

American Pharmaceutical Patents

From a Historical Perspective

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The Congress shall have 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.¹

The Constitutional statement above empowered Congress to establish a patent system that would provide for a potential reward for the inventor and, at the same time, provide benefit to society by making full disclosure of the invention. Congress passed the Patent Act in 1790 and, when the initial system of patent examination proved burdensome, established the Patent Office in 1802. In the ensuing centuries, patent laws and patents have gone through numerous revisions to stay current with changing times.

Revolutionary Period

The pharmaceutical manufacturing industry has its roots in Andrew Craigie's establishment of a large-scale manufacturing plant in Carlisle, Pennsylvania, during the Revolutionary War.² Andrew Craigie was the first apothecary general of the United States. As far as is known, his original appointment as apothecary of the Massachusetts Army was the first recognition of the role by an American military institution.² Although the first patents for medical devices and medicines were not recorded in the United States until 1796, the true formation of the modern industry did not begin until the middle of the 19th century.³ Early manufacturers depended on innovation in manufacturing rather than the discovery of new medicines to grow their businesses. Leaders of the period, such as Edward Robinson Squibb, chose not to patent their innovations; and one firm quickly copied the successes of another. However, the industry was relatively small, with most manufacturers providing a full line of specialty products and items that pharmacists used in their compounding practices, with the distinction being the eponymous name of the owner, such as Squibb, Lilly or Abbott, guaranteeing quality. This state of the industry

continued through the Civil War and into the early years of the 20th century.

19th Century

By the end of the 19th century, German manufacturers dominated pharmaceutical chemistry. Germany protected their inventions such as Aspirin and Salvarsan with patents, even in the United States. These products were manufactured in the United States by subsidiary organizations or licensees who were never told what the complete synthetic processes were. This system came to a halt during World War I, when medicines covered by German patents were no longer available in the United States.

World War I

In 1917, the US government passed the "Trading with Enemy Act," which allowed American firms to produce products that were patent protected by companies in enemy territories. Perhaps the best example of this situation occurred with a product that was the treatment of choice for syphilis, Salvarsan, patented by Hoechst. When prices skyrocketed and supplies dwindled, the Dermatological Research Laboratory (DRL) of Philadelphia obtained permission to produce the German drug under the provisions of the 1917 Act. Similarly, Abbott managed to synthesize several important medicines of German manufacturers that had been patent protected, including barbital, procaine and a medicine for the treatment of gout, cinchopen. After the war, Abbott acquired DRL and the right to produce Salvarsan for the American marketplace. However, perhaps the biggest story of the period was the December 12, 1918, acquisition of the Bayer trademark and many patents by Sterling Products, a manufacturer "...of lavishly advertised laxatives, dandruff nostrums, and impotence cures"⁴ from the Alien Property Custodian for \$5,310,000. This was a bargain at the time and remains one today, as the value in 2003 dollars is only \$63,472,318.⁵

Postwar Period

During the postwar period, the American pharmaceutical industry began to focus its efforts on establishing research laboratories and relationships with universities and independent

research organizations. However, the bulk of the effort was to improve processes rather than to develop new chemical entities that would become medicines. Some American pharmaceutical firms, such as Merck, Lilly and Squibb, took exception to this generalization; but the bulk of new discoveries was again coming from German and Swiss firms. American firms would be licensed to do finishing, manufacturing, bottling and labeling and then to sell the products under their own name. Once again, international warfare threatened the availability of medicines protected by patents held by companies within enemy control. For example, the Japanese military controlled the Indonesian plantations that provided cinchona bark for the production of quinine; similarly, the German Nazi regime controlled I.G. Farben's synthetic production of Atabrine. In the United States, Winthrop had a license from I.G. Farben to do the finished manufacturing and to sell Atabrine. Three months before Pearl Harbor was attacked, the US government, under the Alien Properties Act, severed the ties between Winthrop and Farben; the War Production Board assigned a high priority to developing a process and increasing manufacture of the antimalarial. The process was a complicated one that required over 3,000 pounds of bulk chemicals to produce 100 pounds of bulk medicine. Winthrop licensed its new process without royalty to a number of American manufacturers.⁶

In many respects, World War II led the American pharmaceutical industry into the realm of research for new products and the need to patent its discoveries. Certainly, the experience of anticipated wartime shortages was a wake-up call for self-sufficiency. More important, however, was the realization that research would result in better products that would enjoy a period of protection from direct copying and, therefore, result in increased revenues and profits.

