Expert Review Of Drug Patent Applications: Improving Health In The Developing World

Engaging outside experts in patent review could curtail the granting of unmerited patents, which can lead to high prices for essential drugs in resource-poor countries.

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ABSTRACT: Many developing countries have enacted intellectual property laws allowing patents on pharmaceutical products. These countries now must figure out how to provide legitimate protection of innovative discoveries while avoiding drug patents that do not conform to their laws. Using case-study examples, including the antiretroviral tenofovir disoproxil fumarate (TDF, or Viread), we demonstrate the importance of having outside experts participate in the review of drug patents. Vibrant patent review systems require sharing information among developing countries and active consultation with local public health authorities. [Health Aff (Millwood). 2009;28(5):w948–56 (published online 25 August 2009; 10.1377/hlthaff.28.5.w948)]

Access to medicines has been a long-standing global public health concern. By one estimate, ten million lives per year are lost because of inadequate access.[1] In developing countries, underfunded and uncoordinated health systems contribute to this situation.[2] But growing evidence suggests that patients there bear, on average, more than 70 percent of health care costs themselves and that reductions in the price of medicines can lead directly to greater availability.[3]

For example, a price reduction in first-line antiretroviral agents for HIV, from more than US$15,000 per person per year eight years ago to $99 today in resource-poor settings, has helped improve access to such drugs.[4] Prices could be reduced because the makers of low-cost pharmaceuticals, based in a number of key countries such as India and Brazil, can produce inexpensive drug products, in large

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DOI 10.1377/hlthaff.28.5.w948

part because their governments did not grant exclusive drug patents.

Global supplies of such low-cost medicines are now being threatened by the enactment of laws permitting pharmaceutical patents, mandated by the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). As a result, policymakers in places such as India and Brazil who are implementing intellectual property protections struggle to set up systems that will allow patents on drug product discoveries, as required by TRIPS, while preventing monopoly protection over insufficiently innovative products that can unnecessarily impede access to essential medicines. Experience from countries such as the United States, where drug patents have long been allowed, shows the substantial impact of nonmeritorious patents on health care costs. One analysis found that U.S. government insurance programs could have saved $1 billion between 2000 and 2004 if inappropriate market extensions to just three drugs had not been granted.[5] Such experiences can have a disastrous effect on patients' welfare in resource-poor settings.

The primary mechanisms used by the U.S. Patent and Trademark Office (USPTO) to prevent nonmeritorious patents are postgrant challenges, called reexaminations, and lawsuits. Other countries allow or are introducing pre-grant reviews that permit any person or experts such as public health authorities to submit relevant evidence or other comments that may be helpful to an examiner in deciding whether to grant a patent. There are two main types of pre-grant review: observations and oppositions. Observations are limited to the filing of evidence; oppositions provide a full hearing that may include the right to appeal the decision.

In this paper we review the limitations and benefits of each of the pre- and postgrant strategies in the context of the controversy surrounding the antiretroviral tenofovir disoproxil fumarate (TDF, also known as Viread), one of several HIV drugs whose patents are under scrutiny in India because they might not meet Indian patent law's standards for inventiveness. Although we do not judge the quality of the TDF patents, we find the TDF case useful in framing this issue by demonstrating the effect of patents on drug prices in developing countries. Vibrant pre-grant review and outside experts' participation in the patent-approval process can be powerful tools in countries that are implementing new patent laws.

The TDF Case

First introduced by Gilead Sciences in late 2001, TDF is a commonly used antiretroviral agent in the United States and Europe. TDF originated when scientists at the Czech Republic Academy of Sciences first discovered various nucleotide analogs with antiretroviral properties, including tenofovir, and patented these so-called base compounds in 1985. In human subjects, the tenofovir base compound had poor oral stability and bioavailability, which is a measure of the amount of the drug that reaches the site of action. Gilead entered into an exclusive

license on several nucleotide analogs, including tenofovir, with the goal of creating a marketable formulation. The company developed a stable drug product by first formulating the ester derivative of tenofovir (tenofovir disoproxil, or TD) and then its salt (TDF). In the United States and other wealthy countries, Gilead applied for and obtained drug patents lasting until 2017. TDF, by itself and as a component of combination antiretrovirals, generated more than $3 billion in sales in 2007.[6]

Although TDF is often used as first-line agent in the United States, the World Health Organization (WHO) does not recommend its use in resource-poor settings because of its high price. Instead, TDF is categorized as an option for patients who fail initial therapy because of intolerable side effects or drug resistance. In recent years, global demand for TDF has risen as new HIV strains emerged. For example, Botswana, Ethiopia, Lesotho, Namibia, Nigeria, and Zambia,[7] as well as India and Brazil,[8] have included or are considering TDF as first-line therapy for HIV.

