

HIGH-STAKES ANDA PHARMACEUTICAL LITIGATION AND PARAGRAPH IV CHALLENGES

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*(Originally printed in the Intellectual Property
Supplement to The Legal Intelligencer, April 21, 2008)*

The Food and Drug Administration (FDA) oversees the drug approval process in the United States. In 1984, Congress adopted the Drug Price Competition and Patent Term Restoration Act, known as the “Hatch-Waxman Act” (Act). The Act amended the Food, Drug and Cosmetic Act and expedites the approval process for lower-priced generic drugs, while safeguarding valid pharmaceutical patents and maintaining incentives for innovation. The Act grants generic drug companies a 180-day marketing exclusivity period for a generic drug when a company is the first to file an abbreviated new drug application (ANDA) containing a “Paragraph IV certification” with FDA. However, under the amendments to the Act set forth in the Medicare Prescription Drug, Improvement and Modernization Act (MMA), this highly valued exclusivity period can be “forfeited.” Nevertheless, generic drug companies continue to accept the risks associated with complex and expensive ANDA litigation with the expectation of financially benefiting from the 180-day exclusivity period.

NDA and Orange Book

In order to market a new drug, a New Drug Application (NDA) is filed with FDA containing extensive scientific and clinical data in an effort to convince FDA that the drug is safe and effective for its intended use. NDAs are typically filed by large, brand-name drug companies, like Pfizer, AstraZeneca and Bristol-Myers Squibb, that are willing to make the tremendous investment associated with running clinical drug trials to obtain necessary data for the NDA. The NDA must also include the patent number and corresponding expiration date of

any patent that claims the drug or a method of using the drug with respect to which a claim of patent infringement could reasonably be asserted. If the NDA is approved, FDA publishes this patent information in the Approved Drug Products with Therapeutic Equivalence Evaluations publications, commonly known as the “Orange Book.”

ANDA and Patent Certifications

Under the Act, when a company wants to market a generic version of a previously approved brand-name drug, it files an ANDA with FDA showing that the proposed generic drug is “bioequivalent” to the brand-name drug listed in the Orange Book. Importantly, generic drug companies do not have to repeat the clinical trials required in a NDA and, instead, can rely on data submitted in the brand-name drug company’s NDA. As a result, filing an ANDA is a far less expensive and time-consuming process than filing a NDA, which results in lower-priced generic drugs for consumers.

Prior to filing an ANDA, the generic drug company must refer to the Orange Book to determine whether any patents are listed for the brand-name drug. With respect to each Orange Book listed patent for the drug, the ANDA must include one of the following four certifications (21 U.S.C. §355(j)(2)(A)(vii)(I)-(IV)):

- **Paragraph I**—There are no patents listed.
- **Paragraph II**—The listed patents have expired.
- **Paragraph III**—FDA should approve the ANDA after the listed patents have expired.
- **Paragraph IV**—The listed patents are invalid and/or will not be infringed by the proposed generic drug.

Paragraph IV Notice Letter and 30-Month Stay

Under the MMA, if a generic drug company makes a Paragraph IV certification, it must notify the NDA holder and patent owner (which are usually brand-name drug companies) within 20 days of receiving notice from FDA that the ANDA has been filed. This Paragraph IV notice letter must include the factual and legal bases for the generic drug company's opinion that the patent is invalid and/or will not be infringed by the generic drug that is the subject of the ANDA. The notice can also include an offer of confidential access to the ANDA so that the brand-name drug company can determine whether it should file a patent infringement lawsuit.

Filing an ANDA containing a Paragraph IV certification is considered an "artificial" or "technical" act of patent infringement because it allows brand-name drug companies to sue the ANDA filer for infringement despite the fact that the ANDA filer has not marketed its generic drug. If a brand-name drug company files a patent infringement action within 45 days of receiving the Paragraph IV notice letter, it is entitled to an automatic 30-month stay of FDA "final" approval of the ANDA. As a result, FDA can only grant "tentative" approval of the ANDA thereby preventing the generic drug company from marketing its generic drug during the stay. Assuming FDA is otherwise satisfied with the ANDA, FDA will make the "tentative" approval "final" upon the earlier of expiration of the 30-month stay or a court determination of patent non-infringement or invalidity. If the brand-name drug company does not bring suit within 45 days, the generic drug company may bring a declaratory judgment action for non-infringement or invalidity.

180-Day Exclusivity, Forfeiture and "At Risk" Launch

The Act rewards the first generic drug company to file a FDA finally-approved ANDA containing a Paragraph IV certification by providing it with a 180-day marketing exclusivity

period during which FDA cannot give final approval to another ANDA for the same brand-name drug. That is, the first generic drug company to file a Paragraph IV certification is protected from competition from other generic versions of the same drug for 180 days. The exclusivity period is triggered by the first commercial marketing of either the NDA or ANDA drug by the generic drug company. This allows generic drug companies to stockpile inventory to meet demands for the generic drug during the exclusivity period.

