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Intellectual Property Policy in the Pharmaceutical Sciences: The Effect of Inappropriate Patents and Market Exclusivity Extensions on the Health Care System

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ABSTRACT

Though patents are effective tools for promoting innovation and protecting intellectual property in the pharmaceutical sciences, there has been growing concern about 2 important ways that patents in this field can have a negative effect on patient care and the practice of medicine. First, inventors can seek and receive patents on pharmaceutical products or research tools that stretch the statutory requirements for patenting. Second, patent holders in the pharmaceutical market can use legal loopholes or aspects of the patent registration system to extend exclusivity for inventions beyond what was anticipated by the Patent Act or subsequent legislation. The monopoly control bestowed by such inappropriate patents or manipulation of the patent system can limit options available to patients, increase the cost of health care delivery, and make cooperative research more difficult. In response, several different government and market-based efforts have emerged to promote more equitable patent policy in health care that encourages dissemination of ideas while still supporting the development of innovative products.

KEYWORDS: Patent, intellectual property, health care costs, innovation

INTRODUCTION

Since 1790, the United States has employed a system of patents under the authority of the US Constitution to "promote science and the useful arts."[1] A patent is a grant from the federal government that permits inventors to exclude others from making or using their discoveries. It is a legal monopoly provided, for a limited period of time, in order to spur innovation and encourage investment in the production and dissemination of innovative products and processes.

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The pharmaceutical sciences have long been closely entwined with the patent system. Pharmaceutical products often rely on substantial amounts of upfront investment and technical knowledge but may be relatively straightforward to copy once they are widely distributed. Providing market exclusivity to an inventor through patent protection can encourage the initial outlay of resources needed to develop the product. In fact, most significant pharmaceutical products have at one time been the subjects of patent protection, even including ones that today are considered to be as fundamental as aspirin, whose patent was held by the Bayer Company in the early 20th century.

Since the 1980s, several legal and social forces have strengthened the connection between the pharmaceutical sciences and the patenting system. In 1983, the Bayh-Dole Act allowed universities and other recipients of federal research funds to maintain control of the intellectual property in discoveries made with public support.[2] Previously, such rights were automatically assumed by the federal government. Today, much of the basic science work related to the pharmaceutical sciences occurs in academic settings under the support of federal funds, and researchers are seeking to obtain patents in the same fashion as their industry counterparts. In addition, the Federal Circuit Court of Appeals was created in the early 1980s to provide judicial review of patent-related cases. However, by upholding numerous questionable patents, the Court of Appeals has encouraged patent holders to stretch the limits of patenting by setting low legal hurdles for the types of inventions deserving of patent protection.[3]

In modern times the pharmaceutical sciences, more than any other technology-based industry, has come to rely on patents as the primary mechanism to promote innovation.[4] As the pharmaceutical product market has expanded over the past several decades, the number of drug product-related patents has exploded. For example, from 1994 to 1999, 28 414 of the issued patents were classified by the United States Patent and Trademark Office (USPTO) as relating to "Drugs, bio-affecting, and body treating compositions." Only 8365 similarly designated patents were issued during the years 1975 to 1979 (Figure 1).[5]

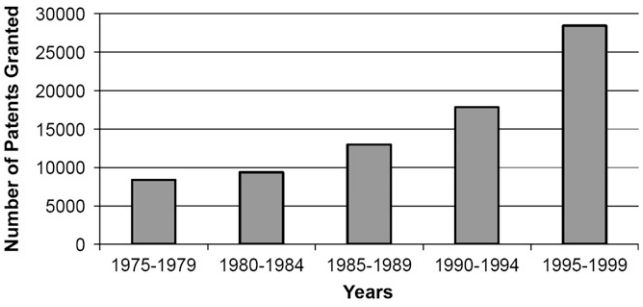

Figure 1. Number of new drug-related patents granted that the United States Patent and Trademark Office designated as falling within the class of inventions related to "drug, bio-affecting, or body-treating compositions." Data source: National Bureau of Economic Research US patent citation data file.

