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Induced Infringement Based on Filing an ANDA: It's All in the Label

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The recent case *AstraZeneca LP v. Apotex Inc.*, No. 2009-1381, 97 USPQ2d (Fed. Cir. Nov. 1, 2010) (81 PTCJ 17, 11/5/10), sheds new light on the law of inducement of infringement under 35 U.S.C. § 271(b) in the context of Abbreviated New Drug Applications. In all inducement cases, the U.S. Court of Appeals for the Federal Circuit requires a plaintiff to show that the defendant had specific intent to induce someone else to directly infringe. *DSU Medical Corp. v. JMS Co.*, 471 F.3d 1293, 81 USPQ2d 1238 (Fed. Cir. 2006) (en banc) (73 PTCJ 206, 12/22/06). The plaintiff must show that the defendant took active steps to induce, such as promoting a drug for infringing uses or encouraging doctors to prescribe the drug for infringing uses. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365, 65 USPQ2d 1481 (Fed. Cir. 2003) (66 PTCJ 732, 10/31/03). In the realm of pharmaceuticals, promotion is limited to the uses for which the drug has received Food and Drug Administration approval, as stated in the approved labeling. For this reason, the Federal Circuit has adopted a strict rule that inducement will be determined by the generic product's package insert (its ''label''). If the generic product's label does not include the use claimed in the patent in suit, there will be no inducement.

AstraZeneca illustrates the converse: if the generic's label includes an infringing use, then inducement will be found. Significantly, *AstraZeneca* shows that the patent holder may establish inducement of infringement even where the patented use is not expressly

stated in the ANDA product's label, so long as the patent holder can argue that the patented use is implicit in the label.

Regulatory Background

To market a drug in the United States, a manufacturer must obtain approval from the FDA by filing a New Drug Application. *See* 21 U.S.C. § 355(a). NDAs must contain comprehensive information on what the drug is composed of, how the drug is manufactured, and what clinical testing the drug has undergone. *See* 21 U.S.C. § 355(b)(1)(A)-(D). Furthermore, as part of the NDA process, the FDA must approve the label that will be provided to end users along with the drug. 21 U.S.C. § 355(b)(1)(F). Finally, NDA applicants must list all patents that claim the drug or a use of the drug in the FDA's Orange Book. 21 U.S.C. § 355(b)(1)(G).

The Hatch-Waxman Act allows generic drug makers to navigate the drug-approval process more quickly by filing an ANDA. *See Warner-Lambert*, 316 F.3d at 1358. ANDA applicants need not include all the rigorous clinical data that NDA applicants are required to submit; instead, ANDA applicants need only show ''bioequivalence'' with a drug that is already approved by the FDA. *Bayer AG v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241, 1244, 54 USPQ2d 1210 (Fed. Cir. 2000) (60 PTCJ 46, 5/19/00); 21 U.S.C. § 355(j). When an ANDA applicant seeks approval to market a generic drug for which a patent is listed in the Orange Book, the applicant must provided either a ''Paragraph III certification'' stating that approval is not sought until after the patent expires, or a ''Paragraph IV certification'' stating ''that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.'' 21 U.S.C. § 355(j)(2)(A)(vii).

Along with the provisions for accelerated approval of generic drugs, the Hatch-Waxman Act made it an act of infringement to submit an ANDA with a Paragraph IV certification (that is, one that seeks approval for a patented drug before the expiration of the patent). 35 U.S.C. § 271(e)(2).

Induced Infringement with Generic Pharmaceuticals

When a brand-name pharmaceutical maker has a patent on a use of a drug, inducement of infringement seems like a natural legal theory to assert against a generic copier. After all, the generic drug maker does not itself use the drug. The manufacturer's infringement is indirect, consisting of encouraging and causing the direct infringement by others: use of the drug by doctors and patients. Moreover, drugs commonly have multiple uses (including so-called ''on-label'' and ''off-label'' indications), and it would seem obvious that the generic manufacturer, wishing to achieve the broadest use of its product, must intend for doctors and patients to use it for all possible indications.

