Banner & Witcoff, Ltd.
Intellectual Property Law

Spring 2008

Intellectual Property UPDATE

Post-*KSR* Pharmaceutical Patent Obviousness Determinations

On April 30, 2007, in *KSR Int'l Co. v. Teleflex Inc.*, and on the question of whether a patent claim was obvious in view of prior art, the Supreme Court rejected the "rigid approach" to obviousness of the Court of Appeals for the Federal Circuit, in favor of an "expansive and flexible approach." This author predicted that the *KSR* decision would make it more difficult to procure and enforce patents that claim new forms of known drugs, even with a showing of unexpected results. *See* "Think *KSR v. Teleflex* Does Not Impact Pharmaceutical Patent Validity? Think Again," Intellectual Property Update (Summer 2007) article at http://www.bannerwitcoff.com/zbios_archived.cfm?attorney=75. Indeed, it was noted in that article that the effect of the *KSR* case began soon after the Supreme Court agreed to hear the *KSR* case, as evidenced by two different pharmaceutical cases in which the Court of Appeals for the Federal Circuit held the claimed inventions were obvious – *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286 (Fed. Cir. 2006), and *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), *rehearing and rehearing en banc denied*, Slip Op. (May 22, 2007) (Newman, Lourie, Radar, dissenting).

Now, three post-*KSR* pharmaceutical cases illustrate key principles for future cases where obviousness is at issue:

(1) where there are no persuasive reasons to start with a lead compound and then modify that lead compound to form the claimed drug, the claimed drug will be found to be non-obvious, *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. June 28, 2007);

(2) *prima facie* obviousness of a claimed compound in view of a prior art racemic mixture comprising the claimed compound and its non-claimed, nonsuperimposable mirror image can be rebutted where the claimed compound showed unexpected benefits, and evidence indicated that the claimed compound and its nonsuperimposable mirror image would have been difficult for a person of ordinary skill in the art to separate, *Forest Labs., Inc. v. Ivax Pharms, Inc.*, 501 F.3d 1263 (Fed. Cir. Sept. 5, 2007); and

(3) *prima facie* obviousness of a purified form of a prior art mixture will not be rebutted where the potency of the purified form was not unexpected, *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, 499 F.3d 1293 (Fed. Cir. September 11, 2007).

Takeda

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. June 28, 2007), the defendant asserted that the patent for the drug pioglitazone (sold as ACTOS® to control blood sugar in diabetes Type 2 patients) would have been obvious at the time of the alleged invention, resting entirely on a prior art "compound b" referenced in the asserted patent. More specifically, the defendant argued that the prior art would have led one of ordinary skill to select compound b as a lead compound, and then make two obvious chemical changes: first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone.

Like the district court, the Federal Circuit disagreed with the defendant. The Federal Circuit found that "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." Moreover, "the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." Thus, the Federal Circuit held that this case failed to present the type of situation contemplated in *KSR* when the Supreme Court stated that an invention may be deemed obvious if it was "obvious to try." In distinguishing its pre-*KSR* decision in *Pfizer*, the Federal Circuit held that in *Takeda* there was nothing in the prior art to narrow the possibilities of a lead compound to compound b.

The Federal Circuit went on to find that even if the defendant had established that one skilled in the art would look to compound b as a lead compound, there was nothing in the prior art to suggest making the modifications to compound b that were necessary to achieve the claimed compounds. More specifically, there was nothing in the prior art to suggest replacing

continues on page 2

In This Issue

continued from page 1

the methyl group with an ethyl group in compound b, or that then changing the position of that substituent on the ring would result in a beneficial change. Indeed, there was no reasonable expectation that the claimed pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b.

Forest

In *Forest*, the defendants attacked the validity of the patent on the drug LEXAPRO®, an anti-depressant/anti-anxiety drug. The defendants argued that the claimed compound, which was an "enantiomer" that had a nonsuperimposable mirror image enantiomer, was obvious in light of a prior art racemic mixture containing the claimed compound and its nonsuperimposable mirror image, and descriptions of techniques available to separate enantiomers from their racemates. The defendants further argued that there was a general expectation in the art that one enantiomer would be more potent than the other provided reason for a person of ordinary skill in the art to isolate the enantiomers.

The patent owner argued that any *prima facie* obviousness based on the racemic mixture was rebutted by the evidence demonstrating the difficulty of separating the enantiomers at issue and the unexpected properties of the claimed enantiomer. The owner argued that it was unexpected that all of the therapeutic benefit of the racemic mixture would reside in the claimed enantiomer over that of its nonsuperimposable mirror image enantiomer, resulting in composition having just the claimed enantiomer having twice the potency of a racemic mixture. The patentee also argued that the district court was entitled to credit evidence that a person of ordinary skill in the art would not easily have turned to an intermediate to attempt resolution of the racemic mixture, both because of the uncertainty involved and because the prior art described compounds less complex than those necessary in the LEXAPRO® case.

The Federal Circuit argreed with the patentee that the district court's key factual findings underlying its conclusions of non-obviousness were not clearly in error, and affirmed the district court's finding of non-obviousness.

Aventis

In *Aventis*, the district court held that the defendant failed to prove that claims were obvious, which covered the high blood pressure treatment drug ALTACE®, even though the claimed composition was a purified form of a mixture that existed in the prior art. The Federal Circuit disagreed and reversed. In so holding, the Federal Circuit acknowledged that a purified compound is not always *prima facie* obvious over the mixture; for example, where it may not be known that the purified compound is present in or an active ingredient of the mixture, or the state of the art may be such that discovering how to perform the purification is an invention of patentable weight in itself. The Federal Circuit stated, however, that "if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is *prima facie* obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified."

The Federal Circuit found that the patentee's protestations notwithstanding, there was no evidence that separating the claimed composition from the non-claimed composition in the known mixture was outside the capability of an ordinarily skilled artisan.

Equally unavailing was the patentee's attempts to rebut the *prima facie* case of obviousness. While the patentee argued that the claimed invention was 18 times more potent than the next potent isomer, the Federal Circuit stated that comparison to this isomer was the wrong comparison. Instead, the Federal Circuit stated that the correct comparison was not the claimed invention over all its stereoisomers, but over the mixture that did not contain the next potent isomer. The Federal Circuit stated that the potency of the purified form in the ALTACE® case was exactly what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers. Indeed, the Federal Circuit noted that all the evidence suggested, and the district court found, that potency varied with the absolute amount of the claimed isomer in a mixture.

Conclusions

In sum, where there are no persuasive reasons to start with a lead compound and then modify that lead compound to form the claimed drug, the claimed drug will be found to be non-obvious (*Takeda*). Even where there is a *prima facie* case of obviousness of a claimed compound in view of a prior art mixture comprising the claimed compound and its nonsuperimposable mirror image, that *prima facie* case can be rebutted where the claimed compound showed unexpected benefits, and evidence indicated that the claimed compound and its mirror image would have been difficult for a person of ordinary skill in the art to separate (*Forest*). However, a *prima facie* case of obviousness of a purified form of a drug in view of a prior art mixture will not be rebutted, where the potency of the claimed invention was not unexpected (*Aventis*). These are three key principals for analyzing obviousness in post-*KSR* pharmaceutical cases.

Robert H. Resis
rresis@bannerwitcoff.com