■ **Global access program for TDF.** To address the needs of health systems outside the wealthiest nations, Gilead announced a Global Access Program in 2002, which designated sixty-eight (later extended to ninety-seven) low-income countries to receive the drug at a not-for-profit price of US$475 per patient per year (subsequently reduced to US$207).[9] Yet several developing countries with large HIV-positive populations, including Argentina, Brazil, China, India, and Thailand, were excluded from the program. These countries either fell into a second (higher) pricing category or received no discounted price. As a result, TDF cost US$2,766 per patient per year in Brazil (subsequently negotiated down to US$1,380) and US$1,700 in El Salvador—prices that have strained health budgets.[10] In addition, Gilead has been criticized by organizations such as Médecins sans Frontières (Doctors without Borders) for moving too slowly to obtain marketing approval for TDF in many countries and has been encouraged to relax its monopoly to increase access.[11] Gilead has accelerated its market-approval process in recent months.[12]

■ **Local threats to Gilead's patent rights.** In the meantime, companies in key low-cost pharmaceutical-producing countries such as India began preparing to produce and obtain marketing approval to sell TDF in many low- and middle-income countries at a starting price of US$195 per patient per year. This potential supply of the drug has been threatened by Gilead's efforts to secure patent rights in these countries. All countries require that a patented discovery be new and not an obvious extension of existing knowledge. The techniques Gilead undertook to transform the base tenofovir compound into an end formulation are arguably obvious in light of existing literature and knowledge on how to formulate poorly bioavailable nucleotide analogs.[13] Even though Gilead invested in turning the initial base compound of tenofovir into a marketable drug and then tested the product, the question of whether it deserves a patent for this work depends on how local laws are constructed. After TRIPS, some countries have enacted legislation that intends to prevent multiple subsequent patents from extending market exclusivity for the under-

lying active ingredient (known as evergreening).[14] India's law, for example, specifically states that esters and salts of known compounds are not new inventions, unless they show enhanced efficacy.[15] Applying this principle, the Delhi Patent Office recently refused the German firm Boehringer Ingelheim's application for a patent on the pediatric syrup of the antiretroviral drug nevirapine on the grounds that improved stability of a product did not constitute enhanced efficacy.[16]

As the TDF example shows, implementation of local patent laws can have major public health implications, as the dissemination of drug patents in resource-poor settings will directly affect the prices of essential medicines. Patent opposition is one way to ensure that local patent standards are upheld.

Patent Oppositions: A Strategy To Promote Patent Quality

Patent review can occur at two different points—during the application process and after the patent has been granted.

■ **Pre-grant patent review.** A number of countries (mostly developing countries and notably not the United States) allow outside experts—members of the public apart from the inventor and examiners in the patent office—to bring forward evidence relevant to the patentability of the product during the patent proceedings. This usually takes the form of experts obtaining and reviewing a published patent document for the claimed invention to see if it has already been disclosed, suggested, or made obvious by common knowledge, an earlier patent(s), or prior published literature.[17] If these experts have reason to question the validity of a patent application, they may submit the relevant evidence to the local patent office. The Indian Patent Act, for example, enumerates twelve grounds available for outside comment, including whether a claimed invention is an obvious improvement on information already in the public domain. Following pre-grant observations filed by experts, the Brazilian Patent Office recently issued a rejection of the TDF patent application there.[18] Pre-grant mechanisms can help improve patent quality by ensuring that applications falling short of the national standards for patentability are denied.

Efficiency gains. Pre-grant review can reduce the financial and social costs of instituting drug patents. Although allowing outside participation increases administrative costs for patent offices already suffering from a shortage of resources, such participation can make patent examiners' work more efficient. A pre-grant system is cheaper than oppositions at a later stage for both administrators and public health authorities. Granted patents have a presumption of validity, and the costs of bringing a challenge are often placed on the party that initiates the opposition. By avoiding this presumption of validity, pre-grant mechanisms make removing a nonmeritorious application easier than removing a nonmeritorious patent. Therefore, pre-grant expert review can be an effective ex ante solution to the related problems of access and affordability. Evidence suggests that merely filing such oppositions can lead to reductions in prices.[19] In the wake of the pre-grant filings on its patent application for TDF, Gilead granted licenses to eleven Indian

generic manufacturers with a relatively low royalty rate of 5 percent.