Intellectual Property: Trade Secrets and Patents

Naturally, inventors wish to gain a return on new intellectual property. In order to do so, the inventor seeks a way to preserve rights that will allow him/her to commercialize the discovery while preventing others from copying the discovery without the cost of the research process. The first way to protect intellectual property is through trade secrets. This approach depends on sharing no information with anyone who is not directly involved with the production of the innovation. While society may gain from an invention that is secret, there is no societal gain through the diffusion of new knowledge that will continue to fuel other inventions. The patent system is a way to protect the rights of an inventor while making the new knowledge generally available. In order to gain patent protection, the inventor must fully describe the new product, process and use, and the disclosure must be published and made available for anyone to learn from. In return, the inventor is given exclusivity over the discovery for a period of time with the right to bar all others from the manufacture and importation of the invention.

The distinction between a patent medicine and a patented medicine clearly shows the differentiation between trade secrets and the patent system. Originally, the term patent was a shortened form for the British Letters Patent, which, in practice, provided a monopoly for the provision of a specific good or service with no requirement for disclosure. Such a use of the term patent disappeared in America with the establishment of the United States after the Revolution. The term patent medicine in the late 19th and early 20th centuries was used to describe proprietary medicines that were sold with all sorts of incredible claims. These products were not patented; indeed, as Steven Pray has pointed out, the last thing that the manufacturers of many of these products wanted to do was to disclose the ingredients and processes under the patent system. Instead, the manufacturers registered the trade name to protect it while relying on trade secrets to keep the contents of the potions unknown.⁷

Patents, Trademarks and Copyright

In the United States, pharmacy and pharmaceutical manufacturers are affected by the rights and requirements of three different protections offered for intellectual property: patents, trademarks and copyright. The US Patent and Trademark Office (PTO) manages patents and trademarks, while copyrights are the responsibility of the Library of Congress. A patent provides protection for the invention or discovery of a new compound, process or use by excluding others from use for a period of time. A trademark is used to identify a specific product or manufacturer to provide a clear distinction between the sources of products or services. A copyright protects published and unpublished intellectual works such as books, music and paintings and prohibits others from using the work without specific permission.

What is a Patent?

The first definition of patent in *Webster's Unabridged Dictionary* is "open" with a later definition "open to view," both emphasizing that the information that establishes patent protection is also open and evident to others who wish to make use of it.⁸ Perhaps the patent system best exemplifies Isaac Newton's statement that he could see more because he stood on the shoulders of giants.

A patent is the grant of a property right for a specific number of years, typically 20. The patent provides "the right to exclude others from making, using, offering for sale, or selling" the discovery or for importing it into the United States. The PTO clearly notes that the patent does not grant the right to make, sell or import the discovery; rather it provides the right to exclude others from doing so. The right to grant patents belongs to the government of the country issuing the patent. Therefore, if one wants to gain patent protection in countries other than the United States, an application must be made in each country where protection is desired.⁹

There are three types of patents—utility, design and plant. For the most part, patents of interest within the pharmaceuti-

cal realm belong to the utility type. Utility patents include discoveries of new composition of matter (such as new pharmaceuticals), machines, processes and improvements upon them. Design patents are largely restricted to inventions of ornamental design for manufacturing. Plant patents are for the asexual development of a new variety of plant. New products must be useful and operational. This means that a new idea is not sufficient for the issuance of a patent. The invention must be developed, a complete set of plans incorporated with the patent application (in the case of a machine) and the processes developed to produce a new chemical or pharmaceutical. Similar to ideas, forces of nature and physical phenomena are not patentable.