Recently, some commentators have become concerned about the problems with the ubiquitous nature of patents in the pharmaceutical sciences.[6] Heller and Eisenberg in the late 1990s argued that too many patents on basic science discoveries could create an "anti-commons," where numerous holders of overlapping intellectual property rights could prevent effective cooperative uses of those rights.[7] There have also been some indications that patents may not be contributing to innovation in the pharmaceutical market as intended. Despite the substantial rise in patenting, the Congressional Budget Office (CBO) issued a report in 2006 showing that the number of new pharmaceutical products on the market has declined in recent years.[8] Finally, recent experiences and studies have identified several ways that patents and the resulting market exclusivity in the pharmaceutical sciences have had important negative effects on the public health.[9]

In this article, I review the 2 major ways that patents in the pharmaceutical sciences can be manipulated to interfere with the practice of medicine. First, there is the problem of "inappropriate patents"; ie, inventors seeking and receiving patents in contexts that stretch the legal requirements for patenting or that protect discoveries that may not have been made by the inventors. Second, the federal government's patent registration and oversight system can be manipulated through various legal means to extend market exclusivity for inventions beyond that which was anticipated by the Patent Act or through subsequent legislation. I conclude by discussing several new proposals that have been put forth to help reform the patent system.

Pharmaceutical Patents Stretching the Bounds of Patentability

A patent is classically thought of as a "quid pro quo," where inventors provide full disclosure of their invention and can allow it to be placed on the market in exchange for a limited monopoly protection. Currently, patent protection extends for 20 years from the date the inventor files for the patent, after which time the product becomes available in the public domain for all to use. A discovery must meet certain conditions for sufficient inventiveness to earn this limited monopoly protection. These requirements are spelled out in the Patent Act.[10] A patent must fall within a certain subject matter; not be previously described publicly (that is, be "novel"); have a credible, specific, and substantial utility[11]; and not be an obvious alteration to an existing product. However, when inventors stretch the limits of these statutory requirements, they can earn patents on discoveries that arguably should be in the public domain. These "inappropriate patents" disrupt the delicate policy balance underlying the patent system when issued for intellectual properties in the pharmaceutical sciences and can directly affect the advancement of medical research or the treatment of patients.

Some patents, for example, have stretched the notion of patentable subject matter. The proper subject matter for most patents is defined as a "process, machine, manufacture, or composition of matter."[12] Though the broad statutory definition may include "anything under the sun made by man,"[13] several potential discoveries are still excluded from patent protection. In *Diamond v Diehr,* inventors patented an algorithm for determining the proper time and temperature for curing rubber in the context of an innovative process for transforming rubber. The patent was challenged because a basic scientific relationship—the parameters of rubber's molecular stability—was integrated into the algorithm. The Supreme Court upheld the patent, clarifying that "laws of nature, natural phenomena, and abstract ideas" are only patentable when they are a part of a transformation of something "into a new state or thing."[14]

Despite the Supreme Court's prior statement on patentable subject matter, several patents have been granted and upheld within the pharmaceutical sciences, especially as related to basic scientific relationships, that may not represent appropriate subject matter for patents. One example that reached the Supreme Court in 2006 is the case of *Laboratory Corporation (LabCorp) v Metabolite Laboratories*. That case arose out of a patent received by 3 scientists who discovered that elevated levels of homocysteine, a protein long known to be involved in inflammation, were associated with a deficiency of either cobalamin (vitamin B_{12}) or folate (folic acid).[15] In addition to claiming rights in the process of assaying total homocysteine levels in patients' blood, the inventors asserted an intellectual property right in

> "A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
> *assaying* a body fluid for an elevated level of total homocysteine; and
> *correlating* an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate."

