

Appendix E

Patent Protection of Pharmaceuticals in the United States

Inventors have two mechanisms to protect the commercial value of their inventions: secrecy or patents. Trade secrets have legal protection if inventors make efforts to prevent the sharing or dissemination of their intellectual property (452). Patents prohibit others from making, using or selling the invention in the United States for 17 years after issuance without the inventor's permission.¹ Because of the relatively wide dissemination of pharmaceutical research results and production techniques through scientific literature and discussion, drug manufacturers rely on patents to protect potential and marketed drug products whenever possible. This appendix briefly examines the nature and limitations of pharmaceutical patent protection in the United States.

Pharmaceutical Patents and Products

Article I of the U.S. Constitution provides Congress with the power "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries," which Congress has implemented by allowing the Federal Government to issue patents. In contrast to many inventions, pharmaceutical products typically do not have a simple one-to-one correspondence with patents to which they relate. Several drugs can share the same patent, and some drugs may be protected by more than one patent. Other drugs are not eligible for patents at all.

According to Federal statute, art invention is patentable only if it is new, useful, and unobvious (35 U.S.C. 35101-103). The heart of a patent application is the

"claims" that the filer makes. The claims succinctly define the subject matter that the inventor regards as the novel contribution. A patent examiner compares the claim against existing public information ("prior art") in deciding whether to award the patent. The claim defines the scope of protection granted to the patent owner and is the basis for future judgments of whether the patent has been infringed (1 1).

For most newly discovered pharmaceutical chemical entities, a patent applicant can make four types of claims:

- A *compound claim* covers the chemical entity, per se, including any and all formulations or uses of the chemical entity.
- A *composition claim* covers a chemical entity formulated for use as a pharmaceutical. These claims sometimes specify a particular dosage form (e.g., oral tablet, injectable drug) or carrier² although they rarely are limited to a particular carrier, dosage form or treatment of a particular ailment.
- A *method-of-use claim* covers the use of a chemical compound or composition in a specified way. For example, the applicant may claim compound X as an antibiotic when administered in an effective dose against bacterium Z.
- A *process claim, or method of manufacture claim*, covers the way in which a compound or composition is produced (124,284). These claims have been particularly important in recent years for drugs that rely on recombinant DNA (deoxyribonucleic acid) technology, and because of

¹ Contrary to trade secrecy, the patent system actually contributes to the dissemination of scientific and technological advances through the publication of inventions and their details at the time the Federal Government issues their patent.

² A pharmaceutical carrier is usually an inert substance which allows or facilitates the active compound to be absorbed by and act upon the body (42).

a 1989 amendment to the patent laws that permits the holder of a U.S. patent to stop the importation of a product made outside the United States by the patented process (35 U.S.C. 271(g)).

Currently in the United States, all four kinds of claims are often found in a single patent. Prior to 1980, the U.S. Patent and Trademark Office (PTO)³ usually granted three patents for the four types of claims: one for the compound claim, one for the composition and method-of-use claim and one for the method of manufacture claim. The transition to a single patent has occurred gradually over the past 10 years and reflects procedural changes within the PTO (284).

For a firm filing an application with a compound claim, there are tradeoffs in deciding how broad the claim should be. A broad claim may encompass thousands of compounds which share common structural characteristics that are thought to be responsible for providing a particular utility. However, the broader the claim, the greater the chance a patent already exists on some version of the compound, thereby defeating the novelty of the broad claim. If a patent already exists on a particular compound or composition, one can still apply for and receive a composition or method-of-use patent for a new use even though the proposed use would infringe the pre-existing patent claiming the compound. A patent, however, does not give its owner the affirmative right to make, use, or sell the claimed subject matter but rather only the right to exclude others from doing so. In granting patents the PTO is only concerned with the patentability of the claimed subject matter and has no authority to consider whether that subject matter infringes an earlier patent. Determination of whether or not art infringement has occurred and enforcement of a patent must be left to the court (124).⁴

Given the broadness with which an applicant can make a compound claim, each patent, in reality, may cover or protect multiple chemical compounds. The PTO estimates that the average pharmaceutical patent contains ten distinct chemical compounds (284). Assuming a single compound may have more than one composition or method-of-use claim, a single patent

could be associated with an unspecified number of potential products. The ability to file new method-of-use claims on existing compound or composition patents (because of a newly discovered use or a new dosage form) increases the likelihood that the intellectual property protection of a single marketed drug product can rest on more than one patent (124,497).

