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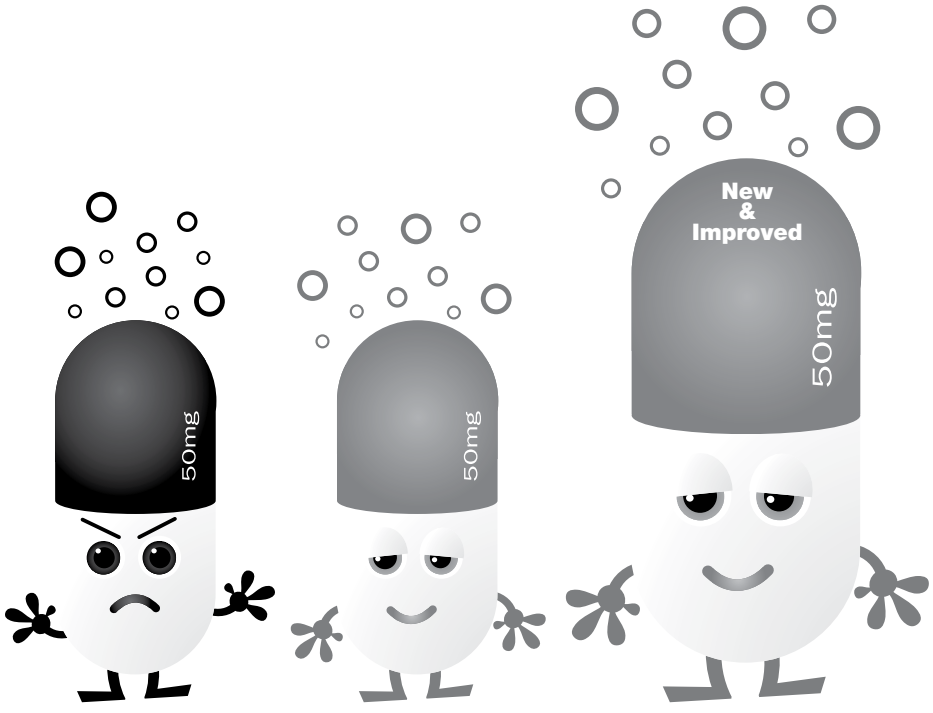
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Second Generation Pharma Patents

When enforcing them under Hatch-Waxman, how vulnerable are they to generic attack?

BY DENISE L. LORING AND KATHERINE A. HELM

THE ENACTMENT of the Hatch-Waxman Act attempted to strike a balance between what seemed to be irreconcilable competing interests. Congress recognized the need to accelerate entry of inexpensive generic drugs into the marketplace, while encouraging branded pharmaceutical companies to make the investments necessary to develop new and innovative drug products. 149 Cong. Rec. S15582, S15584 (Nov. 25, 2003) (remarks of Sen. Kennedy, Medicare Prescription Drug, Improvement, and Modernization Act of 2003).



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Under Hatch-Waxman, generic companies are permitted to file Abbreviated New Drug Applications (ANDAs) that piggyback on the branded drug maker's safety and efficacy data, submitted in its New Drug application (NDA) in connection with approval of the branded product. The ANDA filer need only show that its generic product is "bioequivalent" to the branded product.

The ANDA filer must, with a few exceptions, copy the branded drug's label, including the branded company's information on the drug's safety, efficacy, approved indications and instructions for use. In exchange for the abbreviated approval process for generic products, the NDA holder is provided an opportunity to enforce its patents against the ANDA filer before the generic product enters the market.