But the matter is more complicated than that. To show inducement, a plaintiff must show both that the defendant caused direct infringement to occur and that the defendant had the ''specific intent'' to cause such direct infringement. *Warner-Lambert*, 316 F.3d at 1361. The specific intent element presents a high hurdle for plaintiffs in the pharmaceutical context, precisely because FDA-approved drugs very often have both infringing and noninfringing uses. The Federal Circuit has held that ''[e]specially where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent.'' *Warner-Lambert*, 316 F.3d at 1365. Thus, a plaintiff must establish the defendant's intent with evidence tied to the particular use in question. A general intent to market the drug will not suffice.

Case law tells us that, where the filing of an ANDA is concerned, the issue of intent may be resolved by looking at the label for the generic product. When a generic maker files an ANDA it must submit to the FDA a proposed label, which, essentially, must be a copy of the approved label of the brand-name product. The label instructs doctors and patients on how to use the drug for approved diseases and conditions (''indications''). There is an exception to the label-copying requirement in the situation where the brand-name label addresses more than one indication. In such a case, the ANDA filer has the option of seeking approval for fewer than all such indications.

When the patent at issue claims a method of using a drug for an indication that has been approved by the FDA, the inducement theory is straightforward. Provided that the ANDA filer seeks FDA approval with a label that includes the indication claimed in the patent, courts will readily find induced infringement. This scenario can be described as ''on-label'' infringement because the alleged infringement would occur as a result of a patient using the drug in accordance with the FDA-approved label. Inasmuch as the ANDA-filer in this scenario is seeking permission to sell its product with a label that instructs doctors and patients to use the drug for the infringing indication, the conclusion that the generic maker will induce infringement follows naturally.

This application of the inducement theory of infringement is, however, not the most interesting. In addition to being quite straightforward, it is actually entirely redundant. When the alleged infringement consists entirely of the act of filing an ANDA, the Patent Act provides an even simpler answer. Under 35 U.S.C. 271(e)(2):

> It shall be an act of infringement to submit . . . an [ANDA] for a drug claimed in a patent *or the use of which is claimed in a patent*, . . . if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

(Emphasis added.) Thus, the filing of an ANDA seeking approval for an indication claimed in a patent equals infringement, per se, under Section 271(e)(2). There is no need to resort to an inducement theory under Section 271(b).

The more interesting cases involve off-label uses of an FDA-approved drug and other cases that fall outside the bounds of Section 271(e)(2).

Warner-Lambert Co. v. Apotex Corp.: Inducing Off-Label Infringement

Warner-Lambert Co. v. Apotex Corp. dealt with an off-label infringement claim. Warner-Lambert held two

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patents on uses of gabapentin: one that disclosed a method of using the drug to treat certain forms of epilepsy, and one that described a method of using the same compound to treat neurodegenerative diseases such as Alzheimer's and Parkinson's. 316 F.3d at 1351-52. Warner-Lambert obtained FDA approval to market a drug to treat epilepsy using the method described in the former patent. Although the drug was only approved for treating epilepsy, physicians often prescribed it for certain neurodegenerative diseases. *Id*. at 1352, 1365.

Apotex filed an ANDA with the FDA, seeking approval to market a generic form of the drug upon expiration of Warner-Lambert's epilepsy patent. Warner-Lambert then brought a claim for infringement of the neurodegenerative use patent under Section 271(e)(2), alleging that Apotex's generic drug, like Warner-Lambert's drug, would be prescribed to treat neurodegenerative diseases in addition to epilepsy. Warner-Lambert cited the widespread use of its drug to treat neurodegenerative diseases as evidence of the fact that Apotex had knowledge that its generic drug would be used in a similar manner. *Id*. at 1364-65. The district court granted Apotex's motion for summary judgment, finding that Apotex lacked intent to induce infringement.

On appeal, Warner-Lambert argued that Apotex should have known that its drug would be prescribed for neurodegenerative diseases. Warner-Lambert argued that up to 89 percent of the sales of its drug were for off-label uses such as the treatment of neurodegenerative diseases. *Id*. at 1364. Warner-Lambert also argued that it was common knowledge in the pharmaceutical industry that physicians frequently prescribe drugs for off-label uses.[1] *Id*. The court found evidence that Apotex knew that its drug would be put to infringing uses ''legally irrelevant.'' The question, according to the court, was whether Apotex actively induced those infringing uses. *Id*. To resolve that issue, the court turned to the ANDA, stating ''the ANDA must be judged on its face for what an accused infringer seeks the FDA's approval to do. . . . The infringement case is therefore limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed.'' *Id*. The court summed up its ruling by saying that ''the request to make and sell a drug labeled with a permissible (non-infringing) use cannot reasonably be interpreted as an act of infringement (induced or otherwise) with respect to a patent on an unapproved use.'' *Id* at 1364-65.

