The Interface of Patents with the Regulatory Drug Approval Process and How Resulting Interplay Can Affect Market Entry

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ABSTRACT

All biotechnology and pharmaceutical products must be approved by both the U.S. Patent and Trademark Office (PTO) and the U.S. Food and Drug Administration (FDA). To maximize the impact of a product's market exclusivity, the time spent on getting approval should be minimized. This chapter discusses how the interplay between PTO and FDA applications affect the patent approval process, and by extension the patent term, and how these impact the commercial life of a product.

1. INTRODUCTION

The goals of the public and private sectors of the drug industry are often different. The public sector's main goal is to provide drugs to the public for the lowest possible price, while the private sector is most interested in achieving the greatest possible profit. Many private company tactics are employed for maximizing revenue are important to understand as they can also help the public sector to achieve its goals. For example, price discrimination—the practice of selling health products at different prices to different customers in various markets—is commonly used by private corporations to increase their profit margins. This practice, however, can also be used by nonprofit organizations: if they were to sell their products to developed countries at higher prices—or to license them to manufacturers in developed countries—the organizations would be better able to subsidize drug prices in poorer countries.

There are other ways that companies can maximize their revenue. For instance, companies in the biotechnology and pharmaceutical area must apply for approval from the U.S. Patent and Trademark Office (PTO) and Food and Drug Administration (FDA). Both of these applications are necessary: the PTO approves patents that protect a company's inventions, and FDA approval of a product is necessary before a new product can be marketed. These approval processes are lengthy, and companies should minimize the time spent on the process as part of a profit-maximizing strategy. This chapter outlines various ways to extend a patent's effective life through the strategic management of these approval processes.

2. PTO AND FDA APPROVAL PROCESSES

2.1 *Patent applications*

The PTO grants patents to inventions that are novel, useful, and nonobvious.[1] The *novelty* requirement

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Editors Note: This chapter is included in this Handbook to show the important interface of patents and the regulatory drug approval process and how this interplay affects market entry. It is not intended as an endorsement of effective patent life extensions to delay the market entry of generic drugs.

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prevents anyone from patenting an invention that is already available to the public. The *usefulness*, or *utility*, requirement states that one skilled in the art must be able to utilize the invention in a manner that provides immediate benefit to the public. The *obviousness* requirement prevents applicants from patenting products or processes that are insignificant modifications of already existing products or processes.

The inventor of a patented invention has the right to exclude others from making, using, offering for sale, or selling the invention in the United States or in U.S. territories or possessions. A limited 20-year monopoly[2] is granted to the inventor in exchange for public disclosure of the invention.[3] In the United States, the average time between filing of the application and approval of the patent is 3 ½ years, while the average time for a biotechnology patent is nearly 4 ½ years.

2.2 *Discovery phase and preclinical studies*

Simply put, in the discovery phase of research, scientists identify specific chemical or biochemical entities that are worth testing further. Next, preclinical studies are undertaken comprising in vitro studies and animal testing, pharmacodynamic responses, metabolic profiling, cellular receptor interaction, and/or physiology that is generally analogous to humans. Preclinical studies take an average of five years, but the precise length of time depends on the complexity of the study and the success achieved by initial research.

2.3 *FDA approval process*

The FDA approval process usually requires ten to 12 years and US$100 to US$500 million. The process is accomplished in two phases: clinical trials and new drug application (NDA) approval.

The FDA approval process begins when a manufacturer requests permission, by submitting an investigational new drug (IND) application, to begin human testing. The IND application must provide preclinical data of high quality to justify the testing of the drug in humans. Once the IND application is filed, the manufacturer must allow the FDA 30 days to review the prospective study before clinical trials can begin. IND applications must be re-filed annually until clinical testing is completed. Approximately 85% of all drugs for which IND applications are filed are subjected to clinical trials.

The next stage is Phase I clinical trials, which use human subjects. Phase I trials focus on establishing a drug's safety profile and examining how the drug is absorbed, distributed in the body, metabolized, and finally excreted. Phase I trials usually do not use more than 100 healthy volunteers, and the trials last, on average, from one to three years.