This claim ("Claim 13") covered the act of inferring, on the basis of a test result showing elevated homocysteine levels, that a patient was deficient in either cobalamin or folate. Claim 13 was challenged in court, but the Federal Circuit affirmed its validity, noting that drawing a "simple conclusion that a cobalamin/folate deficiency exists" based on the test result constituted patent infringement.[16] The Supreme Court ultimately decided to allow the Federal Circuit's decision to stand without reviewing the case, probably because it wanted a lower court to comment more specifically on whether the basic scientific relationship at issue was the proper subject matter of a patent.[17] Patents like the one at issue in *LabCorp* extend the statutory interpretation of the proper subject matter of a patent by adding only trivial procedural steps to naturally occurring processes. These patents can increase health care costs through licensing fees and the need to negotiate use agreements. They can also inhibit cooperation among physicians and scientists.[18]

Process patents stretching the bounds of patentability are widespread in the field of pharmaceutical sciences. Many pharmaceutical product patents include claims describing hundreds of theoretical ways that physicians can use the product, even before the product has entered into clinical trials. Other patents have been sought and granted on diagnostic or treatment algorithms. These patents are currently considered valid "process" patents, but many of them also describe, and attempt to assert intellectual property rights over, naturally occurring protein binding or signaling pathways. For example, in the case of *Ariad Pharmaceuticals v Eli Lilly,* a jury upheld a patent covering all processes modulating the naturally occurring NF-κB biological pathway.[19]

Another group of potentially inappropriate patents in the pharmaceutical sciences relies on a loose interpretation of the non-obviousness requirement. According to the Patent Act, proposed invention must be non-obvious in light of the prior art, and the proper way to evaluate what is obvious is from the point of view of a "person of ordinary skill in the art," that is, the field to which the invention relates.[20] The non-obviousness requirement attempts to prevent offering monopoly protection to small changes to currently existing inventions, because such a policy would not successfully promote the progress of science and the useful arts.

Numerous patents in the pharmaceutical sciences, however, push the bounds of the non-obviousness requirement. Pharmaceutical manufacturers routinely apply for and receive patents on biological derivatives of existing products or for combinations of existing products. For example, AstraZeneca developed the proton pump inhibitor omeprazole (Prilosec) and later received a patent on its purified s-isomer (esomeprazole, Nexium). The latter can be considered an obvious subsequent development step. Despite the similar efficacy of these 2 molecules, the company used its marketing resources to promote the more expensive s-isomer when omeprazole, the original product, faced loss of its patent protection. Similarly, many drug combination patents lack the inventive step that should be required for patentability. Pfizer has received a patent on a pill consisting of the combination of the calcium channel blocker amlodipine (Norvasc) and the cholesterol-lowering agent atorvastatin (Lipitor). This patent will last until 2018, even though drugs in these pharmaceutical classes are routinely used in tandem in patient care.[21]

Some arguably obvious patents have classically been allowed by the USPTO and have been upheld by the Federal Circuit because of the relatively low bar established by the Federal Circuit for determining whether a product meets the non-obviousness requirement. In the case of combination patents, the Federal Circuit has held that obviousness can only be established if there are statements in the literature at the time of the invention that include a specific "teaching, suggestion, or motivation" (TSM) to combine the elements.[22] Although the TSM test does not require explicit statements, Federal Circuit cases have been decided on the inability to find such formal references.[23] However, the TSM test has no basis in the Patent Act. In fact, the Supreme Court in 1976 rejected a patent specifically because it was merely the combination of existing products (albeit despite lacking explicit information relating to the combination of these 2 products), noting that the patent "simply arranges old elements with each performing the same function it had been known to perform, although perhaps producing a more striking result than in previous combinations. Such combinations are not patentable under standards appropriate for a combination patent."[24]

Some pharmaceutical patents push the statutory bounds of the Patent Act and earn products undeserved market exclusivity. Patent-protected products such as esomeprazole can increase health care costs. Patent-protected processes such as the one at issue in the *LabCorp* case covering naturally occurring biological pathways and relationships can interfere with physician decision making, and overly broad patents attempting to claim rights in natural biochemical processes can inhibit research that might otherwise lead to innovative new products.