Some drug products are not eligible for patent protection. Most of these have existed so long that all relevant patents have expired. A potential manufacturer can file a patent application for the new use of such a drug. However, the characteristics and actions of long available drugs (e.g., aspirin) may be so well known that it is difficult to establish the novelty (or lack of novelty) of a method-of-use claim. Even where a patent is obtained on a new method of use for an old drug with many shown uses, the patent may be difficult to enforce (497).

Until the 1980s, drugs discovered and developed in Federal laboratories rarely had patent protection because Federal policy dictated that they remain in the public realm. As a result of a series of legislative and policy initiatives developed during the 1980s, the Federal Government now patents drugs discovered in its laboratories and actively attempts to license them to the private sector.⁵

■ Patent Protection of Biotechnology Drugs

As discussed in chapters 5 and 6, major advances in the life sciences over the past 15 years have led to an increased number of biological drugs whose production is based on techniques of biotechnology. Biotechnology, particularly recombinant methods, allow manufacturers to produce sufficient quantities of these medicinal preparations for therapeutic use. Although the U.S. Supreme Court has held that living organisms are patentable, naturally occurring compounds and compositions themselves are not patentable because they are not considered 'novel. Products that exist in nature may be considered patentable if they are given a form, quality or function they do not possess in the natural state or otherwise meet all other criteria for

³PTO is the agency within the U.S. Commerce Department charged with examining patent applications and issuing Patents.

⁴If one inventor receives a patent on an improvement to another inventor's already patented invention, each inventor may find himself or herself blocked from using his or her invention by the other's patent. In such a situation, not uncommon among pharmaceuticals, the two inventors usually negotiate to cross-license their patents so both can use, produce, or sell their inventions (124).

⁵Chapter 9 describes in greater detail patent and technology transfer policies in the U.S. Department of Health and Human Services and their implications for pharmaceutical R&D.

patentability. Those who produce old drugs with the new techniques of biotechnology tend to seek patent protection for the methods by which they produce the drug; the bases for these patents are referred to as “process claims.”

Because of the relative novelty of biotechnology drugs and their patent claims, they have been the subject of much legal uncertainty and dispute over the past few years. The drug recombinant erythropoietin (rEPO), which treats anemia by replacing a deficient enzyme vital to red blood cell production, is a notable example. In 1987, Amgen, Inc. and Genetics Institute each received a patent related to rEPOs. Genetics Institute received a patent on a method of purifying human EPO from natural sources (i.e., not rEPO) and applied for another patent covering the production of a recombinant form of EPO. Amgen’s patent covered an intermediate product in this process. Genetics Institute also licensed its patent rights to Chugai Pharmaceuticals for the Japanese market and to a cooperative venture between Chugai and Upjohn Company for the U.S. market.

In subsequent litigation, a Federal court in Boston ruled that because Chugai produced its rEPO in Japan, it did not violate Amgen’s patent; the court found that Amgen’s protection of an intermediate product in the manufacture of rEPO did not cover production in another country. However, the judge did find that Amgen and Genetics Institute had each violated parts of the other’s patent. In 1990, the court ordered these two firms to cross-license each other’s patents without royalties (45 1). In March 1991, however, the Court of Appeals for the Federal Circuit reversed this decision, upheld Amgen’s patent, ruled that Genetics Institute had infringed on Amgen’s patent, and barred Genetics Institute from marketing rEPO in the United States (12,452).⁶ This action ensured only Amgen’s version

of rEPO would be available in the United States for the duration of its patent protection.⁷

■ Length of Patent Protection

Although the Federal patent statute provides for 17 years of exclusive rights to an invention, the actual amount of time a drug manufacturer is usually able to market its drug without competition is substantially less. Because firms usually seek patent protection once a potential drug compound is identified (284), a large portion of the patent period can be taken up by the sponsor’s research and development (R&D) activities and the U.S. Food and Drug Administration’s review of the marketing application (507). In 1984, Congress passed the Drug Price Competition and Patent Term Restoration (DPCPTR) Act (Public Law 98-417), which allowed PTO to add up to five years to the patent term of drugs when the patent term was eroded by regulatory review.⁸ As of May 1992, the PTO had issued 142 patent extensions most often for a period of 2 years beyond the statutory 17-year exclusivity (497).