Less than three months later, the Federal Circuit reiterated that *Warner-Lambert* forecloses inducement claims for off-label infringing uses. In *Allergan Inc. v. Alcon Laboratories Inc.* a case with similar facts to *Warner-Lambert*, the court stated that ''[u]nder *Warner-Lambert* Allergan is precluded from suing Alcon and B & L under section 271(e)(2) for inducing infringement of [the patents in suit], because Alcon and B & L are not seeking FDA approval for the uses claimed in the patents and because the uses claimed in the patents are not FDA-approved.''

The Federal Circuit thus has established a bright-line rule governing claims of induced infringement under Section 271(e)(2). A claim of induced off-label infringement based on the filing of an ANDA will fail. *See, e.g.*, *Aventis Pharma Deutschland GmbH v. Cobalt Pharmaceuticals Inc.*, 355 F. Supp. 2d 586 (D. Mass. 2005) (granting the defendant's motion for summary judgment of noninfringement on induced infringement claim for the filing of an ANDA requesting approval to market a drug with off-label infringing uses). Conversely, a claim of induced infringement based on the filing of an ANDA, where the ANDA includes a patented use in the proposed label should succeed, as the applicant is demonstrably instructing doctors and patients to use the product for a claimed indication.

AstraZeneca: Inducing On-Label Infringement (Sort Of)

The *AstraZeneca* case dealt with an interesting twist on the above scenarios. AstraZeneca held two patents on methods of using budesonide to treat pediatric asthma. The method claimed in the patents involved administering budesonide ''not more than once per day.'' The label accompanying AstraZeneca's product, however, directed that the drug be taken once or twice daily, while warning patients to ''titrate down'' to the lowest dosage level that would effectively control their asthma.

Apotex submitted an ANDA to market generic budesonide. In an attempt to avoid the patents, Apotex requested approval to market its drug *only* for twice-daily use, and explicitly stated that it was not seeking approval for the once-daily use. Apotex also sought to omit the ''titrate down'' instruction from its label, but the FDA denied that request, requiring Apotex to include the warning to titrate down to the lowest effective dose.

Because Apotex's label did not expressly include once-daily administration, AstraZeneca apparently concluded that it could not claim infringement by the mere act of filing the ANDA and thus could not claim infringement under Section 271(e)(2). Instead, AstraZeneca waited until Apotex's ANDA was approved. The following day, AstraZeneca filed a complaint seeking a declaratory judgment of infringement and moved for a preliminary injunction.

AstraZeneca's theory was that Apotex would induce infringement by instructing end-users to directly infringe AstraZeneca's patents. AstraZeneca argued that titrating down to the lowest effective dosage would result in patients using the drug once daily. Apotex, for its

[1] Specifically, Warner-Lambert cited the following facts: ''(1) it is common knowledge to many in and out of the pharmaceutical field that physicians routinely prescribe approved drugs for purposes other than those listed on the drugs' labels; indeed, such off-label use is supported by both the FDA and the American Medical Association, (2) information regarding both on- and off-label prescriptions is readily available to the public from publications and databases to which most pharmaceutical companies subscribe, (3) 'pharmacists and other drug dispensing organizations . . . commonly substitute generic drugs for name brand drugs wherever possible-unless specifically instructed otherwise by the physician writing the prescription,' and, 'in many states, substitution is mandatory,' (4) Apotex expects to get an 'A-B rating' for its [generic drug], which would allow physicians and pharmacists to substitute [the generic drug for the name-brand drug] regardless of the indication for which it is to be used, and (5) Apotex should be assumed to have considered the market size and growth potential of [the generic drug] when it made the strategic decision to file an ANDA and enter the . . . market''.

part, put forth testimony by its regulatory compliance officer that its original proposed label contained no ''explicit references to once-daily dosing'' and even included the phrase ''by administration twice-daily,'' but that ''the FDA responded by instructing Apotex to delete this phrase and sending Apotex a template containing the language Apotex was to include in the proposed label.'' Apotex's compliance officer further stated that ''it never occurred to Apotex that the downward-titration statements in the proposed label would suggest once-daily use,'' but that once Apotex learned that the label posed infringement issues, it proposed three amendments that ''(1) add[ed] the words 'twice daily' to the downward-titration language; (2) add[ed] language stating the drug is not approved for less than twice-daily use; and (3) remov[ed] the downward-titration language,'' but the FDA rejected each proposed amendment.