Patent Extensions for Pharmaceutical Products

In the pharmaceutical market, it has become common among patent holders of nearly all successful products to attempt to extend the market exclusivity beyond the length of time initially granted by the patent. Several different strategies are available for this purpose. One example is called "patent evergreening," which is the patenting of nonessential features of products, including aspects of their formulation,

their metabolites, or methods of administration. For example, in 1981 Schering obtained a patent on loratadine (Claritin), which became a popular antihistamine medication. Schering applied for and obtained 46 months of patent extensions owing to regulatory review time and changes in patent laws, giving it nearly 21 years of patent protection, which surpasses the standard 20-year time frame.[25] Meanwhile, the manufacturer sought numerous other ways to extend its market exclusivity even further, including patenting the compound desethoxycarbonyl-loratadine (DCL), which is formed in the body during the normal metabolism of loratadine. The patent was challenged in court and was eventually overturned because DCL was "necessarily and inevitably" formed in every patient, and generic loratadine was ultimately marketed in 2002. However, the court noted that its decision did not extend to every metabolite of a pharmaceutical product, suggesting that "the metabolite may be claimed in its pure and isolated form … or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier)."[26]

Research has shown that efforts to extend market exclusivity protection in this way can prevent the marketing of lower cost generic alternatives. In a study published in *Health Affairs,* I, along with my colleagues Michael Fischer and Jerry Avorn, examined 3 brand name pharmaceutical products whose market exclusivity was extended through patent evergreening efforts. These efforts included lawsuits aimed at exploiting federal statutory loopholes and attempts to patent peripheral aspects of products. Our analysis identified $1.5 billion in revenue that the Medicaid system could have saved if generic alternatives to these 3 medications had been available.[27] For example, in the case of omeprazole, the patent on the active ingredient expired in April 2001, but litigation over patents relating to the coating of the pill prevented generic versions from entering the market until the first quarter of 2003. In the intervening time, AstraZeneca introduced an over-the-counter version of omeprazole and promoted its patent-protected esomeprazole for use in place of omeprazole. If a generic version of omeprazole had been available as early as April 2001, and been fully substituted for the over-the-counter price, Medicaid could have saved $860 million. If generic omeprazole was also substituted for Nexium, an essentially identical product marketed by the same manufacturer, savings could have reached $1.2 billion. As Medicaid programs' costs for prescription drugs continue to rise, many programs are cutting back on important areas of coverage or are changing eligibility requirements to maintain their budget. This analysis identified one area where cost savings could be achieved without sacrificing the public health.

Another strategy that pharmaceutical manufacturers have employed to extend market exclusivity has involved the current patent registration and enforcement system. Currently, for example, when a generic manufacturer registers a generic version of a brand-name product, there can be an authorized 30-month stay on the marketing of the generic product to allow for resolution of patent infringement disputes. However, a recent study by the Federal Trade Commission (FTC) revealed numerous instances of widely used brand-name products, where pharmaceutical companies have sought overlapping or concurrent 30-month stays to extend their effective market exclusivity.[28] In the case of the antidepressant paroxetine (Paxil), disputes over a total of 5 different patents listed with the Food and Drug Administration (FDA) led to an extra 35 months of delay in the approval of a generic version. During that time, annual sales of brand-name Paxil reached over $1 billion. According to the FTC, the delays caused by these overlapping stays ranged from 4 to 40 months.

