 of TRIPS explicitly states that practices relating to parallel importation cannot be challenged under the WTO dispute settlement system, provided that no discrimination exists on the basis of the nationality of the persons involved; however, preexisting or new “TRIPS-plus” legislation (see below) often specifies national exhaustion. Here, the patent holder has exclusive marketing rights, and resale is permitted only within the country after first sale. Preferential pricing offers are frequently linked to the prevention of parallel importation between developing and developed markets.

Exceptions to rights conferred (including Bolar exception) (TRIPS Article 30). TRIPS specifies the rights given to a patent owner but allows limited exceptions, subject to specified conditions in Article 30. Of particular interest regarding access to medicines is the so-called Bolar exception to patent rights that allows a country to complete all of the procedures and tests that are necessary to register a generic product before the patent expires on the original medicine. Allowing generics manufacturers to conduct the tests needed to prepare their applications for regulatory approval during the term of the patent enables them either to market their products immediately upon expiration of the patent or, for example, to apply for a compulsory license during the term of the patent.

Protection of undisclosed test data (TRIPS Article 39.3). In many countries, national regulatory agencies require originator pharmaceutical companies to submit extensive data showing the safety and efficacy of a new product before it is approved for the market. These data

Figure 3-1 Compulsory license granted in Zambia

Republic of Zambia
MINISTRY OF COMMERCE, TRADE AND INDUSTRY

The Government of Zambia, conscious that the HIV/AIDS pandemic constituted a serious handicap in the national struggle against hunger, illness, under development and misery;

and taking into consideration that high rates of morbidity and mortality have put Zambia among the ten countries in Africa most hit by this disease. Current estimates are that, at the end of 2003, over **917,718** Zambians were infected by HIV of whom an unestimated number are suffering from full-blown AIDS. The AIDS death toll is so far in excess of **835,904** and about **750,504** children have been orphaned by this pandemic, creating a situation where 75% of households in Zambia are caring for at least one orphan and that children aged below 14 years headed more than 130,000 poverty stricken households out of a total of 1,905,000, and that;

in spite of the multiplicity and diversity of vigorous prevention campaigns, the spread of the virus is still on an upward trend as shown by the high number of infections;

Taking into account the gravity of the situation being faced by most African Countries, including Zambia, the need to ensure access to drugs at affordable prices, while respecting the protection of intellectual property, is well recognised. For this reason;

On 14 November, 2001 the World Trade Organisation, while recognising Members' commitment to the TRIPS Agreement, declared the right of each Member State to take measures aimed at protecting public health and in particular to promote access to medicines for all, by utilising to the full, the flexibilities in the TRIPS Agreement relating to among others, the granting of compulsory licences, in cases which constitute a national emergency or other circumstances of extreme urgency and of public health crisis including those relating to HIV/AIDS, tuberculosis, malaria or other epidemics which can represent a national emergency or other circumstances of extreme urgency.

Considering further that;

A triple compound of Lamivudine, Stavudine and Nevirapine has proved, in the last few years to be one of the most effective and economical anti-retroviral treatment, but that the three different international owners of such single drugs failed to reach an agreement to produce this combination, and therefore;

The Ministry of Commerce, Trade and Industry of the Republic of Zambia making use of the provisions of Section forty of the Patent Act, Chapter 400 of the Laws of Zambia, and Statutory Instrument No 83 of 2004 titled "The Patents (Manufacture of Patented Antiretroviral Drugs) (Authorisation) Regulations, 2004" Regulation 3, has decided to grant a Compulsory Licence No. CL 01/2004 to PHARCO LTD, a company incorporated in Zambia, which has already presented a project proposal for the local manufacture of the mentioned triple compound under the names of Normavir 30 and Normavir 40.

It is further understood that the use or vending of the above mentioned drugs is subject to Regulation 4 of Statutory Instrument No 83 of 2004, titled "The Patents (Manufacture of Patented Antiretroviral Drugs) (Authorisation) Regulations, 2004" and therefore cannot be exported to any place outside Zambia.

Communication of this decision will be given to the applicant and to the patent right holders.

In consideration that the mentioned product, a triple combination of drugs, is not marketed in Zambia by the International Patent owners and that it is in the national interest to keep the final price as low as possible, the total amount of royalties due to the patent right owners shall not exceed 2.5% of the total turnover of the mentioned products at the end of each financial year of PHARCO LTD.

The Ministry of Commerce, Trade and Industry shall in accordance with Section forty one of the Patent Act notify the concerned parties of the expiration of the present Compulsory Licence as soon as conditions of national emergency and extreme urgency created by the HIV/AIDS pandemic will come to an end, or upon expiry of the period of emergency stipulated in Statutory Instrument No 83 of 2004 titled "The Patents (Manufacture of Patented Antiretroviral Drugs) (Authorisation) Regulations 2004."

The Government of the Republic of Zambia reserves the right to review the Compulsory Licence should the conditions and circumstances under which it is granted change.

Dipak K. Patel, MP

Ref: MCT/104/1/1c

MINISTER

Date: 21/09/04

Country Study 3-1**Using voluntary licenses in sub-Saharan Africa to produce antiretroviral medicines**

A number of companies in Africa have obtained voluntary licenses from originator pharmaceutical producers (in some cases through advocacy efforts) to locally manufacture antiretroviral medicines for HIV/AIDS. South Africa led the way with several generics pharmaceutical companies receiving voluntary licenses from patent holders of antiretroviral medicines. Aspen Pharmacare, which is South Africa's largest pharmaceutical manufacturer, and Cipla Medpro are two of the companies that secured the rights to distribute generic HIV/AIDS medicines to other countries in sub-Saharan Africa. Voluntary licenses from several different patent holders allow the generics companies to produce medications that combine multiple products into one tablet (fixed-dose combination), which helps patients adhere to treatment. In addition, the U.S. Food and

Drug Administration qualified Aspen Pharmacare, which allowed U.S.-government-funded organizations in Africa to purchase generic antiretrovirals for the first time.