The Hatch-Waxman scheme works essentially as follows. The branded company submits to the Food and Drug Administration information about patents that cover the branded product or its use for which "a claim of patent infringement could reasonably be asserted." 21 U.S.C. §355(b)(1). The FDA lists these patents in a reference book called the "Approved Drug Products With Therapeutic Equivalence Evaluations," also known as the Orange Book.[1]

ANDA filers wishing to enter the market before expiration of these patents must include in their ANDA a "Paragraph IV certification" that the listed patents are invalid or will not be infringed by the manufacture, use, sale or offer for sale of the generic product, and must notify the NDA holder of the certification. 21 U.S.C. §§355(j)(2)(A)(vii)(IV), 355(j)(2)(B)(ii). The NDA holder has 45 days from the date it receives notice to bring a patent infringement suit. If it does so, FDA approval of the ANDA is stayed for 30 months, or as otherwise ordered by the court, to permit resolution of the lawsuit. 21 U.S.C. §355(j)(5)(B)(iii).[2]

The FDA has promulgated regulations governing the types of patents that should be listed in the Orange Book. Patents claiming the active drug substance, pharmaceutical formulations and compositions and approved methods of using the drug must be listed. Patents claiming metabolites, intermediates or packaging of the approved branded drug are not proper for listing. 21 C.F.R. §314.53(b). The FDA has made clear that it does not review patents submitted by NDA holders to determine whether these patents comply with its regulations. 68 Fed. Reg. 36676, 36678-79 (June 18, 2003).

Hatch-Waxman has spawned considerable patent litigation, which has increased steadily since its enactment. The resulting patent infringement suits involve not only basic patents on the active pharmaceutical agent and formulations as approved, but also so-called "second generation" patents directed to improvements to the pharmaceutical compositions, delivery systems or methods of use of the original product.

NDA holders view second generation drug products as providing improved protection, safety and ease of use for patients, and the resulting second generation patents as protection on their substantial investments in developing and obtaining FDA approval of these improvements.

Not surprisingly, generic manufacturers have a different view. They consider these second generation patents to be attempts to extend the NDA holder's exclusivity and maintain the high profits available for branded products before entry of generics into the marketplace.

This article looks at the vulnerabilities of these hotly contested second generation patents, both in terms of their validity and also with respect to some of the hurdles to proving that these patents will be infringed by the generic products or their use.

Generic manufacturers, not surprisingly, consider them to be attempts by the branded drug makers to extend exclusivity and maintain the high profits available for branded products before entry of generics into the marketplace.

How to Prove Infringement?

Turning first to infringement, because a generic product is not yet on the market at the time suit is initiated, the primary source of evidence for infringement must come from the ANDA itself. The ease with which infringement is proved may depend in large measure on how closely the patent claims track the data set forth in the ANDA and relied on by the ANDA filer to characterize the generic product.

For example, an ANDA filer shows bioequivalence to the branded product by demonstrating that the active ingredient in the generic formulation has the same "bioavailability" (i.e., rate and extent of absorption) as that of the branded product. 21 U.S.C. §355(j)(8). If the patent claims recite the parameters relied on to show bioavailability by the ANDA filer, the NDA holder may prove infringement based on the ANDA itself. See, e.g., *Purdue Pharma. v. Endo Pharms., Inc.*, 438 F. 3d 1123 (Fed. Cir. 2006) (claims of patents in suit recited blood concentration parameters that defendant generic company relied on in ANDA to demonstrate bioequivalence). Infringement may be more difficult to prove if the claims recite parameters that are not directly obtained from the ANDA.

In *Alza Corp. v. Mylan Labs., Inc.*, 464 F. 3d 1286 (Fed. Cir. 2006), the patent claims required that a certain amount of the active ingredient be "delivered" to the patient. The court construed the term "delivered" to refer to the actual amount of the drug released in a patient's gastrointestinal tract ("in vivo" release), which could not be directly measured. The patent owner was thus compelled to rely on an indirect measure of release of the drug inside the patient—data in the ANDA showing dissolution of the drug in a test tube ("in vitro" release).

The court held that the patent owner had failed to prove infringement because it had not demonstrated a correlation between the ANDA's in vitro dissolution data and the in vivo "delivery" required by the patent claims. Claims reciting the in vitro dissolution profile rather than in vivo release would have substantially reduced the patent owner's burden of proving infringement.

