Developing Countries' Access to Patented Pharmaceuticals and the International IP System

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I. Introduction

THE ISSUE of developing countries' access to patented pharmaceuticals is highlighted by the continuing HIV/AIDS epidemic and the knowledge that modern patented drugs can significantly prolong healthy life and prevent mother-to-infant transmission. In addition, the long duration of treatment with current medicines for patients with tuberculosis (TB), the rise of drug-resistant tuberculosis, widespread resistance to most malaria drugs, and lack of appropriate medicines for many tropical parasitic diseases, shows the need to develop new drugs for these diseases – diseases that are most prevalent in developing countries. Most new drugs are developed by large US, European or Japanese pharmaceutical companies which hold patents of up to 20 years duration.

To what extent should developing countries beset by these diseases be able to obtain these drugs at low prices - prices far below the selling price in developed countries, yet often still far above what most of their people can afford in developing countries? This is the central question underlying this paper. The answer involves balancing considerations related to public health against the integrity of an emerging global intellectual property (IP) system – a system intended to meet the business needs of companies in developed countries but also to encourage innovation in developing as well as developed countries. It also involves balancing immediate humanitarian concerns against long term concerns related to incentives to develop drugs to meet the needs of developing countries.

II. The international IP and trade framework and the pharmaceutical industry

Under the Trade Related Aspects of Intellectual Property Rights

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(TRIPS) Agreement which constitutes one of the founding agreements of the World Trade Organization (WTO), all WTO members must establish laws which protect patent rights, allow patents on pharmaceuticals, and afford foreigners and domestic patent applicants/holders equal rights. Patents provide a legal means for pharmaceutical manufacturers and other patent holders to prevent unauthorized copying of their products. Because new drugs take years and much expense to develop and yet are relatively easy to copy once development is complete, patent protection is critically important to pharmaceutical manufacturers that are developing new drugs. By preventing rivals from copying their products, pharmaceutical manufacturers can charge prices that are much higher than their basic manufacturing costs. In this way, they can recoup their research and development (R&D) costs and earn profits that may attract further investment in new drug discovery and development.

Some pharmaceutical companies focus primarily on manufacturing drugs that do not have patent protection – either because patent protection has expired or because their home country does not issue patents on pharmaceuticals.[1] These companies are known as generic drug manufacturers. Their costs are close to the basic costs of manufacturing the drugs, which are small compared to the costs associated with R&D, obtaining first-use regulatory approval from an agency such as the Food and Drug Administration (FDA), and marketing. The business model of generic manufacturers is based upon manufacturing and selling at a cheaper price the same medicines developed by other pharmaceutical companies, as soon as these medicines are off patent. Indian generic manufacturers are currently the world's lowest cost producers of many of the now approximately 15 widely used drugs for HIV/AIDS. They are also the lowest cost producers of certain combinations of these drugs. (Current medical knowledge

1. To my knowledge, the principal developing country with significant drug manufacturing capabilities that still does not provide patent protection for pharmaceutical compounds is India. As a least developed WTO-member country, India has until 2005 to implement the TRIPS agreement with respect to pharmaceuticals. In anticipation of this implementation, India has established a "mailbox" system under which Indian and foreign manufactures can deposit patent applications to the Indian Patent Office. Once protection for pharmaceuticals is implemented in 2005, applications that meet standard patentability criteria will be approved with priority based upon the mailbox filing date. In other words, it is anticipated that in 2005, developed country manufacturers will obtain patent protection in India equivalent to the protection they enjoy in their home countries. Until this time, Indian generic manufacturers will be legally free to manufacture such drugs without permission of the patent holders. But countries that have already implemented patent protection for pharmaceuticals (which now includes most countries of the world – including most Latin American and African countries) could not import drugs from Indian manufacturers without a license from the patent holders unless they meet the conditions set forth in Art. 31 of TRIPS.

suggests that combination therapy using 2-4 different drugs simultaneously is the best way to treat or prevent the disease.) However, generic manufacturers from other countries such as Brazil and Thailand also offer equivalent prices.

Article 31 of the TRIPS Agreement sets forth procedures and conditions under which WTO members, in cases of a national emergency or extreme urgency, can forego negotiations with the patent owners and authorize manufacture or importation of patented medicines. Such use must be of limited duration and primarily to supply of the domestic market only (i.e., there should be no export to third countries), and the patent holder should be compensated. A special declaration issued by the Ministerial Conference of the WTO held in November 2001 in Doha, Qatar, (the so-called Doha Declaration) affirmed and broadened this right in the case of public health emergencies - while keeping within the scope of Article 31. Thus, in the face of a national emergency, a recognized procedure has been in place since 2001 for an effected WTO member (Stricken Country) to authorize its own pharmaceutical manufacturers (Stricken Country Generic Pharma) to produce a drug whose patents are held by a company (Patent Holding Pharma) based in another WTO member country (Patent Holding Pharma Country).[2] Under Article 31 and the Doha Declaration, Patent Holding Pharma Country would not bring a complaint before the WTO against Stricken Country for issuing this authorization. The courts in the Stricken Country would not hear an infringement suit brought by Patent Holding Pharma against Stricken Country Generic Pharma, citing the precedence of WTO rules over any conflicting national patent laws. Presumably for the same reason, courts in Patent Holding Pharma Country also would not hear infringement suits against Stricken Country Generic Pharma brought by Patent Holding Pharma.[3]