Brand-name manufacturers can also delay market entry of generic equivalents to their drug products by entering into settlements with generic manufacturers. By law, the first manufacturer to register its generic alternative with the FDA can receive a 180-day period of generic market exclusivity once it is approved. However, the FTC found instances of settlement agreements between the brand-name and generic manufacturers that delayed the approval of the generic product.[28] In one recent case, Bristol-Myers Squibb and Sanofi had agreed to pay the Canadian generic manufacturer Apotex nearly $40 million to hold off marketing a generic equivalent of clopidogrel (Plavix) until 2011 (when the final clopidogrel patents expired).[29]

One rationale for evergreening and for using similar marketing strategies is that the effective market exclusivity enjoyed by the patent holder may be less than the full 20 years of patent length because patents applications usually occur early in the development of the product. Pharmaceutical products must then undergo preclinical and clinical testing, as well as governmental regulatory review, before being introduced on the market. However, these delays are mitigated by stipulations in the Hatch-Waxman Act that add FDA regulatory review time back into the effective patent life, which can extend the market exclusivity once a product is approved. A monopoly right that is appropriately limited is crucial to helping preserve the policy underlying the Patent Act of promoting innovation while still allowing the intellectual property to enter the public domain.

Promoting Optimal Patent Policy in the Pharmaceutical Sciences

It is important to consider how intellectual property policies in the pharmaceutical sciences affect the health care system. Several strategies have been suggested to reform the patent system to better protect public health, patient care, and medical research.

For example, the FTC has proposed better scrutiny of the patent registration system. Since the FTC's study, the FDA has helped prevent grants of overlapping 30-month stays that can prevent generic products from entering the market. In addition, legislation has been proposed in Congress that will affect pharmaceutical manufacturers that enter into agreements relating to the 180-day generic market exclusivity period. The Drug Competition Act of 2001, required the filing of brand-name and generic manufacturer agreements with the FTC and with the Department of Justice to enable more appropriate government scrutiny over those agreements in the future.[30] However, while that bill passed the Senate with unanimous consent, it was not subsequently voted on in the House.

Some have also investigated market-based alternatives. The Institute for OneWorld Health has emerged as an alternative model for pharmaceutical companies, because of its nonprofit status. It has effectively introduced a treatment for visceral leishmaniasis in underserved markets in India. Currently, it is pursuing cooperative licensing agreements for future products that treat diseases (such as malaria and Chagas' disease) that might not otherwise be pursued by traditional for-profit manufacturers.[31] Similarly, the group Universities Allied for Essential Medicines (UAEM) has advocated for academic centers to proactively seek development licenses with pharmaceutical manufacturers in an effort to produce reasonably priced products that would have otherwise not been available in low-income markets.[32] According to a report in *Nature,* Yale University recently agreed not to enforce patents covering an AIDS drug (developed by Yale researchers) in some low-income countries.[33] Though these examples deal with international health, their lessons are similarly applicable to the pharmaceutical markets in the developed world. These alternative models of intellectual property management emphasize improving access to products and limiting their costs, especially where those products are based on research done at academic institutions supported by taxpayer funds.[34]

Conclusions

According to the National Science Foundation, pharmaceutical research and development spending has risen on average ~5% annually since 1980, but the approval of innovative new drugs has declined in recent years.[8] The respect of basic intellectual property rights is important in drug development to protect innovation. While patents are useful means of encouraging innovation, they can also increase costs, hinder access to diagnostic and therapeutic products, distort clinical practice, and complicate progress in medical research. The central policy goal remains the balancing of legitimate application of patent laws to support innovation, while preventing their improper use and the resultant negative effect such use has on public health. Pharmaceutical scientists can take a more active role in academic, charitable, government, or for-profit organizations regarding patent policy. Scientists should understand the policy implications of seeking patents on products or processes that are not true innovations, as well as how efforts by their patent attorneys (to seek overly broad intellectual property protections that their inventions may not deserve) can have substantial ramifications in the marketplace. Scientists, particularly in the academic setting, can lend their support to efforts by UAEM to encourage patenting practices that provide ways to ensure access to products in low-income settings. The goal ultimately should be to ensure that management of intellectual property does not upset the delicate policy balance and favor pursuit of profits over the public good.

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