Similar issues may arise with method of use claims. FDA regulations provide that patents claiming only unapproved, or off-label, uses may not be listed in the Orange Book. And, 35 U.S.C. §271(e)(2), which makes filing an ANDA that includes a Paragraph IV certification an act of infringement of patents covering the drug or its use, has been construed to apply to method patents only if they are directed to FDA-approved uses or indications. See *Warner-Lambert Co. v. Apotex Corp.*, 316 F. 3d 1348 (Fed. Cir. 2003); *Allergan, Inc. v. Alcon Labs, Inc.*, 324 F.3d 1322 (Fed. Cir. 2003).

Moreover, FDA regulations permit ANDA filers to omit from the proposed generic label patented uses when the branded label includes more than one approved use. 21 C.F.R. §314.94(a)(8)(iv).

Omitting the patented use may sometimes eliminate the requirement to make a Paragraph IV certification as to patents claiming that use, and the availability of a 30-month stay arising from suit on the use patent. 21 U.S.C. §355(j)(2)(A)(viii). Thus, ANDA filers may avoid method of use patents that claim some but not all of the uses in the branded label, by simply carving out the patented uses from the generic label. Yet, once the generic drug has received FDA approval, physicians are free to prescribe it for any use, regardless of whether the use is included in the generic label.[3]

More Hoops for Patent Owners

Other hurdles arise when the patent owner asserts infringement under the "doctrine of equivalents."

Patent claims that are not "literally" infringed because the accused product or process does not include all of the limitations contained in the claim may nevertheless be infringed under the doctrine of equivalents if the differences between the accused product or process and the claim limitations that are not literally present are insubstantial. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 38-40 (1997).

The doctrine of equivalents is tempered by another doctrine, known as prosecution history estoppel, which provides that a patent owner may not expand the scope of its claims under the doctrine of equivalents to recapture subject matter surrendered before the U.S. Patent and Trademark Office (USPTO) in an effort to obtain allowance of the patent claims. Such surrender may arise either by amending claims or making arguments that limit claim scope during prosecution of the patent application. See *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002). An example of the difficulties that a patent owner may face in proving infringement under the doctrine of equivalents is seen in the decision of the Court of Appeals for the Federal Circuit in *Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348 (Fed. Cir. 2004).

In *Glaxo*, the second generation patent at issue claimed a sustained release formulation containing the active ingredient bupropion and an agent used to impart controlled release characteristics to the formulation, hydroxypropylmethylcellulose (HPMC). Impax's proposed generic version of the formulation contained hydroxypropylcellulose (HPC) instead of HPMC. HPC is chemically related to HPMC and served the same sustained release function as the HPMC in Glaxo's formulation.

The Federal Circuit affirmed the district court's grant of summary judgment of non-infringement based on prosecution history estoppel. During prosecution of its patent application before the USPTO, Glaxo amended its patent claims to add a specific reference to HPMC, and argued that HPMC was key to achieving sustained release of the drug. The court found that the amendment and argument estopped Glaxo from asserting that in the generic formulation, HPC was equivalent to HPMC in the patent claims. The court also found that HPC was a foreseeable substitute for HPMC and, therefore, should have been included in Glaxo's patent application when it was filed.[4]

Validity Attacks

Second generation patents are susceptible to certain types of validity attacks as well. One such attack is under the doctrine of inherent anticipation.

An inventor is not entitled to a patent if the invention sought to be patented is not novel over what came before. 35 U.S.C. §102. Such an invention is said to be anticipated by the prior art, and any patent claiming that invention would be invalid.

An invention may be inherently anticipated, even though the prior art does not expressly disclose the claimed invention, if the invention is inherently present in the prior art. It is not enough that the prior art would possibly or even probably produce the claimed invention; rather the invention must flow as a natural consequence from the prior art. See *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991).