There are different categories of invention in the chemical and pharmaceutical field: compounds, compositions, and manufacturing processes and uses.¹⁰ A number of criteria enter into the consideration of whether or not the invention is new and, therefore, patentable:

1. The invention must be something that is new or novel; it cannot be an obvious extension of a known invention. If there is any printed information describing the item or if the object has been for sale anywhere in the world, the inventor has a grace period of 1 year to file for the patent; otherwise, the inventor is unlikely to get a patent. A new form of a patented compound such as a new particle size or crystalline form may be patentable if it provides some additional benefit. For example, the discovery of a macrocrystalline form of nitrofurantoin led to slower absorption and decreased nausea and was patentable.
2. The invention must not be obvious. Consequently, a change in color, size or shape is not sufficient to gain a new patent.

New synthetic processes are also patentable and are frequently cost savers as processes are streamlined and improved. Process patents may also have the advantage of extending the life of a composition patent by making the original process more difficult and costly for others to use and by maintaining exclusivity on more cost-effective processes. New uses for existing products can also be patented; but, in the pharmaceutical arena, these patents are the weakest of all patent protections.

Minoxidil provides a number of examples of patents beginning with the original patents (1967, 1968) that were held by Upjohn for the treatment of hypertension. When bald men receiving minoxidil started growing hair, the unexpected event was investigated and a use patent for minoxidil in the treatment of baldness was filed. The string of innovation continues when, as late as 2000, a new patent for minoxidil combined with an antihistamine for relief of skin irritation was issued to the Taisho Pharmaceutical Company.¹¹

A patent is not a license for the new invention to break a law or to violate the rights of other inventors. For example, the holder of a patent for an improvement on an earlier invention could not make or sell the new discovery if the original invention was still protected by a patent, without first gaining a license from the original patent holder.⁸ Similarly, a patent on a

new antibiotic does not give the patent holder the right to sell a product before successfully meeting all marketing requirements under the Pure Food and Drug Act. It is this fact that has given rise to much of the debate over the length of patent life that is lost during the US Food and Drug Administration's (FDA's) review process.

Who Owns A Patent?

In the United States, only the inventor may apply for a patent. This means that universities, corporations and other bodies cannot apply for a patent, since organizations cannot be the inventor. The courts treat a patent as personal property that can be transferred or bequeathed. Typically, the inventor assigns the patent to an organization to develop or commercialize. For individuals working in many pharmaceutical research units, it is traditional to transfer the patent for a \$1.00 bill.

Unlike other countries, the United States gives the patent to the first [party] to invent, not the first [party] to apply for a patent. This illustrates the importance of laboratory notebooks in research units, whether in industry or academia. Typically, each researcher maintains a laboratory notebook that sets out the research process and results on a daily basis; each page is witnessed by a person other than the researcher. In the case of competing patent applications for a discovery, the laboratory notebook or similar documentation is used to determine the first inventor.

Kefauver-Harris

In 1959, Senator Estes Kefauver began a series of hearings in the Senate Judiciary Committee's subcommittee on antitrust and monopoly. The basic tenet of the investigation was whether pharmaceutical manufacturers had exceptional monopoly powers.¹² Kefauver and his staff attempted to show that the pharmaceutical industry was misusing the protection of intellectual property provided by patents. One of the solutions offered was compulsory licensing to any and all competitors at rates that would be determined by the government. There was also an attempt to show that patent protection did not result in increased pharmaceutical innovation. This attempt was soon discredited when the Commissioner of Patents, D.L. Ladd, pointed out Committee errors such as listing Germany and Switzerland as countries without patent protection. A British economist, Michael H. Cooper, was credited with the observation that in the decade from 1951 to 1960 the pharmaceutical industry was the fifth most profitable industry; the first four were mining and quarrying, cement, electric and gas utilities, and telephone and telegraph.¹³ In 1961, Kefauver introduced a bill in the Senate that would mandate compulsory licensing and change the criteria for marketing new medicines from safe to safe and efficacious. Congressman Oren Harris introduced a bill supported by the Kennedy administration that eliminated the compulsory licensing requirement. Both bills were headed nowhere; 3 days after the Senate Judiciary Committee reported the Kefauver bill out, the story on thalidomide broke in the Washington Post.¹⁴ The result was the passage of the Kefau-