In Kenya, Cosmos Limited was the first producer to receive voluntary licenses from GlaxoSmithKline and Boehringer Ingelheim to produce generic versions of lamivudine, zidovudine, and nevirapine. One of the benefits of producing the products locally is that the packaging will include instructions printed in both English and Kiswahili, but more important, the supply and availability should become more reliable, and prices are expected to fall. As part of the voluntary licensing agreements, Cosmos will be able to sell the generic medicines to five other sub-Saharan countries.

are the result of many years of research and are sometimes very expensive for the originator company to produce. Sometimes, such as in the case of the cancer medicine paclitaxel, a government has underwritten much of the product's R&D. In addition, a multinational company may simply acquire the innovation from an academic institution or biotechnology company.

TRIPS Article 39.3 obliges member countries to protect this confidential test data from "unfair commercial use" including disclosure, except where necessary to protect the public. Countries vary in how they implement the requirements of Article 39.3. Whereas some countries permit pharmaceutical regulatory authorities to rely on the original test data to register generic equivalents, others, such as the United States and European Union countries, grant the originator company a time-limited period that excludes regulatory authorities from using existing test data to register generic products without consent. These laws are known as data exclusivity laws.

The originator company is unlikely to consent to its data being used to register a generic equivalent to its product, and although generic competitors could replicate clinical trials at considerable cost, another significant barrier relates to the ethics of conducting redundant trials on patients. Therefore, data exclusivity laws provide a form of market protection for the originator company.

Consequently, controversy exists about how Article 39.3 should be implemented to ensure the protection of public health. The disagreement centers on whether the phrase "unfair commercial use" means that regulatory agencies can use original data to assess generic product applications,

as long as they do not disclose the data to the competitor. This interpretation would imply that Article 39.3 does not require data exclusivity. On the contrary, the research-based pharmaceutical industry and some trade representatives have argued for the alternative interpretation that Article 39.3 does require data exclusivity.

Exclusive marketing rights (TRIPS Article 70.9). As noted, when TRIPS was launched in 1996, many countries did not offer patents for pharmaceutical products. These countries were given a transition period to phase in patent protection for pharmaceuticals. However, TRIPS Article 70.9 says these countries have to accept patent applications for pharmaceuticals, even though they are not obligated to examine the applications or grant any patents until the end of the transition period.

In cases where the country takes advantage of the transition period, Article 70.9 requires that when a patent application has been filed for a product in that country, the WTO member must grant exclusive marketing rights to the patent applicant for a period of five years after obtaining marketing approval, as long as the product has been patented and received marketing approval in another WTO member country. The rights can expire before the end of the five years if either a patent is granted (in which case the patent holder would rely on the patent instead of the exclusive marketing rights) or the patent application is rejected. Exclusive marketing rights, therefore, are considered a mechanism for the patent applicant to obtain payment for use of the product until the patent is granted.

Least-developed countries have been granted a waiver to Article 70.9—extending the transition period until 2016.

Decision on the implementation of paragraph 6 of the Doha Declaration. Although developing countries have the right to exercise the flexibilities under TRIPS, they often find using these flexibilities in public health policy a challenge. For example, paragraph 6 of the Doha Declaration recognized that while developing countries can issue compulsory licenses, TRIPS did not take into account the difficulties they faced because of a lack of manufacturing capacity. Many developing countries and LDCs cannot produce either active ingredients or formulations because of lack of technology, equipment, human resources, or other domestic production capacity. Although these countries may issue compulsory licenses to import generic versions of patent-protected medicines, TRIPS rules constrain the ability of countries that do have the capacity to manufacture generics, such as India, to export such products. Manufacture must be primarily for the domestic market. Therefore, countries without sufficient manufacturing capacity in pharmaceuticals could issue a compulsory license for the importation of products they cannot manufacture, but they may not be able to find sources for importing affordable new medicines.

Consequently, after the adoption of the Doha Declaration, WTO members spent almost two years in negotiations that culminated in the Decision on Implementation of Paragraph 6. That decision is intended to permit all LDCs (as designated by the United Nations) and developing countries with insufficient or no manufacturing capacity to import a particular medicine to make effective use of compulsory licensing. The Paragraph 6 Decision allows nonproducing countries to issue a compulsory license to import medicines in accordance with a special compulsory license for export issued in the exporting country. However, making use of this flexibility is a complex process, and both importing and exporting countries will need to pass the legislation to make it possible.

The terms of the Doha decision were made a permanent feature of TRIPS through an amendment including a new article, 31*bis*. Essentially, the Paragraph 6 Decision and the amendment eliminate the requirement that pharmaceutical products manufactured under a compulsory license be “predominantly for the supply of the domestic market.” In addition, to prevent duplicating payment to the patent holder, the amendment eliminates the need to remunerate the patent holder in the importing country if the patent holder in the exporting country has already been remunerated.

A publication from WHO gives more information on how countries can implement the Paragraph 6 Decision (Correa 2004).

Decision on the implementation of paragraph 7 of the Doha Declaration. Paragraph 7 permits LDCs to extend the transition period for pharmaceutical patents beyond what is defined in TRIPS to the year 2016. Part of the moti-

vation for paragraph 7 concerns the rights of LDCs to promote technology transfer by giving them additional time to build a technological base for their pharmaceutical sectors. In addition, Article 66.2 seeks to provide benefits specific to LDCs by requiring developed countries to offer incentives to private companies and other institutions in their territories to engage in technology-transfer activities.

Practically, however, the only LDCs that can take advantage of the extension in paragraph 7 are those that do not grant patents for pharmaceuticals. For example, Angola and Eritrea are the only countries of thirty African LDCs that do not grant patents for pharmaceuticals (Correa 2002). To take advantage of the benefit, other LDCs that already grant pharmaceutical patents must amend their legislation and not grant product patents until 2016.

Another consequence of paragraph 7’s transition extension concerns the requirement to grant exclusive marketing rights (TRIPS Article 70.9). After the Doha Declaration, ambiguity existed regarding whether a transition extension for pharmaceuticals applied to exclusive marketing rights as well as to patents. To clarify the situation, WTO members approved a waiver that exempts LDCs from having to provide exclusive marketing rights for any new medicines during the period without patent protection.

3.3 Constraints to establishing health-sensitive intellectual property laws

Although the adoption of the TRIPS minimum standards resulted in developing countries losing some policy flexibilities in regulating pharmaceutical patents and controlling the cost of medicines, the agreement left some room for countries to take measures to protect public health. Furthermore, at Doha, WTO members reaffirmed the right of each member to fully use the provisions of the agreement that provide flexibility for protecting public health; however, the provisions relating to patents and pharmaceutical regulation are confusing even to specialists in the field of intellectual property law and medicine regulation. Therefore, countries with little capacity for interpreting and acting on international trade agreements are most at risk in terms of losing access to medicines. Regulators and legislators must acquire the relevant technical expertise to use the flexibilities, such as compulsory licensing and parallel importation, to improve access to medicines in their countries.

