ASPEN PUBLISHERS

FEBRUARY 2009

DEVOTED TO LEADERS IN THE INTELLECTUAL PROPERTY AND ENTERTAINMENT COMMUNITY

VOLUME 29 NUMBER 2

THE Licensing Journal

Edited by the Law Firm of Grimes & Battersby

Wolters Kluwer
Law & Business

Licensing Markets

Biotechnology and Pharmaceutical Licensing

Ernest V. Linek

More Tales from the ANDA Wars

Litigation involving Abbreviated New Drug Applications (ANDAs) appears to be increasing. Several interesting decisions have been rendered since my last column on this topic. These include: *Sanofi Synthelabo v. Apotex* —Federal Circuit (December 2008); *Takeda v. Mylan Laboratories Inc.* —Federal Circuit (December 2008); *Otsuka Pharmaceutical v. Barr Laboratories* —USDC New Jersey (December 2008); and *Janssen v. Apotex* — Federal Circuit (September 2008). The following discussion analyzes the first two cases listed above, while a treatment of the latter two is scheduled to appear in an upcoming issue of the *Licensing Journal*.

Sanofi Synthelabo v. Apotex

In this ANDA case, on December 12, 2008, the Federal Circuit affirmed the validity of Sanofi's patent covering the blockbuster drug Plavix®. The Plavix patent (US 4,847,256) covers a specific salt of the dextrorotatory isomer of the active ingredient, namely:

> Claim 3 – Hydrogen sulfate of the dextro-rotatory isomer f methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)((2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

Apotex filed an ANDA seeking FDA approval to sell a generic version of Plavix, and in the Paragraph IV Certification Letter, challenged the validity of the '256 patent based on the fact that the racemate of the compound (a mixture of the levorotatory and dextrorotatory isomers) was known and described in earlier Sanofi patents.

In support of its obviousness argument, Apotex noted that separation of racemic mixtures is routine and that there are many examples of separated compounds that exhibit stereoselectivity (activity based upon the specific stereochemistry).

Apotex argued that there was both motivation and means for creating the Plavix compound from the known racemate that Sanofi had previously admitted was an important compound. In fact, the racemate was Sanofi's lead compound until the hydrogen sulfate salt of the dextrorotatory isomer was prepared and found to have all of the antiplatelet activity and none of the adverse neurotoxicity. Experts for both parties agreed that weak stereoselectivity of biological properties is more common than strong stereoselectivity, and that absolute stereoselectivity (as in this salt) was rare. Apotex's expert, when asked whether one (of ordinary skill in the art) could predict in advance the therapeutic and toxic properties of the enantiomers, stated:

> No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anybody presuming anything else.

The Federal Circuit, faced with this fact, held that Apotex had failed to prove that the Claim 3 compound was obvious. The Federal Circuit found no error in the district court's findings that, on the admitted state of the prior art, a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity.

Takeda v. Mylan

On December 8, 2008, the Federal Circuit affirmed the decision of the Southern District of New York, awarding Takeda (Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc.) attorney fees, expenses, and expert fees of $16.8 million, to be paid by the ANDA defendants Mylan Laboratories Inc. ($11.4 million) and Alphapharm Pty. Ltd. ($5.4 million) with interest.

Alphapharm and Mylan are two generic drug companies that sought approval under the Hatch-Waxman Act to produce generic versions of Takeda's antidiabetic drug pioglitazone, which Takeda sells commercially as the drug ACTOS®, a highly popular type 2 diabetes drug that helps improve the action of the liver, muscles, and fat tissues by making them more sensitive to insulin. That legislation provides the mechanism for a generic drug

company to file an abbreviated new drug application (ANDA).

The defendants each filed the required Paragraph IV ANDA Certifications stating that the Takeda patent for Actos (US 4,687,777) was invalid. By filing the ANDAs, the defendants infringed the '777 patent, and Takeda brought suit against the two defendants.

At trial, Alphapharm and Mylan each changed the focus of their invalidity arguments from those in their ANDA certification letters. Alphapharm selected a different prior art compound (compound b) and scientific literature as evidence that pioglitazone was structurally obvious at the time the invention was made. Mylan attacked the '777 patent with an inequitable conduct argument, based on alleged misrepresentations by Takeda to the USPTO.

In a 2006 bench trial, the district court held the invention of the '777 patent to be nonobvious and enforceable. The decision of the district court was affirmed by the Federal Circuit in two separate appeals. Takeda then moved the district court for an award of attorney fees against both Mylan and Alphapharm on the theory that this was an exceptional case.

When a patent has been infringed by the filing of an ANDA, 35 U.S.C. § 271(e)(4) provides for the grant of attorney fees under 35 U.S.C. § 285, which in turn allows the court to award reasonable attorney fees to a prevailing party in exceptional cases. Takeda contended that Mylan and Alphapharm each lacked a good faith basis for their Paragraph IV letters and engaged in misconduct throughout the litigation.

On September 20, 2006, the district court agreed with Takeda in an opinion that discussed the Paragraph IV letters and litigation conduct of Alphapharm and Mylan in the same thorough manner as the court's previous decision regarding the validity of the '777 patent.

Regarding Alphapharm, the court held that the Paragraph IV certification letter was "so devoid of merit and so completely fail[ed] to establish a prima facie case of invalidity that it must be described as 'baseless.'" [September USDC Opinion, 459 F. Supp. 2d at 235.] The court also analyzed what it saw as Alphapharm's litigation misconduct, which mainly consisted of a shifting theory of obviousness that did not explain why compound b would have been identified as the lead compound. As a result, the court found that this was "the exceptional case where an examination of the totality of the circumstances amply justifies, indeed compels, the award of attorneys' fees." [*Id*. at 245.]