ver-Harris Amendment to the Federal Food Drug and Cosmetic Act. Proof that new medicines were both safe and effective became a requirement for FDA approval and marketing. All provisions for compulsory licensing were eliminated. However, the requirement for increased FDA review set the stage for what would eventually become a key issue for the industry and Congress in the years leading up to changes in patent protection in 1984.

The Drug Lag

The passage of the 1962 Kefauver-Harris Amendment quickly gave rise to a situation referred to as an increasing drug lag. The first issue was that it took longer for manufacturers to develop the evidence required to submit a New Drug Application (NDA). The increased regulatory oversight increased the time between the identification of a potential medicine and its final approval as companies developed sufficient evidence that their new product was both safe and effective. Equally troubling, however, was the increased time that it took the FDA to review an application once it had been filed. In spite of the increased regulatory requirements, matching resources were not provided for the review process. The process time for new entities in 1962 was 17 months; but, by 1969, it had increased to 44 months, before declining to 22-months in 1978.¹⁵ These two factors were just one influence, although a major one, in the ensuing decline of new pharmaceutical introductions. From 1950 to 1967, the United States was responsible for approximately 50% of all new drug discoveries; but this declined to less than 25% by 1971 to 1973, and new medicines were increasingly marketed first outside of the United States.¹⁶ Another way of looking at the shift in the marketing of new chemical entities was that in the biennial period from 1960 to 1962, two thirds of innovative medicines were launched in the United States first; by 1972 to 1974, this had decreased to approximately 30%.⁷

In 1983, in an attempt to gain early market entry for a generic flurazepam, Bolar Pharmaceutical imported bulk chemical from a foreign manufacturer to use in performing tests required for an NDA. Roche Products, the holder of the patent, sued on the basis that such use violated its patent. The basis for the suit included the facts that Bolar was using and importing a patented item without the approval of the patent holder. Bolar's defense was that there was no attempt to sell a generic flurazepam before the expiration of the patent; rather the purpose was to be ready to file the required regulatory documents as soon as possible. The courts held that Bolar did violate the intellectual property of Roche. The issue of using patented items as part of the required research for a subsequent generic applicant became part of the push for changes in the protection offered by a patent.

Economics continued to play a role in the ongoing debate about pharmaceutical products with the movement to repeal state ant substitution laws and open the market place to generic competition. The initial push for the increased use of lower-cost substitutes came from publicly funded programs—notably

Medicaid. Prior to the repeal of the state ant substitution laws, the generic industry was very small; most multisource products were manufactured by the large companies as branded generics. For example, Smith Kline & French (now SmithKline Beecham) marketed a line of products with the prefix SK, such as SK-APAP, SK-Bamate and SK-Estrogen,⁸ and Robbins (now part of Wyeth Pharmaceuticals) used the prefix Robi to identify its line of branded generics. Other companies formed subsidiary organizations, such as Pfizer's Pfipharmecs and Squibb's Princeton Pharmaceuticals, to market a line of multisource products.

The forces of decreased patent protection and the push for lower prices for generic products came to a head in 1984. The research-based companies of the pharmaceutical industry took the position that the increased time for regulatory review decreased the period of patent exclusivity and negatively affected the profits needed to sustain and grow research. Other forces, including the generic drug industry, third-party payors, such as health maintenance organizations, and Medicaid and pharmacy, pushed for quicker approval of generics as a mechanism to restrain the increasing cost of medicines. In addition, the *Roche v. Bolar* case provided a real-world case of an obstacle to expedited generic approvals.