From time to time Congress has passed special legislation granting additional patent extensions for individual drugs.⁹ In 1992 Congress considered, but did not enact, a bill granting patent extensions for Upjohn’s nonsteroidal anti-inflammatory drug flurbiprofen (AnsaidTM) (S. 102-1165) and U.S. Bioscience’s antiradiation drug ethiofos or amifostine (EthyolTM) (S. 102-526). The PTO had already issued a certificate of patent term extension for 2 years though February 1993 under the DPCPTR Act on the patent for which Upjohn seeks a further extension, but the company claims that unwarranted delays by FDA in the approval of its drug justify a further 4+ years. U.S. Bioscience seeks a 10-year extension for ethiofos because of its claim that the U.S. Army prevented the drug’s timely development for the potential treatment of persons with human immunodeficiency virus and cancer (439).

⁶ Amgen received U.S. Food and Drug Administration approval to market its rEPO for the treatment of anemia among patients with end-stage renal disease in June 1989.

⁷ In another suit brought by Amgen, the U.S. International Trade Commission ruled that it lacked jurisdiction and sent the case to the Federal Circuit Court of Appeals which ruled in 1990 that Amgen’s patent did cover a process for producing rEPO (13).

⁸ This legislation represented a compromise that also allowed easier FDA approval for generic drugs after patent expiration. The law also allows two types of exclusivity not related to patent status—a 5-year exclusivity for new chemical entities not eligible for a patent and a 3-year exclusivity for new uses of approved chemical entities. TMs appendix discusses the 3-year exclusivity in greater detail in the following section.

⁹ For example, in 1983, as part of the Federal Anti-Tempering Act (Public Law 98-127), Congress extended two patent terms covering an anesthetic drug to compensate for a delay in marketing approval while the firm conducted research at the request of the FDA that Congress deemed unnecessary (497). In another case, Congress granted a patent term extension for the drug gemfibrozil to Warner-Lambert Company after it was shown to have a new use in combating high cholesterol (Public Law 100-418).

■ Patents and “Follow-On” Products

Once relevant patents protecting the exclusive marketing rights of a drug expire, the manufacturer of the original form of the drug often seeks to maintain its market share by developing new, but related products. These new products may include previously unmarketed dose forms of the drug such as one that might require less frequent or easier administration. Once on the market, physicians and patients may prefer such a dose form over generic versions of the old dose form. Alternatively, the originator firm may develop a new (and patentable) drug product that is chemically related to the first but offers some clinical superiority. For example, the new drug may have fewer adverse reactions than the first generation product that is losing its patent protection. Although all companies theoretically may attempt to develop “follow-on” products to drugs losing patent *protection*, Federal law may offer the originator company an advantage in developing them more quickly. In a series of legal decisions, the

Federal courts have determined that researchers may use patented materials and processes for noncommercial scientific inquiry, but that any research related to a possible commercial product constitutes a patent infringement. Hence, the originator may conduct R&D activities on follow-on products, while all other competitors must wait until any relevant patents expire before beginning to develop their own (452).

Furthermore, the DPCPTR Act (Public Law 98-417) contains a provision that may reinforce the advantage originator firms have in getting “follow-on” products to market. The law provides for 3 years of market exclusivity for companies receiving approval of a new drug application (NDA) that is not for a new chemical entity, or of a supplemental NDA for a new use of an already approved drug.¹⁰ To be eligible, the new or supplemental NDA must be based on new clinical research (other than bioavailability studies) conducted or paid for by the drug’s sponsor and essential to FDA approval (83).

¹⁰The law also allows for a 5-year market exclusivity for new chemical entities not otherwise guaranteed a period of market exclusivity through patent protection of their active ingredients (83).