Similarly, the court held that Mylan's certification letter was filed in bad faith and with no reasonable basis to claim the '777 patent invalid. The court discussed how Mylan argued in its Paragraph IV letter that the invention of pioglitazone was obvious based on Takeda's disclosure of a compound in another Takeda patent and a scientific publication (Sohda II), only to abandon this theory entirely during the litigation. In addition, the court discussed Takeda's numerous allegations of litigation misconduct committed by Mylan in its pursuit of an inequitable conduct claim, which principally addressed Takeda's representations to the PTO regarding a different compound disclosed in the prior art, compound 3894. The court also found that the inequitable conduct claim was "always frivolous" and unsupported, as Mylan did not present any evidence that Takeda hid or misrepresented any information to the PTO. [*Id*. at 249.] The court concluded that the totality of the circumstances, including other instances of Mylan's untimely conduct, justified the award of attorney fees against Mylan as well.

On March 21, 2007, the district court quantified the fees at $16,800,000, with Alphapharm to pay $5,400,000 and Mylan, $11,400,000. When allocating the attorney fees, the court accepted the division proposed by Takeda, with Mylan responsible for two-thirds of the total amount. The court also awarded Takeda its expert fees under its inherent power to impose sanctions, along with expenses and interest beginning on the date of the September USDC Opinion.

Mylan and Alphapharm filed separate appeals and the Federal Circuit consolidated the appeals on December 17, 2007.

A district court's decision to award attorney fees is within the discretion of the trial judge, but the conclusion that a case is exceptional is a finding of fact reviewable by the Federal Circuit only for clear error. [*Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989).]

A number of different circumstances may support the finding of an exceptional case, including "vexatious or unjustified litigation" or "frivolous suit," of which there must be clear and convincing evidence. [*Id.* at 1551.] Indeed, one of the purposes of Section 285 is to prevent "'gross injustice' when the accused infringer has litigated in bad faith." [*Id*. at 1552.] In *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*, the Federal Circuit stated that "[t]he joint operation of §§ 271(e) and 285 require the paragraph (2) infringer to display care and regard for the strict standards of the Hatch-Waxman Act when challenging patent validity. . . . The Hatch-Waxman Act thus imposes a duty of care on an ANDA certifier." [231 F.3d 1339, 1347 (Fed. Cir. 2000).]

In affirming the decision of the district court against Alphapharm, the Federal Circuit relied on the district court's familiarity with the parties and the issues and its thorough discussion of Alphapharm's Certification Letter and litigation strategy, stating:

> we cannot say that the court committed clear error in finding that this was an exceptional case due in part to the misconduct of Alphapharm. See *Beckman*, 892 F.2d at 1552 & n.1 (noting that the district judge was in "the best position" to monitor litigation strategy and find bad faith).

Similarly, in affirming the decision of the district court against Mylan, the Federal Circuit relied on the district court's familiarity with the parties and the issues and its thorough discussion of Mylan's Certification Letter and litigation strategy, stating:

> We conclude that the court did not commit clear error in finding that Mylan's misconduct contributed to this being an exceptional case. In fact, Mylan's invalidity argument in its certification letter appears even more baseless than Alphapharm's.
>
> ***
>
> In light of the scientific errors present in Mylan's certification letter, the fact that the court was unmoved by Mylan's decision not to pursue this obviousness claim at trial can hardly be deemed clear error. We believe the court had ample reason to hold that Mylan's certification letter was filed in bad faith and with no reasonable basis to claim the '777 patent invalid.
>
> ****
>
> Rather, the court determined that Mylan's initial certification letter was completely baseless and that the claims Mylan offered as substitutes were similarly frivolous. In short, the district court, which was in the best position to evaluate the entire strategy pursued by Mylan, did not commit clear error in finding litigation misconduct.

Question of a Chilling Effect

Will *Takeda* have a chilling effect on future ANDA filers? In making a Paragraph IV certification, appellants are statutorily required to "include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid." [21 U.S.C. § 355(j)(2)(B)(iv)(II) (2006).] It is clear from the district court's opinion that it was not faulting Alphapharm or Mylan for the act of filing an ANDA that challenged the pioglitazone patent, nor did it limit the filers to the theories raised in their certification letters. Rather, the district court found the case exceptional based on the specific circumstances involved in this case, viz., baseless certification letters compounded with litigation misconduct.

In fact, the district court addressed the deterrence argument directly:

> There is no basis to find that this award of fees will deter ANDA filings and litigation. This award addresses baseless ANDA filings and the pursuit of frivolous ANDA litigation in bad faith and other litigation misconduct. The Hatch-Waxman Act cannot be read to immunize such conduct. [September USDC Opinion, 459 F. Supp. 2d at 251.]

Given the district court's specific articulation that its ruling was directed toward baseless ANDA filings and litigation in bad faith, the Federal Circuit declined to disturb the court's finding of an exceptional case as potentially chilling non-frivolous ANDA filings under the Hatch-Waxman Act. Well-supported ANDA filings challenging the validity and infringement of patents owned by an NDA holder should not raise the specter of an unjustified holding of an exceptional case.

Ernie Linek is a partner with Banner & Witcoff, LLP in Boston, MA.

Reprinted from *The Licensing Journal,* February 2009, Volume 29, Number 2, pages 19-21, with permission from Aspen Publishers, Inc., Wolters Kluwer Law & Business, New York, NY, 1-800-638-8437, www.aspenpublishers.com