Waxman-Hatch Act (Drug Price Competition and Patent Restoration Act of 1984)

In 1984, Congress passed the Drug Price Competition and Patent Restoration Act, better known as the Waxman-Hatch Act, as an amendment to the Federal Food Drug and Cosmetics Act. A compromise allowed for the extension of a patent's life for the NDA holder, while providing a streamlined system for the approval of generic copies of the innovator's product.

The extension provisions of the Act required the NDA holder to provide information on all relevant patents, composition of matter, process and use as part of the submission process. This information must be updated as part of the routine reporting. In turn, the patent information was to be incorporated into the FDA's Approved Drug Products With Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book. The Act established mechanisms for the extension of patent life when the manufacturer could successfully show that a period of market exclusivity was lost because of regulatory delays. In addition, the Act established several additional patent extensions for companies undertaking additional clinical research.

It allowed up to a 5-year extension for new chemical entities, depending on time lost in regulatory review. During the extension, no generic equivalent could be submitted or approved. The sole exception to exclusivity was the situation involving a generic manufacturer's certification that it was challenging the patent status of the NDA holder. A 3-year extension was provided to manufacturers that undertook new clinical studies to support a change in dose form, different salt or expanded indications. It was possible for a generic product

to be approved for the original dose form and indications, but the package insert must clearly elucidate that the indications for the generic were limited. The Act also provided a 7-year exclusivity for orphan drugs for medicines with a single indication for diseases that had a population of less than 200,000 in the United States. In addition to the other periods of exclusivity, NDA holders could obtain a 6-month extension when studies were conducted to support pediatric use.

An abbreviated new drug application (ANDA) process was established that removed the requirement for a generic manufacturer to repeat preclinical and clinical testing that the innovator was required to perform to establish safety and efficacy. The generic manufacturer was required to prove that its product had similar bioequivalence to the innovator patent. The product also had to contain the same active ingredient, be in the same dosage form and be used in the same route of administration as the branded product. The labeling had to be the same as the originator's unless some of the information or indications of the innovator were still covered by patent. Finally, the generic manufacturer had to certify that it was in compliance with patent protection as part of the ANDA submission and had to notify the NDA holder of its intent to file for marketing approval. The Act also permitted a generic company to

begin testing its product prior to the expiration of the innovator patent, thus addressing the Bolar situation.

The Waxman-Hatch Act added a new factor to patent protection to facilitate public disclosures of new inventions – market exclusivity. The first company to file a successful ANDA is granted a 180-day period of exclusivity when other ANDAs may not be approved. This rush for exclusivity led directly to the generic drug scandal involving a number of companies and the FDA Generic Drugs Division. In 1987, Mylan Laboratories shared information with the House Committee on Oversight and Investigations that its applications were being delayed in favor of other manufacturers. In response, Congress enacted the Generic Drug Enforcement Act of 1992.¹⁸

General Agreement on Tariffs and Trade

The most recent changes to the patent situation occurred as a result of the General Agreement on Tariffs and Trade Uruguay Round in 1994. This international agreement established an international uniform standard for a 20-year patent life. The agreement sets the beginning date for patent protection as the first filing of the patent.

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Conclusion

While there has been a long-standing debate over the issue of pharmaceutical patents, several conclusions remain uncontested. We all want products that will help us preserve and protect the health of our loved ones and ourselves. There is no question that the only way to find new cures and treatments for disease is through research and innovation. Discovery and testing are expensive propositions with no guarantee of success. Without some incentive to provide the funding for research, we are all losers—of a longer and healthier life than we might have had otherwise. The alternative for innovation and protection of intellectual property is not a positive thought. It would be folly to accept a 19th-century urban myth attributed to the Commissioner of the Patent Office, Charles Duell, when he stated in 1899 that “Everything that can be invented has been invented.”

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