In the pharmaceutical context, the doctrine of inherent anticipation has been broadened to include later recognition of the prior art's inherent characteristics. So, for example, in *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373 (Fed. Cir. 2003), a patent that claimed an antihistamine drug and described its administration to patients was found to inherently anticipate later claims to a metabolite that formed in the bodies of patients treated with the drug, even though the metabolite was not disclosed in the prior art patent and its existence was not previously appreciated.[5]

To the same effect is the Federal Circuit's recent decision in *Abbott Labs. v. Baxter Pharm. Prods.*, No. 06-1021, -1022, -1034, 2006 U.S. App. LEXIS 27734 (Fed. Cir. Nov. 9, 2006), in which the claims directed to a formulation comprising the drug sevoflurane and a Lewis acid inhibitor (e.g., water) in an amount effective to prevent degradation of the drug were inherently anticipated by the prior art first generation patent claiming a water-saturated sevoflurane composition, even though that composition did not display the same stability as the improved formulation.

Another area in which second generation patents are susceptible to validity attacks is an assertion that the patents claim inventions that are not distinct from the inventions claimed in the first generation patent.

Such patents would be invalid under a doctrine referred to as obviousness-type double patenting. This doctrine prohibits a patent owner from obtaining a second patent containing claims directed to obvious variants of inventions claimed in an earlier commonly owned patent. See, e.g., *Eli Lilly & Co. v. Barr Labs.*, 251 F.3d 955, 968 (Fed. Cir. 2001).

For example, where the later patent claims the same invention more broadly than an earlier patent the later patent may be invalid for double patenting. In *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368 (Fed. Cir. 2005), a patent claim directed to a method for treating damaged or aged skin was held invalid for double patenting in view of an earlier claim to a method for treating a sunburn. The court reasoned that sunburn was a species of skin damage that rendered the broader claim invalid.[6]

Conclusion

Given the high stakes involved, we can expect litigation under Hatch-Waxman to continue to increase, especially litigation involving second generation patents.

Branded companies will continue to seek patent protection for improvements they make to their drug products and new inducations. They will take steps to prepare and prosecute new patent applications so as to avoid the infringement and validity vulnerabilities of the patents at issue in the cases discussed above. ANDA filers will find new and different ways to challenge those patents to try to achieve rapid entry into the marketplace with new generic products.

The caselaw in this field is in flux. New wrinkles appear almost weekly, both for the branded companies and their ANDA competitors, making it an exciting and challenging field in which to practice. Stay tuned.

1. The Orange Book is available online at www.fda.gov/cder/orange.

2. Hatch-Waxman was amended in December 2003, as part of the Medicare Modernization Act. The amendments were aimed at closing some of the loopholes of the original act. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, Title XI, 117 Stat. 2448-2469.

3. Moreover, an ANDA filer that has omitted an indication from its label may not be liable for inducing physicians who prescribe the drug for the omitted use to infringe the patent under 35 U.S.C. §271(b), absent evidence that the generic directly encouraged or promoted the patented use. See *Warner-Lambert*, 316 F.3d at 1363-65; Allergan, 324 F.3d at 1331-34.

4. Under the Supreme Court's *Festo* decision, claim amendments raise a rebuttable presumption of surrender of subject matter falling between the original and amended claims. One basis for rebutting that presumption is showing that the accused equivalent was not foreseeable at the time of the amendment. *Festo*, 535 U.S. at 738; see also *Ranbaxy Pharms., Inc. v. Apotex, Inc.*, 350 F.3d 1235, 1241 (Fed. Cir. 2003). The *Glaxo* decision appears to push back the Supreme Court's foreseeability requirement to the time of filing of the application, rather than the time of claim amendment.

5. The *Schering* court noted, however, that claims directed to the metabolite in its pure, isolated form or to a method of treatment by administering the metabolite itself could have been patented. Id. at 1381; see also *Glaxo Group Ltd. v. Teva Pharms. USA*, No. 02-219 GMS, U.S. Dist. LEXIS 16750 (D. Del. Aug. 20, 2004) (method claims directed to the new use of a drug to treat nausea and vomiting were patentable over a patent disclosing the drug as useful to treat migraine pain).

6. The court noted that the double patenting defect could have been cured if the patent owner were to file a "terminal disclaimer," surrendering the term of the patent that extended beyond the expiration date of the earlier patent. Id. at 1375. A terminal disclaimer may not always be available, however, to cure obviousness-type double patenting.

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