Substantial legal and administrative obstacles exist to introducing and implementing these complex provisions. Several constraints that developing countries face at the national level in their efforts to use TRIPS flexibilities are mentioned below, but countries can address many of these constraints by adopting complementary policy and legal measures.

Country Study 3-2 Countries in Asia, Latin America and the Caribbean, and Africa that are using TRIPS flexibilities

Although TRIPS establishes minimum standards that WTO members must follow related to intellectual property rights, certain flexibilities in the agreement allow exemptions to developing countries, especially regarding pharmaceutical patents. However, taking advantage of these flexibilities requires that the eligible countries amend their national intellectual property rights legislation.

An analysis of forty-nine countries in Asia, Latin America and the Caribbean, and Africa looked at the extent to which countries have incorporated the TRIPS flexibilities affecting pharmaceuticals and public health. Updated use of flexibilities in selected African countries is also available (Munyuki and Machedmedze 2010; UNAIDS, WHO, and UNDP 2011).

Countries implementing selected TRIPS flexibilities

National law provisions	Asia (n = 13)	Latin America/ Caribbean (n = 19)	Africa (n = 17)
Pharmaceutical products are patentable	10 (77%)	18 (95%)	11 (65%)
Data protection	6 (46%)	16 (84%)	6 (35%)
Government or noncommercial use allowed	7 (54%)	9 (47%)	17 (100%)
Exhaustion of rights			
• National exhaustion	2 (15%)	4 (21%)	6 (35%)
• International exhaustion (allowing parallel importation)	6 (46%)	13 (68%)	7 (41%)
• No exhaustion	3 (23%)	1 (5%)	1 (6%)
Early working exception	4 (31%)	6 (32%)	5 (29%)
Compulsory licensing grounds			
• Failure to work/exploit	10 (77%)	14 (74%)	15 (88%)
• Anticompetitive practice	5 (38%)	14 (74%)	5 (29%)
• Dependent patents	7 (54%)	10 (53%)	10 (59%)
• Demand not met on reasonable terms	3 (23%)	5 (32%)	13 (76%)
• Public interest	10 (77%)	15 (79%)	8 (47%)
• National emergency	5 (38%)	11 (58%)	6 (35%)
• No provision	2 (15%)	0 (1 unknown)	0

Source: Musungu and Oh 2006.

Lack of technical expertise to incorporate TRIPS flexibilities into national law

Countries can use the flexibilities offered by TRIPS only if they incorporate them into their legislation; however, many developing countries have not done so for various reasons, including a lack of technical expertise and information on best practices. Resource-limited countries are generally not aware of the measures undertaken by their counterparts around the world. As a result, countries within a region with similar access problems may adopt different strategies, with varying degrees of success. Country Study 3-2 summarizes the extent to which TRIPS flexibilities are being used in forty-nine different countries. For example, while 100 percent of the countries surveyed in Africa provided for government or noncommercial use in their laws, less than half the countries in Asia or Latin America/Caribbean had done so.

Insufficient domestic research and manufacturing capacities

Most developing countries have limited pharmaceutical research and manufacturing capacities. The challenge for these countries is how to enlarge their capacity for research through increased investment in basic sciences, R&D, and technological innovation. As technology evolves and becomes an important tool for development, it also becomes more of a means of gaining competitive advantage.

Developing countries face significant barriers that may block their own R&D efforts or opportunities for collaboration with other countries, such as insufficient numbers of trained researchers and inadequate research support at local universities or institutions. In addition, an individual country's interest in bolstering indigenous, national manufacturing capacity may limit regional, multicountry collaboration

Country Study 3-3**Differences between bilateral trade agreements and TRIPS**

Many countries that trade with the United States are members of the WTO and therefore are obligated to abide by the TRIPS provisions. However, they may enter into bilateral trade agreements that commit them to more stringent intellectual property rules than TRIPS (TRIPS-plus) in exchange for concessions in other areas of trade—often access to the U.S. market for agricultural or manufactured goods. Evaluating the implications of bilateral trade agreements on public health can be difficult. The benefits and costs associated with protecting pharmaceutical patents vary by country, and these agreements will take many years to take full hold. The public health community has raised concerns regarding these bilateral agreements and their possible effect on access to medicines, especially how they may limit the availability of generic medicines in developing countries.

The following are key differences in intellectual property provisions between bilateral trade agreements and TRIPS:

Use of compulsory licenses. Under TRIPS, governments may issue a compulsory license to obtain generic medicines by temporarily overriding a patent. Compulsory licensing is an important tool for governments to protect the public interest or to remedy anticompetitive behavior. Four bilateral agreements now limit the use of compulsory licensing to emergencies, antitrust remedies, and cases of public noncommercial use.

Test data protection. Getting approval to market medicines requires a company to submit test data to regulatory authorities to prove a medicine's safety and efficacy. The protection of such data differs from country to country. TRIPS requires only that test data be protected against "unfair commercial use." However, most bilateral

agreements require governments to guarantee exclusive use of test data for pharmaceutical products for five years, which is the U.S. standard. Furthermore, some free-trade agreements require an additional data exclusivity period for new uses of already approved medicines, and some go even further by prohibiting generic manufacturers from using test data submitted to a regulatory authority in another territory—even outside the trade agreement territory. These new test data provisions may be an obstacle for governments using compulsory licensing.

Patent terms. Bilateral agreements mandate the extension of patent protection beyond the current twenty-year limit mandated in TRIPS to compensate for procedural delays in granting patents or in securing marketing approval for pharmaceuticals.

Use of parallel imports. Parallel importation allows a government to import pharmaceuticals that have been placed on the market more cheaply in foreign markets, which can help reduce medicine prices. TRIPS allows WTO members to establish their own national policies regarding whether to permit parallel importation of patented medicines. By contrast, many bilateral agreements allow patent holders to prevent parallel importation.