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2. To my knowledge, no country has yet formally invoked the Art. 31 emergency procedures. Ironically, the United States considered doing so when it appeared that Bayer's ability to supply its patented antibiotic, ciprofloxacin, would not be sufficient to deal with the 2001 anthrax attacks. Brazil has threatened to implement Art. 31 emergency procedures, but at the last minute it worked out license agreements with the US and European patent holders under which they agreed to sell their HIV/AIDS drugs in Brazil at substantially reduced prices or to license Brazilian generic manufacturers to make these drugs. But even though Art. 31 has not been formally invoked, the threat of doing so puts pressure on patent holding pharmaceutical companies to reach accommodations.
3. Conceivably these courts could rule that Stricken Country inappropriately authorized emergency procedures under Art. 31 or Stricken Country has not provided Patent Holding Pharma sufficient compensation. But then the task of assessing and collecting appropriate damages might prove formidable. They would not be in a position to order injunctive relief (i.e., stopping of manufacturing in Stricken Country).

Until recently, however, the procedure was not clear for countries lacking pharmaceutical manufacturing capabilities to apply Article 31 emergency provisions to authorize the importation of generic copies of patented drugs from third countries such as India or Brazil. This becomes a crucial issue for many Sub-Saharan African countries, which have high prevalence of HIV/AIDS, and which lack the ability to manufacture HIV/AIDS drugs.[4] The agreement announced on 30 August 2003 by the Ministerial Council of TRIPS allows Article 31 emergency provisions to cover the export of pharmaceutical products from third countries (India, Brazil and conceivably even generic manufacturers in developed countries) in response to public health emergencies in Stricken Countries.[5] Such third countries can now issue compulsory licenses to their companies to export "only the quantity necessary" to meet the needs of the Stricken importing country. The exported medicines must be easily identifiable so as to track whether they are resold to other countries. The responsibility of compensating the patent holder is shifted from the importing country to the exporting country.

III. Public health implications

As noted in the introduction, access to medicines for HIV/AIDS at reduced prices will save many lives in developing countries. However, the lowest price for a year's supply of AZT – the first of the effective anti-HIV drugs - is about $140 for that single drug alone. The price offered by the cheapest generic manufacturers for a year's supply of a single pill that combines at least two different classes of anti-HIV drugs[6] is still around $250 per year – a price that is difficult for many patients in least developed countries to afford. Therefore, confronting the AIDS epidemic effectively must continue to rely upon education and prevention – as well as drug therapy.

Recently, some major US and European patent holding pharmaceutical companies have been selling drugs in developing countries at substantially reduced prices. For example, Abbott sells a year's supply of ritonavir, one of the protease inhibitor (PI) class of anti-HIV drugs, for $83 to NGOs, UN organizations and national health institutions in all African countries and

4. All countries in this region are classified by the WHO either to have no pharmaceutical industry or to be able to produce finished medicines from imported ingredients only.
5. It is interesting to note that the agreement is not limited to emergencies in least developed countries. Perhaps taking into account the US's recent experience with the anthrax attacks, any WTO member can avail itself of these provisions.
6. Currently the three main classes of drugs are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Combinations that mix PIs with one of the other classes are still rare.

least developed countries outside of Africa.[7] Such price reductions are undoubtedly the result of political and humanitarian pressure, and competition from Indian generic manufacturers. However, they are also the result of efforts by importing countries, international organizations and the pharmaceutical manufacturers to ensure that medicines sold at concessional prices are identified as such and are not re-exported to other countries. Assurance that such re-export will be minimal has been a key factor behind the patent holding companies' willingness to substantially lower prices in least developed countries.

What will happen after 2005 when TRIPS takes effect in India? Patent holding companies will be able either (a) to require the Indian pharmaceutical manufacturers to agree to licenses requiring royalty payments for the right to make and export their patented products or (b) to prevent them from making such products altogether. My prediction is that if they do try to drive the Indian companies out of business with respect to their patented drugs, they will sell such drugs on their own in least developed countries at low prices. In other words, the prices of the drugs will not increase significantly, although there is a danger that they will.

With respect to other diseases that cause high mortality in least developed countries – pneumonia, diarrhoea, tuberculosis, malaria and tropical parasitic diseases – most standard drugs are either off patent, are not effective due to resistance (the case with many new malaria medicines), or non-patented substitutes are available (the case with most new antibiotics that are used to treat pneumonia in developed countries). However, particularly in the case of tuberculosis, malaria and parasitic diseases, there is a great need for new and better drugs.