Finally, Apotex cited a letter that the FDA sent to AstraZeneca setting out the FDA's opinion that the language on downward titration did not teach once-daily use. Apotex argued that it relied on this letter in determining that its proposed label would not induce infringement of AstraZeneca's patent. The district court ruled in favor of AstraZeneca, granting a preliminary injunction.

On appeal Apotex first argued that the district court based its finding of specific intent on the fact that it intended to distribute a generic drug, and that such an inference was incorrect as a matter of law because the drug had substantial noninfringing uses. The Federal Circuit disagreed, explaining:

> Apotex is correct that ''where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the [alleged inducer] has actual knowledge that some users of its product may be infringing the patent.'' W*arner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed.Cir.2003). However, ''liability for active inducement may be found 'where evidence goes beyond a product's characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement.' '' *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1341, 89 USPQ2d 1577 (Fed.Cir. 2008) (quoting *Metro-Goldwyn-Mayer Studios Inc. v. Grokster Ltd.* (''*Grokster* ''), 545 U.S. 913, 935, 125 S.Ct. 2764, 75 USPQ2d 1001 (2005)).

In this case, the court found that Apotex, with knowledge of potential infringement issues, submitted a proposed label that, if followed, would cause many end users to infringe AstraZeneca's patent.

Apotex next argued that not all users would follow the instructions in its proposed label. The court dismissed this argument, stating that ''it is irrelevant that some users may ignore the warnings in the proposed label. The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of Apotex's affirmative intent to induce infringement.'' *Id*.

Finally, Apotex argued that its proposed label could not be evidence of specific intent because the instruction to titrate down was required by the FDA. In other words, Apotex affirmatively tried to avoid instructing end users to infringe, but was thwarted by the FDA. The court was unsympathetic to this argument for two reasons. First, the court noted that ''Apotex was free to submit a Paragraph III certification and wait until the patents expired before distributing its generic drug.'' Second, Apotex had not exhausted all administrative avenues within the FDA, including appealing the FDA's rejection of a label that did not contain the offending language. In addition, the court noted that Apotex's reliance on the FDA's earlier letter to the effect that the downward titration language did not teach once-daily use was ''misplaced'' because ''the FDA is not the arbiter of patent infringement issues.''

In sum, the Federal Circuit concluded that AstraZeneca had shown that it was likely to succeed at trial on the issue of inducement and affirmed the issuance of the preliminary injunction. Consistent with prior cases involving ANDAs, the court reached its conclusion almost entirely on the basis of what was stated in the generic product's label. Apotex's protestations of innocence were rejected because, in the final analysis, Apotex had a choice: with the FDA insisting that the label must include the ''titrate down'' instruction, Apotex could have chosen not to pursue approval of its ANDA.

Conclusion

Taken together, *Warner-Lambert* and *AstraZeneca* define a bright-line rule for ANDA inducement cases. These cases show that ANDAs will be taken at face value, and intent will be inferred from the ANDA product's label. Inducement of infringement will not be found when the patent in suit is on a use not found in the label of the ANDA product. Inducement will be found when the patent is on a use that is included in the label. *AstraZeneca*, significantly, shows that inducement of infringement may be established even where the patented use is not expressly stated in the ANDA product's label, so long as there is a hook in the label that allows the patent holder to argue that the patented use is implicit.

It remains to be seen whether a brand-name pharmaceutical company can make out a claim of induced infringement for a truly off-label use, one where there is not even an implicit tie-in to the ANDA product's FDA-approved label. Brand-name companies often have patents on off-label uses of their drugs, and the generics surely know that their products will be put to such uses and intend to collect all the profit they can from all sales for all uses.

The brand-name companies typically do not pursue patent infringement claims after a drug has ''gone generic'' due to an ANDA-filer's product launch, and an off-label inducement claim would face a steep uphill fight in view of the precedent discussed here. The Federal Circuit, however, seemed to leave the door open just a crack in *Warner-Lambert*, stating, ''That a generic maker may someday induce someone to infringe can only be determined when that act occurs.''

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