No abuses to the system. Some may worry that opening up patent examination to outside experts could result in abuses of the system, such as frivolous delay tactics. In India, this outcome has yet to materialize: out of approximately 9,000 pharmaceutical-related patent applications, pre-grant oppositions have been filed in only 200 (2 percent).[20] Indeed, as the patent application process and rules of the pre-grant opposition procedure favor applicants in a way that makes it difficult for opponents or the patent office to obtain final refusal of a patent application, experts' participation in India has remained low overall. The Indian government recently has improved some of these procedural inconsistencies to encourage greater participation.[21]

Concerns about the costs of delay. Another frequent criticism of pre-grant challenges is the sizable cost of delay to patent applicants. This is because the twenty-year patent term commences from when the patent is filed, but the applicant's rights exist only from the time the patent is granted. These legitimate concerns can be alleviated if pre-grant challenges are dealt with expeditiously. At the same time, the cost to the patent owner should also be weighed against the cost to patient welfare, health systems, and the public when nonmeritorious patents are issued. Finally, going through a more rigorous review process involving external expert evidence may actually help innovators avoid future litigation.

■ **Post-grant patent review.** Similar review strategies can be established to allow a granted patent to be reconsidered. The United States permits such patent reexamination based on evidence presented by interested parties. This process was used to challenge the validity of the U.S. TDF patents on obviousness grounds by the nonprofit Public Patent Foundation. The Foundation argued that the development of the drug into its salt form lacked the legal requirement of inventiveness, as it would have been obvious to any person skilled in the art to develop it in such a manner. The USPTO found that the patents warranted a reexamination and held them preliminarily invalid in early 2008, but has since reaffirmed their validity under U.S. law.[22]

After other avenues have been exhausted, lawsuits have been used to invalidate drug patents that do not meet legal requirements. For example, a U.S. court found that patents relating to the proton-pump inhibitor omeprazole (Prilosec) were erroneously granted, thus permitting a generic drug supplier to enter the market.[23] The European patent system, the United Kingdom, Australia, China, India, and Brazil offer more robust post-grant opposition procedures. Post-grant oppositions are determined at the patent-office level and can achieve the desired result of removing unmerited patents at much less financial cost than litigation. Recent U.S. proposals for patent reform have considered instituting similar post-grant opposition mechanisms to reduce expensive and excessive patent litigation.

Post-grant opposition mechanisms are useful in countries setting up new drug patent systems under TRIPS because patent examiners in these countries are often trained by the U.S. or European patent offices, which could result in high rates

of granting drug patents. A study of selected drug patents showed that at the European Patent Office, up to 75 percent of patents that are challenged after grant are revoked or the protection is narrowed.[24] Although strict legal standards for inventiveness can help prevent evergreening, in countries such as India, nonmeritorious patents are still granted because of lax application of those standards.[25] Post-grant review can serve as a safety net for examiners who lack the resources or understanding to examine patent applications appropriately.

However, even a robust post-grant opposition procedure is still problematic. First, as indicated above, granted patents have a strong presumption of validity and are difficult to revoke. There is also a growing trend among patent holders and generic companies to resolve post-grant challenges by entering into anticompetitive settlements.[26] Second, post-grant oppositions occur after competitors have been prevented from entering the market.[27] From a public health point of view, the delay of legitimate lower-cost versions of drugs during the time it takes to challenge a patent is cause for concern. When invalidation of the patent occurs after the patent holder has established its product in the market, such patents may have already prevented others from selling the drug in developing countries. This happened in the case of the antihypertensive drug amlodipine (Norvasc), which was sold by Pfizer in other developing countries at a cheaper price than in the Philippines. Pfizer used its Philippines patent to prevent the government from importing a generic version of its drug from India.

Policy Implications

The pre-grant review and post-grant reexamination processes prevent access to medicines being hindered by patents that do not meet the level of innovation required by local intellectual property law. If such patents are not overturned, few alternatives remain for addressing nonmeritorious patents on drug products that make low-cost production difficult in resource-poor settings.