Bolar exception. TRIPS does not limit generics companies from starting the process of entering a new market before a patent has expired. Generics producers often take this action so they can be ready to sell their product immediately after the patent expires. Most bilateral agreements prevent marketing approval of a generic medicine during the patent term without the consent of the patent holder, which could make compulsory licenses an ineffective way to allow competition from generics manufacturers.

to produce medicines unless the benefits of investment in R&D and procurement of locally manufactured products can be shared across the region.

Insufficient capacity for medicine registration and regulation

Pharmaceutical registration is the process by which a country's regulatory authority assesses the safety, quality, and efficacy of medicines to approve their use. Countries normally require that all medicines offered for sale in their territories be registered locally. Although the ultimate role of medicine

regulation is to protect public health, national regulatory authorities in developing countries often lack the facilities and expertise needed to review medicines destined for their national markets.

Regulatory authorities handle applications for new chemical entities, generic medicines, new fixed-dose combination products, and even herbal medicines. Innovative new products, including important antimalarials and antiretroviral medicines for HIV/AIDS, require more complex assessment than their generic equivalents; therefore, most countries carry out a fast-track review based on prior approval by U.S. or EU regulatory agencies. Where a comparable product is

Country Study 3-3 Differences between bilateral trade agreements and TRIPS (continued)

Differences between bilateral trade agreements and TRIPS: specific examples

Intellectual property provisions	U.S.-Vietnam (2001)	U.S.-Jordan (2001)	U.S.-Singapore (2003)	U.S.-Chile (2003)	U.S.-Morocco (2004)	U.S.-Australia (2004)	U.S.-DR-CAFTA ^a (2005); U.S.-Bahrain (2006)
Patent term	Extension given for delays caused by regulatory approval process.	Extension given for delays caused by regulatory approval process.	Extension given for delays caused by regulatory approval process. In addition, extension given when a delay in the granting of the patent exceeds four years from the filing of the application (five years for U.S.-Chile) or two years after a request for examination (three years for U.S.-Chile).	Extension given for delays caused by regulatory approval process. In addition, extension given when a delay in the granting of the patent exceeds four years from the filing of the application (five years for U.S.-Chile) or two years after a request for examination (three years for U.S.-Chile).	Extension given for delays caused by regulatory approval process. In addition, extension given when a delay in the granting of the patent exceeds four years from the filing of the application (five years for U.S.-Chile) or two years after a request for examination (three years for U.S.-Chile).	Extension given for delays caused by regulatory approval process. In addition, extension given when a delay in the granting of the patent exceeds four years from the filing of the application (five years for U.S.-Chile) or two years after a request for examination (three years for U.S.-Chile).	Extension given for delays caused by regulatory approval process. In addition, extension given when a delay in the granting of the patent exceeds four years from the filing of the application (five years for U.S.-Chile) or two years after a request for examination (three years for U.S.-Chile).
Grounds for issuing compulsory licenses	Compulsory licenses limited to national emergencies, remedy, and for public noncommercial use.	Compulsory licenses limited to national emergencies, remedy, and for public noncommercial use.	Compulsory licenses limited to national emergencies, as antitrust	Compulsory licenses limited to national emergencies, as antitrust	Compulsory licenses limited to national emergencies, as antitrust	Compulsory licenses limited to national emergencies, as antitrust	Compulsory licenses limited to national emergencies, as antitrust
Link between patent status and pharmaceutical marketing approval	No specific provision.	Patent owner must be notified when marketing approval is sought during the patent term.	Marketing approval of a generic medicine is prohibited during the patent term, unless authorized by the patent owner. In addition, the patent holder must be notified of the identity of the generic company requesting marketing approval.	Marketing approval of a generic medicine is prohibited during the patent term, unless authorized by the patent owner. In addition, the patent holder must be notified of the identity of the generic company requesting marketing approval.	Marketing approval of a generic medicine is prohibited during the patent term, unless authorized by the patent owner. In addition, the patent holder must be notified of the identity of the generic company requesting marketing approval.	Marketing approval of a generic medicine is prohibited during the patent term, unless authorized by the patent owner. In addition, the patent holder must be notified of the identity of the generic company requesting marketing approval.	Marketing approval of a generic medicine is prohibited during the patent term, unless authorized by the patent owner. In addition, the patent holder must be notified of the identity of the generic company requesting marketing approval.
Test data protection for pharmaceutical products	Data exclusivity for a "reasonable" period, normally not less than five years.	TRIPS standards apply. In addition, length of protection should be the same as in the originator's country.	Data exclusivity for five years. In addition, where pharmaceutical regulators rely on foreign marketing approvals, data exclusivity applies automatically at home.	Data exclusivity for five years.	Data exclusivity for five years. Additional three-year data exclusivity triggered by "new clinical information."	Data exclusivity for five years. In addition, data exclusivity applies in all free-trade agreement member countries, once first obtained in another territory. In the case of U.S.-Bahrain, additional three-year data exclusivity triggered by "new clinical information" (with equivalent provisions on cross-border application).	Data exclusivity for five years. In addition, data exclusivity applies in all free-trade agreement member countries, once first obtained in another territory. In the case of U.S.-Bahrain, additional three-year data exclusivity triggered by "new clinical information" (with equivalent provisions on cross-border application).
Parallel imports	No specific provision.	TRIPS standards apply.	Patent holders may limit parallel imports of pharmaceutical products through licensing contracts.	TRIPS standards apply.	Patent holders may limit parallel imports through licensing contracts.	Patent holders may limit parallel imports through licensing contracts.	TRIPS standards apply.

Source: Fink and Reichenmiller 2005.

^a Dominican Republic, Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua.

already on the market, the assessment of generic medicines tends to take place at the national level (see Chapter 6).

When a country's pharmaceutical regulatory process is unwieldy, that can delay the entry of needed medicines in a particular market and act as a barrier to access as well as to growth of the local pharmaceutical industry. Many developing countries have no reliable fast-track procedure for registering new essential medicines, such as antiretroviral medicines. The requirement for local clinical trials can also deter and delay registration. With growing demand for rapid registration of new and more complex medicines, pharmaceutical regulatory capacity needs to develop in a way that also protects public health.