However without the incentive of future profits, pharmaceutical companies will not invest resource to discover and test such new drugs. This holds true even in the case of Brazilian and Indian companies which are based in countries with high rates of these "tropical diseases". I reviewed all pharmaceutical patent applications between 1995 and 1999 filed in the Indian Patent Office - applications now waiting in the mailbox system. As expected, the applications by foreign companies reflected the drugs they have developed for developed country markets. But surprisingly, the applications by major Indian pharmaceutical companies also were mostly for chronic diseases associated with industrialized country lifestyles.[8] Very few were for drugs to treat tropical diseases. In other words, the drug discovery

7. According to data from Medicins sans Frontiers, this is the least expensive price offered for any PI drug. This may be particularly important since PI drugs are not included in most single-pill combination therapies. In other words, if patients want to receive the added benefit of a PI drug, they usually have to take a medicine such as ritonavir separately.
8. Data to be presented in another paper.

efforts of Indian companies themselves are directed to chronic diseases affecting relatively well to do persons.[9]

One reason that such a vigorous debate exists today about access to HIV/AIDS drugs – rather than drugs to treat tuberculosis, malaria and parasitic diseases - is because effective HIV/AIDS drugs exist. The main reason for the existence of such drugs is because the disease affects persons in developed countries. This provided financial incentives for pharmaceutical companies to discover such drugs, and the political and scientific impetus for the NIH to support basic research related to AIDS – which has contributed significantly to HIV drug discovery. But without a large developed-country market for drugs to treat tropical diseases, pharmaceutical companies will be discouraged from developing drugs to treat such diseases by the prospect that, under Article 31, generic manufacturers could quickly gain entry into developing country markets. In other words, by providing a way for generic manufacturers and Stricken Countries to circumvent patent protection, Article 31 becomes a double-edged sword with respect to diseases that affect primarily persons in developing countries. This is not to suggest that the 2001 Doha Declaration and the 2003 Ministerial Agreement are mistaken. They may well reflect the best balance between humanitarian needs, business incentives and current scientific knowledge related to drug discovery and development. Nevertheless, this concern may be a reason not to invoke Article 31 emergency provisions too frequently.

IV. Alternative approaches

Several approaches are being explored to work around the problem of lack of incentives for pharmaceutical companies to produce drugs for diseases of less developed countries. "Supply side" approaches aim to decrease the costs of developing new drugs. A number of consortia have been organized to develop new medicines for such diseases. Typically these combine (a) publicly funded academic research into issues of basic biology, (b) pharmaceutical companies which contribute resources in drug screening and pre-clinical and clinical trials, (c) charitable contributions that help pay for much of the development work, and (d) developing country scientists and health institutions that help plan and conduct the clinical trials. IP is usually held by the consortium, which is a non-profit organization. A consortium can transfer licenses covering developed country markets to the pharmaceutical partner. Several drugs and vaccines are now under development by consortia, such as the Medicines for Malaria Venture,

9. Medicines against chronic diseases are generally more attractive for pharmaceutical companies because they offer larger revenue streams than drugs to treat acute infectious diseases.

Malaria Vaccine Initiative (MVI), Global Alliance for TB Drug Development and International AIDS Vaccine Initiative.

Another approach is for a major public research institution, such as the NIH to take an active role not only in basic research related to drug discovery, but also in drug development – even all the way through human clinical trials. For example, as one of the MVI projects, the NIH in collaboration with the Medical School of the University of Barnako in Mali, the US Agency for International Development, GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR), is supporting phase 2 clinical studies in Mali of a new malaria vaccine whose early development was carried out by WRAIR and GSK. Similarly, NIH is starting clinical trials of a new drug to treat West Nile Virus in cooperation with the Israeli biotechnology that invented the drug. In other words, by planning and funding human clinical trials, some publicly funded medical research institutions in developed countries are venturing deep into activities that were considered to be the sole domain of private pharmaceutical companies. They are doing so not only to develop drugs deemed vital to national public health interests (which in the case of the US can be broad), but also to control the IP and to license the final drug in a way that guarantees adequate supplies at "affordable" prices – even in developing countries. In other words, for developing country markets, the licensees would be pharmaceutical companies that pledge to make the drug available at affordable prices. Another approach would be for an organization such as the NIH, or university scientists funded by the NIH, to work collaboratively with pharmaceutical companies in countries such as India, Brazil and Korea to help them discover and test candidate drugs. In this case, IP would be held by the pharmaceutical companies but their development costs would be reduced.

Whether such approaches are successful should become evident within a few years. Hopefully they will be. But even while celebrating their success, it will be important to ask about incentives to discover the next generation of drugs to treat tropical diseases, and how it might be possible to shift the locus of discovery of such drugs from developed country laboratories to laboratories in developing countries. For this purpose, it might be wise for relatively strong patent protection to be in place in developing countries so that pharmaceutical companies in such countries will have incentives to make the second generation drugs.[10]

10. In contrast to these "supply side" approaches, "demand-side" approaches involve increasing the ability of patients in developing countries to pay for medicines. These might involve combinations of insurance and loan programs as well as economic and social policies that are important in their own right but beyond the scope of this paper.