The MMA established several forfeiture events that, if triggered, cause the first ANDA filer to lose the 180-day exclusivity period. The forfeiture provisions are intended to prevent various perceived abuses by brand-name and generic drug companies, including agreements to forego or delay marketing a generic drug thereby stalling generic competition without having the agreements approved by the Federal Trade Commission (FTC). The 180-day exclusivity period is forfeited when any of the following events occurs:

- First ANDA filer fails to market its product by the *later of*: (1) the *earlier of* 75 days after it receives FDA approval or 30 months after its ANDA submission; or (2) 75 days after a favorable, nonappealed district court or favorable appellate court decision, or a favorable settlement is entered, or the patent(s) expires or is withdrawn;
- Orange Book listed patent(s) expire;
- First ANDA filer withdraws its ANDA;
- First ANDA filer withdraws or amends the Paragraph IV certification;
- First ANDA filer enters into an agreement that violates antitrust laws;
- FDA deems ANDA withdrawn for failure to meet approval requirements; or
- First ANDA filer fails to obtain tentative approval from FDA within 30 months of filing the ANDA.

There is a significant risk to a generic drug company that markets its generic drug without first obtaining a court decision holding the listed patent invalid or not infringed. This

scenario is referred to as an “at risk” launch of the generic drug because if the patent is later held valid and infringed, then the generic drug company will be subject to damages, including lost profits, as a result of marketing its generic drug.

Nevertheless, some generic drug companies are willing to “launch” their generic drug “at risk” causing brand-name companies to seek a preliminary injunction in an effort to enjoin further sales of the generic drug. For example, Apotex Corporation had the largest “at risk” launch in pharmaceutical history when it marketed a generic version of the blockbuster drug Plavix® before a final court decision. The brand-name companies for Plavix® responded by moving for a preliminary injunction and enjoined further sales of a generic version of Plavix®.

Multiple First Filers and Shared Exclusivity

The original Act did not address the scenario where multiple generic drug companies would file ANDAs with Paragraph IV certifications for the same brand-name drug on the same day. Not surprisingly, there are reports of instances in which ANDA filers took drastic measures in an effort to be considered the “first” Paragraph IV ANDA filer.

Under the MMA, if more than one generic drug company files a “substantially complete” ANDA containing a Paragraph IV certification for a previously unchallenged drug (regardless of what time of day), each ANDA filer shares the same 180-day exclusivity period. Thus, the 180-day exclusivity provision does not guarantee that a generic drug company will be the sole competitor to the brand-name drug company during the exclusivity period.

Settlement Agreements and ANDA Litigation

Any agreements between ANDA filers or an ANDA filer and a brand-name drug company related to the 180-day exclusivity period, or the manufacturing, marketing, or sale of

the brand-name or generic drug must be filed with FTC and the Department of Justice within 10 days of executing the agreement. However, most ANDA cases go to trial.

ANDA litigation is similar to other types of patent infringement cases as it requires developing an in-depth understanding of the patents and subject matter at-issue, extensive pre-trial discovery and a knack for simplifying complex and scientific technology to convince the trier of fact that your client should prevail. While in discovery and preparing for trial, the attorneys are mindful of when the automatic 30-month stay expires because it could trigger an “at-risk” launch requiring a preliminary injunction hearing.

Also, like other patent infringement cases, ANDA cases almost always require that the parties retain experts early in the litigation to help prove their case. Due to the complexity of drug formulations and their affect on human physiology, several highly specialized scientific experts are usually retained. Such experts can include pharmacologists, toxicologists, specialized medical doctors, and the like to opine in expert reports and at trial on a variety of scientific issues, including the molecular structure of the drug. In addition, marketing/economic experts are often retained to opine on commercial aspects of the drug.

Because of the complexity of ANDA litigation, Judges sometimes request a tutorial early in the case to educate them on the technology and patents-at-issue. Courtroom technology is also critical in presenting each party’s case in order to simplify and effectively present the scientific concepts involved in the case.

Like other patent infringement cases, ANDA litigation includes a *Markman* hearing where the parties present their understanding of the patent claim elements in dispute so that the Judge can issue a claim construction ruling. Because of the high-stakes involved, a district court opinion rarely results in the end of ANDA litigation. Both the brand-name and generic drug

companies have a tremendous financial incentive to appeal to the Court of Appeals for the Federal Circuit, a specialized court that has jurisdiction of patent appeals from all district courts. The Federal Circuit can decide the issues on appeal or remand the case to the district court to make findings consistent with the Federal Circuit's opinion.

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