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IN FOCUS

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Drug Pricing and the Law: Pharmaceutical Patent Disputes

Patent rights play an important role in the development and pricing of pharmaceutical products. Patent law seeks to encourage innovation by granting the holder of a valid patent a temporary monopoly on an invention, potentially enabling him to charge higher-than-competitive prices. Patent disputes relating to the entry of follow-on pharmaceuticals are subject to specialized procedures. Because patent rights may deter or delay competition from generic drug and biosimilar manufacturers, these procedures can affect whether and when follow-on products can enter the market, influencing the prices of patented pharmaceuticals. This In Focus provides an overview of the complex procedures governing pharmaceutical patent disputes.

FDA Regulation of Drugs and Biologics

Drugs and biological products (biologics) are both articles used in the diagnosis, cure, mitigation, treatment, or prevention of human disease. Nonbiological drugs do not derive from living organisms, and are generally artificially synthesized, small-molecule chemicals. In contrast, biologics are generally large, complex molecules produced by or derived from living organisms, such as a virus, toxin, antibody, vaccine, blood component, or protein.

Both drugs and biologics are subject to a premarket approval process administered by the Food and Drug Administration (FDA), but under different laws. Before they can be marketed or sold, nonbiological drugs must be approved by FDA under the Federal Food, Drug, and Cosmetic Act (FD&C Act), whereas biologics are licensed by FDA under the Public Health Service Act (PHSA).

General Patent Dispute Procedures

Patents can be obtained on almost any new and useful invention made by humans. For example, many different aspects of new pharmaceutical products—such as active ingredients, formulations, or methods and technologies to manufacture drugs and biologics—may be patented.

To obtain a patent, the claimed invention must be novel, useful, and nonobvious, and the inventor must be the first person to file a patent application with the U.S. Patent and Trademark Office (PTO). If the PTO grants the patent, the patentee generally has the exclusive right to make, use, sell, and import the invention for a set term, usually 20 years from the date that the application was filed. Any other person wishing to use the invention during this period needs permission from the patent holder. A person who practices a validly patented invention without permission infringes the patent and risks legal liability.

To enforce the patent, the patent holder may sue alleged infringers in federal court to seek injunctions, damages, and other remedies. Patents are presumed to be valid, but accused infringers may defend against lawsuits by claiming noninfringement (i.e., what they did was not covered by the patent) or invalidity (i.e., the patent should never have been issued because, e.g., the invention was not novel).

Specialized Pharmaceutical Patent Dispute Procedures

Federal law contains specialized procedures for certain pharmaceutical patent disputes. Instead of traditional acts of patent infringement—such as making, using, or selling the allegedly infringing product—these procedures are triggered by the act of filing an application with FDA for approval of a follow-on product. Under certain circumstances, the law treats the filing of these FDA applications as an "artificial" act of patent infringement, allowing for the resolution of patent disputes before the follow-on is marketed. These procedures can affect whether and when a generic drug or biosimilar can be marketed, and so determine when a brand-name product becomes subject to direct competition.

To encourage the market entry of follow-on pharmaceuticals, federal law provides abbreviated regulatory pathways for approving generic drugs and biosimilars. Under the Hatch-Waxman Act, generic drug manufacturers seeking FDA approval can rely on a brand-name drug's safety and efficacy information, if the follow-on product is pharmaceutically equivalent and bioequivalent to the previously approved brand-name drug. Similarly, under the Biologics Price Competition and Innovation Act (BPCIA), a biosimilar manufacturer can obtain an FDA license to market a biologic by demonstrating that it is biosimilar to (or interchangeable with) an already-licensed brand biological product.

Patent Procedures Under the Hatch-Waxman Act

Under the Hatch-Waxman Act, new drug manufacturers must list patents that claim the drug or a method of using that drug as part of their application for FDA approval. FDA includes information on listed patents in a publication known as the *Orange Book*.

When a generic drug manufacturer seeks approval from FDA, it must make one of four certifications with respect to patents listed in the *Orange Book*: (i) there are no patents listed; (ii) the patent has expired; (iii) the generic will delay FDA approval until the patent expires; or (iv) the patent is invalid or not infringed. This final certification, called a "paragraph (iv) certification," often results in litigation. If the generic manufacturer makes a paragraph (iv)

certification, it must notify the patentee and the brand-name drug manufacturer, who then have 45 days in which to bring a lawsuit against the generic applicant.