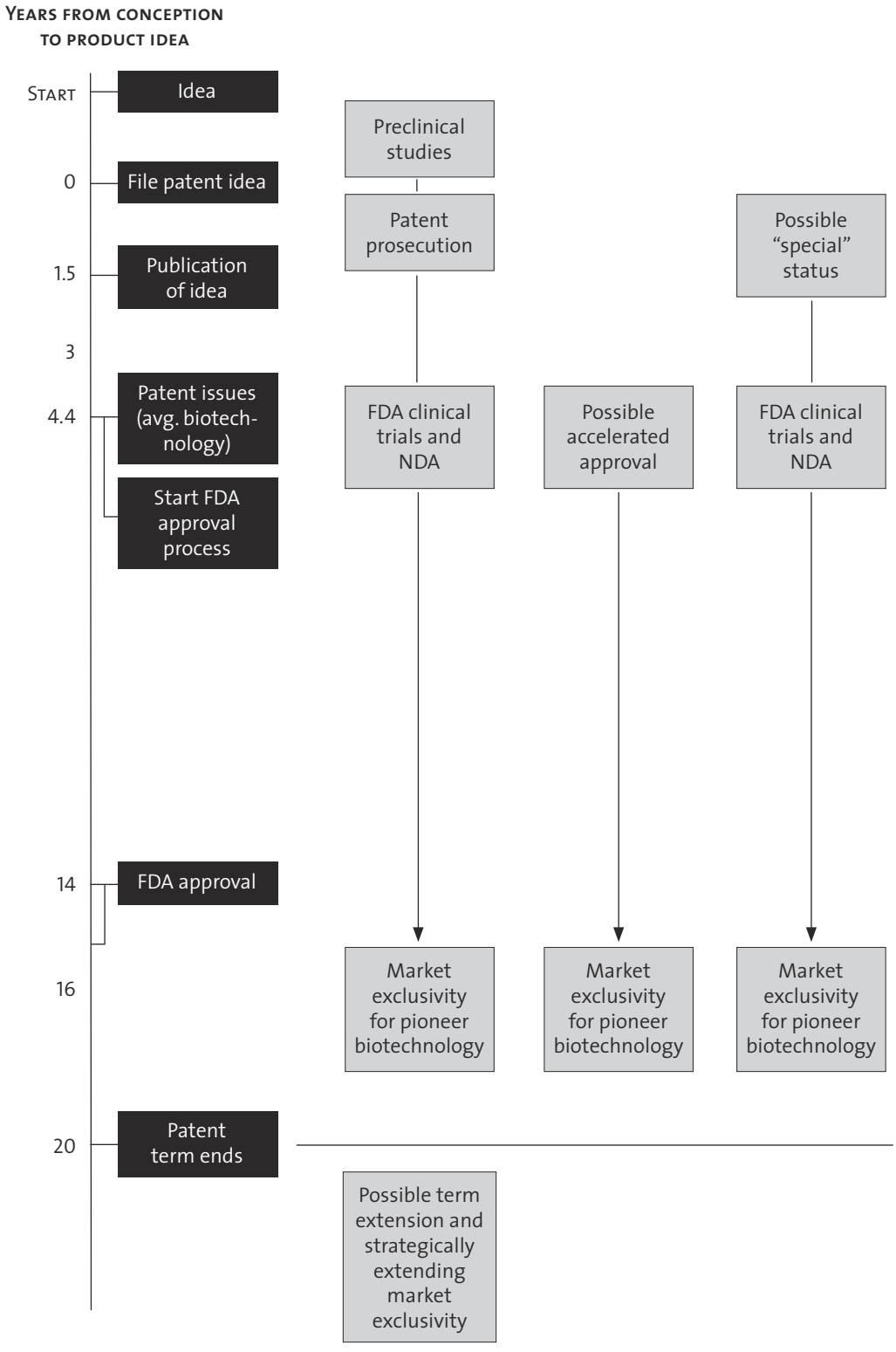
If the drug successfully passes Phase I, it is submitted to Phase II trials, which evaluate dosage, broad efficacy and additional safety. In this phase, volunteers who suffer from the targeted disease are given the drug. Phase II lasts two years, on average.

