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U.S. Courts Look At Method Of Use Patents In Generic Drug/ANDA Litigation

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Last month both the U.S. Supreme Court and the U.S. Court of Appeals for the Federal Circuit issued important decisions relating to method of use patents in the Hatch-Waxman Abbreviated New Drug Application (ANDA) patent litigation framework. These cases underscore unique aspects of method of use patents in the ANDA context.

The Hatch-Waxman ANDA Framework

The Orange Book

When a brand manufacturer obtains FDA approval for a new drug product or method of treatment, it submits to the FDA a list of relevant patents and their expiration dates. For method of use patents, the brand manufacturer must provide a description of the methods, which is referred to as the "use code narrative." The FDA does not investigate or verify the identified patents or uses, but publishes the information in its "Approved Drug Products With Therapeutic Equivalence Evaluations," a/k/a, the Orange Book.

A generic drug manufacturer may seek FDA approval to market a generic version of an approved drug by filing an Abbreviated New Drug Application (ANDA). An ANDA must include a certification regarding each patent listed in the Orange Book for the product at issue, chosen from the following:

A paragraph I certification states that there is no patent information listed in the Orange Book
A paragraph II certification states that the listed patent has expired
A paragraph III certification seeks approval on the date on which the listed patent will expire
A paragraph IV certification states that the listed patent is invalid or will not be infringed by the generic product

Generic Carve-Out Labeling

When a product is covered only by one or more method of use patents (as opposed to product patents), a generic manufacturer can file an Abbreviated New Drug Application (ANDA) that seeks FDA approval for a use that is not covered by the patent(s). Under these circumstances, the generic manufacturer must make a "section viii" statement certifying that the method of use patent "does not claim a use for which the [ANDA] applicant is seeking approval," as reflected in the generic manufacturer's proposed labeling. When reviewing this type of ANDA, the FDA compares

the brand product's use code narrative with the generic manufacturer's proposed labeling to confirm that there is no overlap between the uses.

ANDA Litigation

According to the Hatch-Waxman Act, the filing of an ANDA with a paragraph IV certification constitutes an act of patent infringement. By its express terms, 35 USC § 271(e)(2) makes it an act of infringement to file an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent." In accordance with the 2003 Federal Circuit decision in *Warner-Lambert Co. v. Apotex, Corp.*, the artificial infringement pertains only to "a patented use that has been approved by the FDA."

The Hatch-Waxman ANDA litigation framework enables a patent owner to bring an infringement action against an ANDA applicant who has made a paragraph IV certification, permitting resolution of the patent issues before the generic product enters the market. Indeed, the FDA will approve the generic drug notwithstanding the Orange Book listed patent(s) unless the patent owner brings an infringement action against the ANDA applicant within 45 days of receiving notice of the paragraph IV certification. If the patent owner commences ANDA litigation, the FDA will not approve the drug for thirty months (this is often referred to as a "thirty month stay"), unless the litigation is resolved earlier.

ANDA Litigation Counterclaim

The Hatch-Waxman Act ANDA litigation provisions include a clause introduced by a 2003 amendment (21 USC § 355(j)(5)(C)(ii)(I)) that permits a generic manufacturer to challenge the Orange Book listing under certain circumstances:

> [The ANDA] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either–
> (aa) the drug for which the application was approved; or
> (bb) an approved method of using the drug.

The Supreme Court Decision in *Caraco*

In a decision issued April 17, 2012, the U.S. Supreme Court issued a unanimous decision in *Caraco Pharmaceutical Labs., Ltd. v. Novo Nordisk A/S*, finding that 21 USC § 355(j)(5)(C)(ii)(I) provides a mechanism for a generic drug manufacturer to challenge the accuracy of a use code associated with an Orange Book listed patent.

The issue presented in *Caraco was* whether this statute permits a counterclaim when the listed patent does claim ***an*** approved method of using the drug, but the use code narrative (allegedly) describes the use over-broadly.

The product at issue was the drug repaglinide, which Novo Nordisk A/S markets under the brand name Prandin®. The FDA has approved the drug for three uses:

1. repaglinide by itself (i.e., monotherapy)
2. repaglinide in combination with metformin
3. repaglinide in combination with thiazolidinediones

The Orange Book listed two patents for Prandin®:

1. U.S. RE 37,035, which includes product claims and expired March 14, 2009
2. U.S. 6,677,358, which includes combination product and method claims using repaglinide and metformin, and which is set to expire June 12, 2018:

> A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

The Orange Book listing for the '358 patent was amended to have the following use code:

> U-968–A method for improving glycemic control in adults with type 2 diabetes mellitus.

Caraco asserted a counterclaim in the ANDA litigation, "requesting an order requiring Novo to change the use code for the '358 patent" and alleging that the new use code "was overbroad because it incorrectly suggested that the '358 patent covered all three approved methods of using repaglinide even though it claimed only one approved method."

The Supreme Court Decision

In a unanimous decision, the Supreme Court held

> a generic manufacturer can use the counterclaim provision of 21 U. S. C. §355(j)(5)(C)(ii)(I) to "force correction of a use code that inaccurately describes the brand's patent as covering a particular method of using the drug in question."