Procurement is also affected. A country's procurement agency must determine whether a medicine is locally under patent before it can import a generic version of the medicine; however, finding this information can be complicated and difficult (Tayler 2004). The procurement agency can ask the national patent office to help, but staff may not have the capacity to undertake such a request. Professional firms will search for patents, but the fees may be prohibitive. Médecins Sans Frontières has published the patent landscapes for HIV/AIDS medicines in developing countries, although it notes that it cannot promise complete accuracy. WHO's AIDS Medicines and Diagnostics Service maintains a drug regulatory database and additional information related to HIV/AIDS products (http://www.who.int/hiv/amds/patents_registration/en/index.html). Other organizations have called for the creation of a global patent database, including the World Health Assembly in its *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property* (WHO 2008).

TRIPS-plus provisions

"TRIPS-plus" refers to the incorporation into national legislation of intellectual property rights that are stricter than those mandated by TRIPS. This includes efforts to extend patent life beyond the twenty-year TRIPS minimum, limit compulsory licensing in ways not required by TRIPS, limit exceptions that facilitate the prompt introduction of generics, and extend the period of data exclusivity. Because the public health effect of TRIPS requirements has yet to be fully assessed, WHO recommends that developing countries be cautious about enacting legislation that is more stringent than the TRIPS requirements. From a public health perspective, countries that are not bound by TRIPS should evaluate TRIPS requirements and incorporate into national legislation and trade-related practices those elements that clearly benefit national public health interests.

Existing intellectual property protection in many resource-limited countries is often stronger than the mini-

um required by TRIPS; so in countries such as Kenya and Malawi, the existing legislation is already considered TRIPS-plus (DFID 2004). These countries will not be able to use TRIPS-compliant flexibilities unless they amend their national legislation. Moreover, almost all developing countries will need to change their legislation to take advantage of the import/export mechanisms in the Paragraph 6 Decision.

Free-trade agreements. One form of TRIPS-plus is bilateral and regional free-trade agreements that have intellectual property components. Most developing-country members face difficulties in trade negotiations, where they are asked to accept obligations in the public health sector in exchange for concessions in areas such as market access for agricultural products, which may be important to their economies (see Country Study 3-3). For example, both Vietnam and Cambodia entered into bilateral trade agreements with the United States that contain intellectual property requirements, including compliance with TRIPS standards, when these countries were not members of the WTO.

International patent law harmonization. An indirect influence on the evolution of TRIPS-plus provisions is the World Intellectual Property Organization (WIPO) Patent Agenda initiative. WIPO is a specialized agency of the United Nations whose primary objective is the promotion of creative intellectual activity and the facilitation of the transfer of technology to developing countries. The WIPO Patent Agenda initiative comprises a set of interrelated activities designed to harmonize the international patent system by building a legal framework that would create something comparable to a global patent. Such a system would, in essence, reduce the need for countries to have national patent offices, but more important, it would eliminate the flexibilities permitted by the TRIPS agreement that allow developing countries exceptions to rules on patents—essentially creating TRIPS-plus standards for everyone. A WIPO forum in 2006 allowed stakeholders to present their arguments both for and against the harmonization efforts and how such efforts might affect public health (WIPO 2006). Opinions on the benefits of harmonization have been sharply divided, and as of 2011, the WIPO standing committee was still trying to finalize recommendations for an international patent system.

3.4 Access to medicines in the TRIPS era

The globalized intellectual property system is one factor among many that affects access to pharmaceuticals in developing countries. Sometimes, countries may adopt policies that adversely influence access, such as applying tariffs or taxing medicines. Other restraints include a lack of human and financial resources, reliance on the public sector, and absence of an adequate infrastructure to supply and admin-

ister medicines effectively. For example, in sub-Saharan Africa, medicines for HIV/AIDS treatment are increasingly available from multiple sources: Indian-manufactured copies of patented antiretrovirals, generic purchases, brand-name purchases, and donations from pharmaceutical companies; bilateral and multilateral programs provide funding for procurement. Still, less than half the patients who need treatment are getting it, in part because of weak pharmaceutical management infrastructures and too few trained health professionals.

As intellectual property rights are strengthened globally, the cost of medicines in developing countries is likely to increase unless effective steps are taken to facilitate their availability at lower costs. Moreover, countries need to adopt a range of policies to improve access to medicines. Additional resources to improve services, supply mechanisms, and infrastructure are critical. Countries need to ensure that their intellectual property protection legislation does not run counter to public health policies and that other economic policies are in harmony with health policy objectives.

Box 3-2 includes a list of issues for country-level policy makers to keep in mind regarding intellectual property rights and access to medicines.

Using available resources to develop expertise

A lack of clarity often exists about the options available on the patent status of medicines and importing generic medicines from foreign producers. Within developing-country governments, experience in implementing TRIPS and its flexibilities is limited, and the political will to act is often low. Making changes to a country's intellectual property regime requires effective cooperation between different government departments, including health, trade, and industry, which may have limited experience in developing common policy.

The international rules regarding intellectual property are developing quickly. Active participation by developing countries in discussions of the future of the global intellectual property system is essential to ensure both

Box 3-2

Issues on intellectual property and pharmaceuticals for policy makers

Governments should—

- Avoid provisions in bilateral trade agreements that could reduce access to medicines in developing countries
- Increase funding for research projects run by public-private partnerships and by developing countries, and make that funding more sustainable
- Develop advance-purchase schemes for vaccines, medicines, and diagnostics
- Incorporate digital libraries of traditional medical knowledge into their patent offices' data to ensure that data contained in them are considered when patent applications are processed
- Make available reliable information on the patents they have granted
- Amend their laws to allow compulsory licensing for export consistent with TRIPS
- Eliminate tariffs and taxes on health care products

Governments of developing countries should—

- Identify a trade and pharmaceuticals focal point within the ministry of health
- Establish contacts, perhaps a working group, with trade and other key ministries
- Obtain reliable specialized legal advice
- Develop a mechanism to monitor the health effect of new trade agreements

- Promote health research that is in line with public health needs
- Promote the use of research exemptions as part of their patent law
- Invest appropriately in health-delivery infrastructure
- Improve financing of the purchase of medicines and vaccines
- Make use of compulsory licensing provisions where they will promote innovation or access to medicines

National patent and related legislation should—

- Promote standards of patentability that take health into account
- Establish process and product patents for twenty years
- Incorporate exceptions, trademark provisions, data exclusivity, and other measures to support generic competition
- Permit compulsory licensing, parallel importation, and other measures to promote availability and ensure fair competition
- Permit requests for extension of the transitional period for TRIPS implementation, if needed and if eligible
- Carefully consider national public health interests before instituting TRIPS-plus provisions

Sources: WHO 2001; CIPIH 2006.

the legitimacy of standard setting and its appropriateness to countries at very different levels of development. As the rules evolve, their impact must be properly understood if policies are to be based on relevant evidence.