Phase III trials attempt to verify the effectiveness of the drug with double-blind studies that involve at least 1,000 patients. (A double-blind study is a stringent way of conducting clinical trials whereby subjective bias is eliminated by neither doctors/nurses nor patients knowing whether they administer/receive a placebo or experimental drug.) This phase continues to build the drug's safety profile by monitoring any side effects that result from long-term use of the drug. This phase lasts, on average, between three and four years.

If the drug successfully passes the first three phases of clinical trials, researchers can then file a new drug application (NDA) that includes the drug's proposed labeling. A team of physicians, statisticians, chemists, pharmacologists, and other scientists at the Center for Drug Evaluation and Research review the company's NDA by examining the preclinical and clinical reports and using risk-benefit analysis to determine whether or not the product's beneficial effects outweigh its possible harmful effects. Approval of an NDA can take from two months to several years, but, on average, approval is granted within two years. Once the NDA is approved, the innovating company is allowed to distribute and market the drug.

Once the drug is distributed in the public market, it is considered to be in Phase IV trials. The manufacturer must continue to monitor and

Figure 1: Timeline for Patent/Product Approval and Profit-Maximizing Options



evaluate the drug's safety during routine use (see Figure 1 for a timeline of the above process).

2.4 *Filing PTO and FDA applications*

The "effective life" of a patent is defined as the period of time between a product's introduction to the market and the patent's expiration date. The manufacturer of a product with a long effective life will enjoy extended market exclusivity and thereby recover research and development costs. When the patent expires, the manufacturer will be at a real disadvantage: on average, generic drug companies capture 57.6% of the market for drugs with expired patents. Obviously, the faster the drug is approved and thus comes to market, the longer the marketing period and thus the generation of revenues and profits.

Preclinical studies are the rate-limiting step in the FDA approval process because clinical trials cannot begin until there is sufficient data to justify human testing. Therefore, as many preclinical studies should be performed as early as possible and preferably before a patent application is filed, as the results of such studies also help support claims for the utility of an invention.

There are several reasons why innovating companies should file patents for their products before seeking FDA approval for them. In the first place, the PTO has lower safety standards than the FDA;[4] although a patent application must demonstrate that a drug has a "sufficient probability" of safety in humans, the applicant is not required to provide any clinical evidence of its safety.[5]

Next, patents are important IP (intellectual property) safeguards. If an innovating company were to begin the FDA process before filing a PTO application, another company could patent the invention before them. The innovating company would either have to license the biopharmaceutical from the other company (losing royalties, market exclusivity, and company value in the process) or abandon the FDA process altogether and forfeit millions spent in research and development.[6] Even if another company does not patent the product, the innovating company must be careful not to disclose the invention, otherwise the innovating company would have one year to file the patent before the patent enters the public domain (internationally, the patent application must be filed before disclosure).

There are two other reasons to file patents before beginning an FDA application: (1) FDA approval is accelerated for patented compounds, and (2) patents attract the notice of potential investors who can provide the capital to fund FDA clinical trials. Ideally, preclinical studies should end before, or concurrently with, patent issuance, and FDA clinical trials should begin immediately thereafter. But before clinical trials can begin, the manufacturer must turn over several documents justifying the conduct of the trial, verifying the quality of the data produced, and demonstrating the compliance of the investigator with all regulatory requirements. These documents include: scientific journal publications, in vitro and animal data, trial subject information, financial analysis, and laboratory protocol. The FDA must review and approve these documents before clinical trials can begin. As mentioned above, the filing of the patent should be done first, or the drug manufacturer runs the risk of missing the one-year deadline for establishing priority of invention.

Once the FDA has approved the drug for U.S. consumers, the innovating company will enjoy market exclusivity for the patent's effective life. A strategically written patent will effectively and efficiently protect against product infringement by other companies. The innovating company should take pains to develop brand recognition and build consumer reliance on its products in order to retain the largest possible market share once the patent term ends.

3. EXTENDING A PATENT TERM

Once the patent term ends, the innovating company need not lose its market exclusivity immediately. Various tactics can be used to extend a patent term and delay generic market entry.