If the patent holder timely files suit after a paragraph (iv) certification, the FDA generally cannot approve the generic drug application for 30 months while the parties litigate their patent dispute. If the courts determine that the patent is invalid or not infringed, FDA can approve the drug immediately. If the courts conclude that the patent is valid and infringed, then FDA generally cannot approve the generic application until the patent expires.

Patent Procedures Under the BPCIA

A different set of procedures applies to patent disputes relating to biosimilar market entry under the BPCIA. In contrast to the Hatch-Waxman approach, biologic manufacturers need not provide any patent information to FDA as part of their licensure applications. As a result, patent information is not included in the *Purple Book*, FDA's list of approved biological products.

Instead of Hatch-Waxman's listing and certification process, patent disputes regarding biosimilars may be resolved through the BPCIA's "patent dance." The patent dance is a complex scheme through which brand-name biologic and biosimilar manufacturers exchange information about their patents and products in preparation for potential litigation. The Supreme Court has held that biosimilar manufacturers cannot be judicially compelled to engage in the patent dance, so biosimilar manufacturers may choose whether or not to initiate the patent dance.

To initiate the patent dance, the biosimilar applicant must provide its FDA application and information about how the biosimilar is manufactured to the brand-name biologic manufacturer no later than 20 days after FDA accepts the biosimilar application. The biosimilar applicant and brand-name biologic manufacturer then engage in a series of back-and-forth information exchanges regarding the relevant patents and the parties' positions as to the validity and infringement of those patents. The parties may have the opportunity to litigate patent disputes (1) at the conclusion (or breakdown) of the patent dance, and/or (2) when the applicant provides notice that the biosimilar will be actually marketed. (Such notice must occur no later than 180 days before the date of commercial marketing.)

Unlike patent listing under Hatch-Waxman, the BPCIA contains an express statutory penalty for failing to list relevant patents during the patent dance. If the biosimilar applicant commences the patent dance, the brand-name biologic manufacturer must provide a list of all patents for which it believes a claim of patent infringement could reasonably be asserted. The patent holder may forfeit his right to sue on patents that are not included on this list.

Table 1. Comparison of Patent Provisions in the Hatch-Waxman Act and the BPCIA

	The Hatch-Waxman Act	The BPCIA
Pharmaceutical Product	Drugs—usually small molecules, chemically synthesized (e.g., Aspirin: $C_9H_8O_4$)	Biologics—often large, complex molecules (e.g., Humira: $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$)
FDA Approved Product List	The *Orange Book* (includes patent information)	The *Purple Book* (no patent information)
Patent Listing Requirements	New drug manufacturer is required to list any patent that claims the drug or a method of using the drug.	If the patent dance is initiated, brand-name biologic manufacturer must list patents for which a claim of patent infringement could reasonably be asserted.
Patent Listing Consequences	If no patent listed, generic applicant need not certify; brand drug manufacturer may not obtain 30-month stay of FDA approval.	Patentee may forfeit right to sue on patents that should have been included on list provided during the patent dance, but were not included.
Patent Dispute Procedures	**Patent Listing and Certification Process**: 1. Generic applicant makes certifications with respect to patents listed in the *Orange Book*; 2. Generic applicant must notify patent holder and brand-name drug manufacturer of paragraph (iv) certifications challenging a patent; 3. Brand-name drug manufacturer may sue within 45 days after notice of paragraph (iv) certification; 4. If suit is filed, FDA generally cannot approve generic application for 30 months while the parties litigate the patent dispute.	**The "Patent Dance"** (simplified steps): 1. Biosimilar applicant provides application and manufacturing information to brand-name biologic manufacturer; 2. Parties exchange lists of relevant patents, positions on patent validity and infringement, and negotiate to try to reach agreement and/or narrow disputed issues; 3. Eventually, "first phase" of litigation may result at conclusion of patent dance (or if the dance breaks down); some patents may be reserved for "second phase" of litigation when biosimilar applicant gives notice of commercial marketing.

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