Box 3-3 contains a list of organizations and resources that provide information on intellectual property rights and public health.

Regional collaboration

The constraints on national efforts to implement TRIPS flexibilities to improve public health show that developing countries need significant additional resources and technical assistance. One way to provide such support is through regional mechanisms that can complement national efforts. A regional approach to using the TRIPS flexibilities creates better policy conditions for addressing the challenges of implementing TRIPS flexibilities, which can be daunting for each individual country. Politically, a collective regional position on matters of public health and access to medicines can provide bargaining advantage for developing countries in their negotiations within WTO and with developed-country trading partners.

A regional approach to the use of TRIPS flexibilities could enable similarly situated countries to address their constraints jointly by drawing on each other's expertise and experience and by pooling and sharing resources and information. Policies that are likely to benefit significantly from regional collaboration in implementing TRIPS flexibilities include those related to production of pharmaceuticals, regulatory approval of medicines, market surveillance and maintenance of quality standards, and import rules and competition issues (Musungu, Villanueva, and Blasetti 2004).

3.5 Intellectual property and R&D for new medicines

Patent protection is an incentive for R&D for new medicines. The patent-holding company has exclusive rights over the product for a defined period, protecting it from competition in the country where the patent is recognized. Patent protection allows the manufacturer to set prices according to what the market will bear, which is likely to be well above production cost for medicines that treat widespread and severe illnesses in high-income markets. The temporary monopolies that patents create reward firms for taking expensive risks in developing new medicines.

Trends in new medicine innovation

Following years of rapid innovation from 1980 to the mid-1990s, evidence suggests an overall decline in the output

of global R&D into new medicines. Although R&D spending tripled between 1990 and 2000, the annual number of new medicines approved fell from its peak of more than fifty in 1996 to thirty-two in 2000, the lowest output in more than twenty years (WHO 2004). The increasing costs of R&D and the decrease in productivity have been factors in encouraging mergers between pharmaceutical companies. Rising R&D costs are also prompting manufacturers to develop strategic alliances with small research companies, particularly biotechnology companies, reflecting the emerging commercial potential of genomics-based discoveries.

In general, patents are most effective at attracting investment in products that have commercial prospects, leaving important gaps where R&D is the most commercially risky. The diseases and conditions that affect people in the world's major markets largely determine where the pharmaceutical industry's investments go. Of the 1,393 new chemical entities developed between 1975 and 1999, only 16 were for the treatment of tropical diseases and tuberculosis (Trouiller et al. 2002). The Global Forum for Health Research highlights the fact that only 10 percent of R&D spending is directed to the health problems that account for 90 percent of the global disease burden—the so-called 10/90 gap (see <http://www.globalforumhealth.org>). For example, no new class of anti-tuberculosis medicine had been developed in almost twenty years, despite the high global burden of this disease. Therefore, the debate centers around how to reach a balance between meeting the high costs of pharmaceutical R&D and creating incentives to stimulate access to those medicines in poor and developing countries.

Encouraging R&D in neglected diseases

Various initiatives are being used to encourage R&D into medicines for neglected diseases. Public-sector or donor funds or research mandates often address gaps in research that are not adequately provided for by intellectual property rights incentives. Some “push” mechanisms work by reducing costs and risks, including tax credits, grants, and support for clinical trials. “Orphan” medicine laws are examples of this type of mechanism. Another mechanism, called a “pull” initiative, creates a market for medicines or increases their profitability; for example, when a company develops a medicine for a neglected disease and in return gets the right to extend the patent on one of its more profitable products. Another type of proposal to tackle the problem of R&D for these forgotten medicines is the creation of public-private partnerships that mobilize expertise, capacity, and funding from both the public and private sectors (see Box 3-4). In fact, recent research has shown that two-thirds of projects developing medicines for neglected diseases involve these sorts of public-private collaborations (Moran 2005).

Box 3-3**Sources of information on intellectual property rights and public health**

Business and Industry Advisory Committee to the OECD (BIAC). BIAC is the business community's representative to the Organisation for Economic Co-operation and Development (OECD). BIAC's members are the major business organizations in the OECD member countries. BIAC ensures that business and industry needs are adequately addressed in OECD policy decisions. <http://www.biac.org>

Commission on Intellectual Property Rights. The British government set up the commission to look at how intellectual property rights might work better for developing countries. The commission's final report (in seven languages) and supporting documents are available on its website. <http://www.iprcommission.org>

Commission on Intellectual Property Rights, Innovation and Public Health. The World Health Assembly (WHO's highest body) set up this independent commission in 2003 to collect and analyze data and proposals on intellectual property rights, innovation, and public health. The commission presented its final report in April 2006. Documents relating to the commission's work are available on its website. <http://www.who.int/intellectualproperty/en>

Knowledge Ecology International. Knowledge Ecology International is a nonprofit organization that focuses on issues related to intellectual property and health care. Its website includes links to many intellectual property documents and several related listservs. <http://www.keionline.org>

Health Action International/WHO Drug Prices Project. This project seeks to gather and publicize accurate data on pharmaceutical price structure as a first step to negotiation, management, and policy to bring prices down and make medicines more affordable. <http://www.haiweb.org/medicineprices>

Intellectual Property Watch. This nonprofit, independent news service reports on the interests and activities that influence the design and implementation of international intellectual property policies. <http://www.ip-watch.org/index.php>

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). IFPMA is a global organization that represents research-based pharmaceutical, biotechnology, and vaccine companies and national industry associations in developed and developing countries. <http://www.ifpma.org>

International Generic Pharmaceutical Alliance (IGPA). IGPA is a network of associations representing manufacturers of generic medicines; it comprises the generic medicine associations of Canada, Europe, India, Japan, and the United States, with Brazil, Jordan, Taiwan, and South Africa having observer status. <http://www.egagenerics.com>