The Supreme Court arrived at its interpretation of the statute after considering together both its "statutory text and context." The Supreme Court also noted that the FDA itself does not review the accuracy of the use code information provided by the innovator patent holder, but "takes that code as a given." The Supreme Court explained:

> The statutory scheme, in other words, contemplates that one patented use will not foreclose marketing a generic drug for other unpatented ones. Within that framework, the counterclaim naturally functions to challenge the brand's assertion of rights over whichever discrete use (or uses) the generic company wishes to pursue. That assertion, after all, is the thing blocking the generic drug's entry on the market. The availability of the counterclaim thus matches the availability of FDA approval under the statute: A company may bring a counterclaim to show that a method of use is unpatented because establishing that fact allows the FDA to authorize a generic drug via section viii.

The Federal Circuit Decision in Bayer v. Lupin

On April 16, 2012, the Federal Circuit issued its decision in *Bayer Schering Pharma AG v. Lupin, Ltd.*, holding that the Abbreviated New Drug Applications at issue did not infringe the asserted patent related to Yasmin. In particular, the Federal Circuit agreed that the FDA had not approved Yasmin for the method of use claimed in the patent, and so filing the ANDAs could not amount to infringement of the patent. While this case is similar to *Caraco* in that it relates to a method of use

patent in the ANDA framework, it raised different issues.

The Product At Issue

The product at issue was Bayer's Yasmin product, which is approved for oral contraception. The patent at issue was U.S. Patent 5,569,652, which claims methods of "simultaneously achieving . . . a gestagenic effect, antiandrogenic effect, and an antialdosterone effect …." (Two other patents listed in the Orange Book for Yasmin are not at issue in this case.)

The ANDA Litigation

The defendants in this case—Lupin, Watson and Sandoz—each filed ANDAs with paragraph IV certifications regarding the Orange Book listed patents, including the '652 patent. Bayer sued each defendant, alleging infringement under 35 USC § 271(e)(2) of the '652 patent (only).

Watson and Sandoz moved for judgment of noninfringement on the pleadings (under Federal Rule of Civil Procedure 12(c)), arguing that "their ANDAs related to the use of the generic form of Yasmin only for oral contraception and not for the combination of uses claimed in the '652 patent." The district court agreed, and granted their motions. In so doing, the court "noted that the FDA had approved the use of Yasmin only for oral contraception, and not for the simultaneous treatment of three conditions . . . [as] claimed in the '652 patent." Moreover, because "there was nothing in the record to indicate that the defendants sought to promote their generic versions of Yasmin based on the anti-androgenic or anti-aldosterone properties claimed in the '652 patent, the court rejected Bayer's claim that the defendants were liable for inducement of infringement." Based on that ruling, Bayer and Lupin stipulated to, and the court entered, final judgment in that suit as well.

The Federal Circuit summarized the governing principles as follows:

> Based on *Warner-Lambert* and *Allergan*, the defendants' conduct would constitute infringement under section 271(e)(2)(A) (or inducement of infringement under section 271(b)) only if the defendants' ANDAs sought approval for the use protected by the '652 patent, i.e., for the combination of a gestagenic effect, an anti-androgenic effect, and an anti-aldosterone effect in patients needing that combination of effects.

Given the ANDA framework, "the use or uses for which the ANDAs seek FDA approval are necessarily the same as the uses for which the FDA has given its approval by granting Bayer's NDA." Thus, the "narrow" question before the court was:

> > whether the FDA has approved the use of Yasmin to achieve the combination of the three effects claimed in the '652 patent.

In deciding this issue, the Federal Circuit noted that the "Indications and Usage" section of the approved Yasmin label states:

> Yasmin is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

The court noted that "that characterization tracks the FDA's approval letter for Yasmin, which stated that the NDA 'provides for the use of Yasmin . . . for oral contraception.'" Although

information in the “Pharmacodynamics” subsection of the “Clinical Pharmacology” section of the label referenced the effects claimed in the ‘652 patent, the Federal Circuit disagreed that the presence of that information indicated that the FDA had approved Yasmin for those uses. To the contrary, the court found no indication that the FDA had determined that Yasmin is “safe or effective in inducing those effects.”

The court concluded:

> The defendants’ ANDAs seek approval to market the generic form of Yasmin solely for contraceptive use, and there is no valid patent on the use of the drug for that purpose alone. The FDA-approved label for Yasmin does not indicate to physicians that the specific use claimed in the ’652 patent, i.e., producing contraceptive, anti-mineralocorticoid, and anti-androgenic effects in premenopausal and menopausal women with a specific need of all three effects, is safe and effective. Therefore, we agree with the district court that the FDA has not approved such use and that the defendants cannot be held liable for infringement of the patent.

The Unique Role of Method of Use Patents

In addition to addressing specific issues that surround method of use patents in the ANDA patent litigation framework, these cases underscore the unique role of method of use patents in the pharmaceutical context. In both cases, patents directed to the drug and to first therapeutic uses of the drug had expired or were close to expiring. The brand manufacturers were able to supplement their patent positions by obtaining new method of use patents, but ultimately were not able to prevent regulatory approval of generic products. Once generic products are on the market, however, the brand manufacturers can police their marketing programs for activities that might amount to inducing infringement of the method of use patent(s).

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