Assuming a patent satisfies certain basic criteria,[7] the PTO will grant patent extensions when its approval process takes longer than three years. If, for example, a patent took four years to issue, the patent term may be extended by an additional year.[8]

Two laws also allow for patent terms to be extended: the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act) and the Generic Animal Drug and Patent Term Restoration Act of 1988. Title II of the Hatch-Waxman Act (the "patent term restoration" or "extension" clause) gives certain patent holders the opportunity to extend patent terms for human drug products, including antibiotics and biologics, medical devices, food additives, and color additives. The Generic Animal Drug and Patent Term Restoration Act provides a similar opportunity to holders of patents for animal drug products (excluding those derived from recombinant DNA technology). These laws were designed to stimulate innovation by domestic drug companies. Both acts allow a patent term to be extended by up to five years. However, the total effective patent life cannot exceed 14 years from the date of FDA approval.[9]

In order for an innovating company to obtain a patent term extension, certain criteria must be met:

1. The patent has not expired.
2. The patent has not previously been extended.
3. The patent owner or its agent submits the application.
4. The product has been subjected to a regulatory review period with the FDA or the U.S. Department of Agriculture (USDA) before its commercial marketing or use.
5. The permission for commercial marketing or use represents the first permitted commercial marketing or use of the product for which the regulatory review occurred (see below). For products produced using recombinant DNA technology, excluding animal drug products, the product must be the first produced using that technology.
6. The patent restoration application must be submitted within 60 days of the product's initial FDA approval.[10]

The regulatory review period is composed of a testing phase and an approval phase. The testing phase is the period between the effective date of an investigational product exemption (for example, an IND application) and the initial submission of a marketing application (for example, an NDA). The approval phase is the period between the submission and the approval of the marketing application.[11] The PTO calculates the length of the extension by considering both the lengths of the aforementioned testing and approval phases. It is important to note that the PTO does not consider times the applicant did not exercise due diligence[12] during the regulatory review period.

After the innovating company's patent term expires, generic companies may enter the market with generic drug equivalents. Whereas the initial FDA approval process may have taken ten to 12 years, the Hatch-Waxman Act allows generic companies to use the abbreviated new drug approval (ANDA) process to gain approval for generic equivalents within six months. There are three requirements for filing an ANDA application:

1. The company must show that the proposed generic drug is the same as, or bioequivalent to, an FDA-approved drug.
2. The company must certify that a patent protected the approved drug.
3. The company must not use a production method that has been patented by the innovating company (a so-called *production method patent*).

Because of the third stipulation, it is wise to file the drug production method patent a few years after filing the original patent (generally focusing on the composition of the drug). This will ensure that even when the drug composition enters the public domain, the production method will continue to be protected. This strategy is even more effective for biopharmaceuticals than for traditional chemical pharmaceuticals because it is so difficult to create production methods using complex microbiological systems.

Another strategy is known as the *metabolite*[13] *defense* involves filing patents for useful drug metabolites in years subsequent to the filing date of the main patent. Once the generic version of the drug is marketed, the innovating company can bring a patent infringement claim against the

generic company, since the company will inevitably be manufacturing infringing products via its customers' metabolic processes.[14] While the effectiveness in court of the metabolite defense may be debatable,[15] litigation can delay market entry of generics.

Finally, an innovating company can file a citizen petition with the FDA, citing safety concerns regarding a generic biopharmaceutical. Although the majority of citizen petitions are eventually rejected by the FDA or withdrawn by innovating companies, filing such a petition can delay generic market entry for six months or more.

4. ACCELERATING MARKET ENTRY

There are essentially five ways in which companies may accelerate the introduction to market of a new drug:

- *PTO special status:* The PTO awards special status to certain biotechnology inventions, processing them ahead of all others. To qualify for a special status the company must be a small entity (a company with fewer than 50 employees) or a nonprofit organization. The petition must state that the patent applicant's technology will be significantly impaired if a patent examination is delayed.
- *FDA well-characterized status:* The FDA can designate a biopharmaceutical as a well characterized biotechnology product if its identity, purity, potency, and quality can be substantially determined and controlled. As long as the manufacturer is able to produce the same product, the manufacturing technologies of a well-characterized pharmaceutical can be altered without having to repeat clinical trials. If a company develops a well-characterized biotechnology product, it can begin FDA clinical trials immediately and improve the manufacturing process at a later date.
- *FDA expanded access exception:* This exception allows manufacturers to market the product before completing clinical trials (before completing the approval process). Expanded access is available for a very limited number of new drugs that are pending final FDA approval. This program allows drugs to be used and marketed before the FDA approval process is completed. The manufacturer must apply for a drug to be made available through an expanded access program. To acquire such status, the company must provide sufficient evidence that the drug will be effective against a given disease and that the drug has not been linked to unreasonable health risks. The provision is somewhat uncommon because the FDA generally allows expanded access only if there are no other satisfactory treatments available for the given disease.
- *FDA accelerated approval process:* The FDA may accelerate approval of a biopharmaceutical if adequate and well-controlled clinical trials indicate that it will provide considerable therapeutic benefit over existing therapies, particularly in cases of serious or life-threatening diseases.

5. CONCLUSION

The PTO and FDA approval processes are expensive and time-consuming. By the time a drug can be marketed to the public, part of its patent term will have already expired. In order to maximize profits, FDA processing time should be minimized as far as possible. In addition, patent terms can sometimes be extended, and various strategies can be used to prevent generic companies from taking too much of market share. Nonprofit organizations in particular may benefit from the strategies outlined in this chapter, especially if they are used in conjunction with price discrimination. ■

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1 35 U.S.C. § 102; 35 U.S.C. § 103.

2 On December 8, 1994, President Clinton signed the Uruguay Round Agreements Act into U.S. law. The Uruguay Round Agreements Act gives all patents that were in force or filed as of 8 June, 1995 an effective term of 17 years from the date the patent was granted or 20 years from the date of the first filing of the patent application. All patents filed after 8 June, 1995 have a patent expiration date of 20 years from the date of the first filing of the patent application.

3 *Nelson v. Bowler* 626 F.2d 853 Cust. & Pat. App., 1980 (C.C.P.A. 1980), *"Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility."*

4 35 § U.S.C. 102; 35 U.S.C. 103.

5 See *In re Hartop*, 311 F.2d 249 (C.C.P.A. 1962).

6 The Federal Circuit recognized such concerns of pharmaceutical companies in In re Brana, 51 F.3d 1560 (Fed. Cir. 1995): *"FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. . . . Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer."*

7 21 C.F.R. Part 60.

8 35 U.S.C. § 155; 35 U.S.C. § 156.

9 If the patent was issued before 24 September, 1984 and the product's regulatory review period began before that date, then the limit is two years. For animal drug products whose regulatory review periods began before 16 November, 1988 the limit is three years. In all cases, the total patent life for the product cannot exceed 14 years from the product's approval date.

10 The FDA defines product approval as the date the FDA sends a letter notifying the marketing applicant that (1) the FDA approved the marketing application, (2) the product development protocol was completed, or (3) the listing of used food or color additives. The 60-day term begins on the day after approval; the PTO must receive the application for patent extension on the 60th day (or the next business day after the 60th day if this day falls on a weekday or holiday).

11 The FDA has 30 days by law to determine the regulatory review period for a product. After this period, there is a 60-day comment period during which parties can request revisions to the regulatory review period determination. The end of the 60-day comment period marks the end of the regulatory-review period stage.

12 Due diligence is defined as *"that degree of attention, continuous directed effort, and timeliness as may reasonably be expected from, and are ordinarily exercised by, a person during a regulatory review period."* 35 U.S.C. § 156(d)(3).

13 Metabolites are the metabolized derivatives of a drug.

14 In *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 759 (Fed. Cir. 1997), the court *"recognized that a person may infringe a claim to a metabolite if the person ingests a compound that metabolizes to form the metabolite."* See also *Zenith Labs., Inc. v. Bristol-Meyers Squibb Co.*, 19 F.3d 1418 (Fed. Cir. 1994) (stating that a compound claim could cover a compound formed upon ingestion).

15 In *Schering Corporation v. Geneva Pharmaceuticals, Inc.,* 339 F.3d 1373 (Fed. Cir. 2003), a Federal Circuit panel recognized that patent protection is available for metabolites of known drugs: *"[A] patentee may obtain patent protection for an inherently anticipated compound through proper claiming."*