IPRsonline.org. IPRsonline.org is an Internet portal containing a selection of online documents and resources

related to intellectual property rights and sustainable development, including discussion papers from various organizations, a calendar of related events, latest news on intellectual property rights, and links to listservs and relevant institutions. <http://www.IPRsonline.org>

Médecins Sans Frontières Campaign for Access to Essential Medicines. The campaign is an advocacy effort to promote policies to lower medicine prices and push for increased research into neglected diseases. <http://www.accessmed-msf.org>

Pharmaceutical Research and Manufacturers of America (PhRMA). This industry organization represents the United States' leading pharmaceutical research and biotechnology companies. <http://www.phrma.org>

Science and Development Network. This Internet-based network, also known as SciDev.Net, provides up-to-date information on science- and technology-related issues that affect developing countries, including news, policy briefs, key documents, and feature articles. It includes a section devoted to intellectual property. <http://scidev.net>

South Centre. South Centre is an intergovernmental organization that promotes the interests of developing countries by analyzing development problems and experience and providing intellectual and policy support on global issues including trade, development, and intellectual property rights. <http://www.southcentre.org>

World Health Organization (WHO). In 2006, WHO member states established an Intergovernmental Working Group (IGWG) on Public Health, Innovation and Intellectual Property. The working group's mandate was to prepare a global strategy and plan of action on public health, innovation and intellectual property to address conditions disproportionately affecting developing countries. Documents related to IGWG activities can be found on its website <http://www.who.int/phi/documents/en/>. In addition, the website of WHO's unit on Trade, Foreign Policy, Diplomacy and Health includes an updated list of related publications and links to other WHO sites related to globalization. <http://www.who.int/trade/en>

World Intellectual Property Organization (WIPO). This specialized agency of the United Nations administers twenty-three international treaties dealing with different aspects of intellectual property protection. It also provides technical assistance to member countries needing help with developing national systems for intellectual property. <http://www.wipo.org>

World Trade Organization (WTO). This international organization deals with the rules of trade between nations at a global or near-global level. See Box 3-1 for a detailed discussion. <http://www.wto.org>

Box 3-4**Using public-private partnerships to develop medicines for neglected diseases**

Some partnerships act like pharmaceutical companies that develop their own medicines, whereas others act more like funding agencies. An example of the former type of partnership is the Drugs for Neglected Diseases Initiative, started by Médecins Sans Frontières, with the support of several ministries of health, research institutes, and pharmaceutical manufacturers—including partnerships with southern research centers. Initially focused on treatment for sleeping sickness, leishmaniasis, and Chagas disease, this nonprofit research organization develops or adapts medicines for patients suffering from several different diseases with little profit-making potential. The initiative's first commercial development, in collaboration with Sanofi-Aventis SA, is a new anti-malarial medicine. This inexpensive, fixed-dose combination of artesunate and amodiaquine was launched in 2007 and by 2011, more than 80 million treatments had been distributed.

The Medicines for Malaria Venture, founded in 1999, is a public-private partnership concerned with the discovery, development, and registration of new medicines for the treatment and prevention of malaria; similarly, the Global Alliance for TB Drug Development is committed to delivering new anti-tuberculosis medicines; it has three medicine candidates in clinical trials, including moxifloxacin, which is the nearest to approval. Moxifloxacin should

shorten the treatment duration for drug-sensitive, adult tuberculosis cases. The business model of the nonprofit pharmaceutical company Institute for One World Health is to take promising leads on new medicines that lack a profitable market and complete the development process. The company then collaborates with other companies and nonprofit hospitals and organizations in the developing world to conduct medical research and to manufacture and distribute the newly approved therapies.

In the vaccines area, the International AIDS Vaccine Initiative researches and develops HIV vaccine candidates by directing and financing partnerships with private companies and academic and government agencies, including those in developing countries; the Malaria Vaccine Initiative operates in a similar fashion for malaria vaccine projects. Further downstream in the R&D process, the Global Alliance for Vaccines and Immunization works to enhance the commercial attractiveness of vaccines by stimulating demand in developing country markets, strengthening infrastructure, and guaranteeing some product purchase. The idea is that a strong advance commitment to purchasing safe and effective vaccines will reduce the financial risks faced by private-sector manufacturers and help redirect research toward the vaccines that are a priority for resource-limited countries.

These mechanisms fill some important gaps between the opportunities that face commercial medicine manufacturers, on the one hand, and the global burden of disease, on the other. Strong public-sector involvement is needed to ensure that new medicines are created to address priority health problems in developing countries. To help address such issues, WHO created an intergovernmental working group to develop a framework that identifies and prioritizes needs-based research for diseases that disproportionately affect developing countries. As a result of the group's work, in 2008 the sixty-first World Health Assembly adopted Resolution WHA 61.21: Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. In 2009, the World Health Assembly adopted Resolution WHA 62.16: Final Agreement on Stakeholders in the Plan of Action on Public Health, Innovation, and Intellectual Property. The global strategy and plan of action comprises eight elements, which are designed to promote innovation, build capacity, improve access, and mobilize resources. Additional information and materials are available at

WHO's website: http://www.who.int/phi/implementation/phi_globstat_action/en/index.html.

Technology transfer

Technology transfers involve knowledge sharing between developed and developing countries. TRIPS recognizes that “the protection and enforcement of intellectual property rights 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.

As encouraged by TRIPS, the transfer of technology is potentially an important source of growth in developing countries. One of the reasons that developing countries do not use the compulsory licensing mechanism in TRIPS is because of a lack of mechanisms for technology transfer. Although compulsory licensing permits an invention to be used without the consent of the patent holder, it does not guarantee that the country will have

the appropriate technology available, including facilities for manufacturing.

Increasingly, technology transfer is a component in non-profit initiatives and public-private partnerships that involve developing-country governments and the private sector. For example, several R&D companies are linking with industry partners in India, China, and elsewhere to increase the supply of patented medicines. In the cases of South Africa and Kenya, advocacy efforts on the part of governments and civil society resulted in patent holders granting voluntary licenses to local manufacturers. WHO, international philanthropic groups, and nongovernmental organizations are brokering collaborations between R&D and generics companies.

In all of these partnerships, both the research-based company and the developing country stand to benefit. For example, a company benefits from being seen as committed to corporate social responsibility, and developing-country partners get increased access to scientific technology and skills, new products for new markets, and experience in working with international standards.