■ **Voluntary licensing.** Many commentators have encouraged voluntary licensing, as Gilead did with TDF, permitting other manufacturers to supply the drug to the Indian market in exchange for a royalty. The advantages of this approach are that, in theory, it is nonconfrontational and can speed low-cost access to essential drugs.[28] However, voluntary licenses may fail to materialize in an expeditious time frame and may be accompanied by strict conditions such as the price the licensee can charge or geographical restrictions on sales.

■ **Compulsory licensing.** Another alternative is a compulsory license, which a government can issue to generic manufacturers to circumvent the patent barrier. The patent holder is entitled to adequate compensation, and TRIPS requires the government to negotiate with the patent holder first for a reasonable period of time, unless it is a case of extreme urgency. Compulsory licensing has proven to be both controversial and cumbersome. Disputes have arisen over what constitutes a legitimate public health emergency, what royalties are appropriate for the patent holder,

and whether a country negotiated adequately. In practice, developing countries face international political pressure not to use compulsory licensing. In addition, some countries limit the application of compulsory licenses. Indian law, for example, requires that a compulsory license can only be granted three years after the issue of a patent, except in the limited cases of a national emergency, public noncommercial use, or anticompetitive behavior.

■ **Maintaining a vibrant patent process.** Compared with these alternatives, permitting outside experts' participation in the patent process (preferably before patents are granted) offers a more durable and direct means of ensuring affordability and access in cases of questionably innovative patent applications for drugs. However, creating and maintaining a vibrant patent challenge process entails overcoming a number of obstacles, particularly in low- and middle-income countries. First, the United States has pressured countries informally in the context of free-trade agreement negotiations, or more explicitly through the threat of trade-related sanctions, to abandon their review procedures as part of an effort to push for expanded intellectual property protection.[29] For example, in its report on the U.S.-Peru Trade Promotion Agreement, the U.S. Industry Trade Advisory Committee on Intellectual Property stated that it is "critical that future free trade agreements place restrictions on pre-grant oppositions."[30] The recent free-trade agreement with South Korea allows review proceedings only after patents have been granted.[31]

In addition, it can be difficult to track patent applications on key drugs to assess when challenges are needed; as a result, developing countries' patent offices can help support a vibrant challenge process by organizing searchable databases of patent applications. Patent-challenge processes would benefit greatly from a global register that makes transparent all opposition and examination files so that resource-poor patent offices can use the data to examine corresponding patents according to their national laws. Such a register would build on the examination data that are already available through International Preliminary Examination Reports, the European Patent Office, and the USPTO.

Finally, low-income countries require more scientific and legal resources to support patent examiners. Some countries, such as South Africa and Morocco, simply grant patents without examination. One possible way of infusing resources without requiring additional public funds would be to direct patent examiners to cooperate with outside experts during the examination of patent applications. For example, countries may consider requiring a review by government public health experts before a patent is granted, as Brazil does. Since 1999 the Brazilian Sanitary Surveillance Agency (ANVISA) has used its own technical expert committee, which has the final say on whether pharmaceutical patents meet the criteria for patentability.[32] This could help bring to light information on patent applications that patent offices might not be aware of without the administrative burden of patent challenges or reexaminations.

Naturally, there are potential consequences from improving the patent exami-

nation process with stronger challenge procedures. Upholding current Indian patent law, for example, may decrease pharmaceutical companies' incentive to develop formulations of base compounds. It may be possible to provide reasonable reimbursement to drug makers for their investment in this important process—for example, through prize funds administered by international aid organizations—without granting them the same twenty years of exclusivity rights they would earn for a truly innovative compound.

But in the current system, the participation of outside experts needs to remain paramount. The patent-challenge process remains the most direct mechanism for ensuring that important new drug products are not protected by undeserved patents in resource-poor settings, which can have a substantial impact on public health. Outside experts' participation could be a highly effective tool to curtail unmerited patents. Policymakers should ensure that the pre- and post-grant challenges remain an option to ensure that only meritorious patents are granted. Similarly, they should draw on outside experts to supplement local patent-examination processes.

The Initiative for Medicines, Access, and Knowledge, a nonprofit group of which two authors are codirectors, helped prepare the pre-grant patent oppositions for TD and TDF on behalf of Indian patient groups but was not paid for its work. The authors thank Harlan Krumholz, Yochai Benkler, and Amy Kapczynski for comments on earlier drafts.

NOTES

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