Alternative paradigms in R&D of pharmaceuticals

In addition to public-private partnerships, a different R&D paradigm for pharmaceuticals is the use of an open collaborative model, such as the Human Genome Project's successful international effort to sequence the human genome,

which used a nonproprietary system sanctioned by the governments of six major countries. One of the innovative aspects of this model is the publicly available results, which has been a growing trend in biomedical research (see additional discussion in Chapter 34). The collaborative and transparent nature of this kind of openly accessible research is appealing, but its application to pharmaceutical R&D is still unclear.

Others have suggested creating a global decision-making process to name targets for R&D funding, with each individual country deciding how it will meet those targets (Hubbard and Love 2004). The theory is that to meet the R&D targets, some countries will choose public-sector management of investments, while others will rely on a more private (profit or nonprofit) approach. Most will choose mixed approaches. Another idea is to set up a global fund to pay for research into medicines for neglected diseases; such medicines would then be supplied free or at greatly discounted prices to resource-limited countries. One R&D paradigm or another is unlikely to be chosen explicitly. Box 3-5 illustrates how some developing countries are approaching R&D for new medicines.

UNITAID is working to establish an international patent pool that would, in theory, increase access to patents and promote the development of more affordable medicines in developing countries. The concept of the pool is for patent holders to give up their patents and allow their intellectual

Box 3-5 How developing countries are approaching R&D

Only 4 percent of the entire global spending on health research is by low- or middle-income countries, and the majority is public-sector funded. Researchers in all but the most technologically advanced countries find developing new and innovative pharmaceutical products difficult without adequate infrastructure or equipment, and few countries have the regulatory framework to oversee the process of ensuring pharmaceutical quality, efficacy, and safety. However, developing and transitional countries such as India, Indonesia, South Africa, and Brazil have created successful industries specializing in the manufacture of generic medicines, while a few countries have even developed new medicines.

For example, in the 1970s, Pliva, a small Croatian company, developed a new antibiotic called azythromycin, which looked promising in animal trials. Pliva did not have the resources necessary to mass produce and market the new medicine in the world market. It patented the product globally, which led to a licensing agreement with the U.S. pharmaceutical giant Pfizer to market the medi-

cine worldwide, while Pliva retained marketing rights in Eastern Europe. Zithromax became one of Pfizer's top antibiotic products.

Although this kind of R&D success may not be realistic for every small company, other ways exist to make progress. For instance, the generic pharmaceutical industry in India was the first to create a fixed-dose combination of antiretroviral medicines for HIV/AIDS, which is less expensive, and by simplifying the dosage improves patients' ability to adhere to their treatment. Scientists in other countries, such as South Africa and China, are focusing their R&D efforts on taking centuries-old herbal preparations used in traditional medicine and creating modern medicines. Some of these R&D efforts are advancing with the help of public-private partnerships, with large pharmaceutical companies providing the technology and expertise, and some are using a combination of state and private financing or nonprofit foundation funding to develop their pharmaceutical sectors.

Source: Fleck 2005.

property rights to be managed by the pool under certain conditions. By giving up a period of exclusive marketing rights, patent holders receive royalties from the pool in exchange for a license to produce the medicine in a developing country (UNAIDS 2009). WHO's Expert Working Group on Research and Development Financing rated the patent pool model high for operational efficiency, feasibility, and impact on health in developing countries. As it is based on the voluntary donation of intellectual property, however, questions remain about the quantity and quality of intellectual property that patent holders would choose to donate, particularly outside the area of HIV/AIDS. For the pool to work well, a minimum critical mass is needed, and it is not clear whether this would be achieved voluntarily for many diseases (WHO 2010). ■

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★ = Key readings.

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Glossary

- Bioequivalence:** Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and the rate and extent of bioavailability are similar to such a degree that their effects can be expected to be essentially the same.
- Bolar (early working) exception:** An exception to patent rights allowing a third party to undertake, without the authorization of the patentee, acts in respect of a patented product necessary

for the purpose of obtaining marketing approval for the sale of a product.

- Compulsory license:** A license to exploit a patented invention granted by the state upon request of a third party.
- Data exclusivity:** A legal provision that data collected (for example, the results of clinical trials) for obtaining marketing approval may not be used for a specified period by the regulatory authorities to grant approval to a generic equivalent.
- Data protection:** An obligation imposed on third parties to protect test data, such as the results of clinical trials, that are usually collected to comply with government regulations on the safety, efficacy, and quality of a broad range of products (for example, drugs, pesticides, medical devices). For example, TRIPS provides for the protection of such data against unfair commercial use.
- Differential pricing:** The practice of setting different prices for different markets, typically higher prices in richer markets and lower prices in poorer markets.
- Doha Declaration:** The Declaration on the TRIPS Agreement and Public Health agreed upon at the Doha WTO Ministerial Meeting in 2001.
- Downstream research:** Applied research usually directed at the development of a product or process with a potential commercial application.
- Evergreening:** A term popularly used to describe patenting strategies that are intended to extend the patent term on the same compound.
- Exhaustion of rights:** Principle whereby the right holder's intellectual property rights in respect of a product are considered exhausted (that is, he or she can no longer exercise any rights) when that product has been put on the market by the right holder or by an authorized party.
- Incremental innovation:** Innovation that builds incrementally on previous innovation, as compared with “breakthrough” innovation, which is a completely novel means to prevent, treat, or cure a particular disease.
- Intellectual property rights:** Rights awarded by society to individuals or organizations over inventions, literary and artistic works, symbols, names, images, and designs used in commerce. They give the titleholder the right to prevent others from making unauthorized use of their property for a limited period.
- Interchangeability:** A pharmaceutical product that is therapeutically equivalent to a comparator (reference) product.
- Parallel imports:** The purchase of a patented medicine from a lawful source in an exporting country and its importation without seeking the consent of the “parallel” patent holder in the importing country.
- Patent:** An exclusive right awarded to an inventor to prevent others from making, selling, distributing, importing, or using the invention, without license or authorization, for a fixed period of time. In return, the patentee discloses the invention to the public. Three requirements usually exist for patentability: novelty; inventive step or nonobviousness (knowledge not obvious to one skilled in the field); and industrial applicability or utility.
- Patent pools:** An agreement between two or more patent owners to license one or more of their patents to one another or third parties.

Source: Adapted from CIPIH 2006.