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REPORT

Secondary Pharmaceutical Patents Post-*KSR*: Do They Have A Future?

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By this time virtually everyone who deals with patents in some capacity has heard of the U.S. Supreme Court's decision in *KSR International Co. v. Teleflex, Inc.* While the repercussions of that decision are not yet entirely clear, certain themes have emerged in the pharmaceutical patent arena, especially with respect to secondary pharmaceutical patents. The end result: it is likely going to be more difficult to obtain secondary pharmaceutical patents and to defend them against validity challenges.

This change in the law could not have come at a more critical time for the pharmaceutical industry. Approvals of New Chemical Entities (NCEs) by the FDA have dropped in recent years, with only 18 approved in each of 2005 and 2006, and only 14 approved as of Nov. 30, 2007. With the decrease in NCEs comes a corresponding decrease in new blockbuster drugs, making it more important than ever for innovator companies to extend patent protection on their current portfolio of drugs to maintain profits and recoup their investments.

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The Supreme Court's *KSR* Decision and the PTO's New Guidelines

The Supreme Court's April 2007 decision in *KSR* (127 S.Ct. 1727; 5 PLIR 487, 5/11/07) rejected the Federal Circuit's ''rigid'' application of the teaching, suggestion, or motivation to combine (TSM) test, instead espousing an ''expansive and flexible'' approach it considers consistent with the ''broad inquiry'' set forth in *Graham v. John Deere*. To be sure, the Court did not reject the TSM test outright; it called it a ''helpful insight'' consistent with its precedent that ''a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.'' *Id.* at 1741. But, it cautioned that ''[h]elpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents.'' *Id.* And some things the Court said ring true, such as the fact that common or well-known techniques or combinations may not be discussed in the literature or patents in a particular field. Unfortunately, it is unclear from the Supreme Court's decision just how far one can go in deciding that prior art references can be combined. According to the Court, a person of ordinary skill in the art is ''a person of ordinary creativity, not an automaton'' and ''in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.'' *Id.* at 1742. The question, of course, is when does that puzzle become so complex that it results in innovation, rather than an obvious combination of known elements.

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The answer to that question is not clear. The Court relied heavily upon *United States v. Adams*, 383 U.S. 39 (1966), in which the inventor combined known elements, in a way the prior art countenanced against, to form a ''wet battery,'' stating that ''the fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art.'' *Id.* at 1740. It contrasted that case to *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976), both of which held patents obvious as combinations of old elements performing the same function they were known to perform, yielding the result one would expect from the combination. *Id.* The Supreme Court is thus drawing a distinction between that which is new and useful but the expected result of a combination of elements, and that which it considers to be truly novel. Whereas before, the absence of a teaching, suggestion, or motivation to combine elements in the prior art could overcome an invalidity challenge, now a patentee may need more evidence of unexpected results, a teaching away in the prior art, or failure of others to overcome that challenge.

The Supreme Court made another monumental change to the obviousness analysis—it rejected the Federal Circuit's precedent that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. Federal Circuit precedent stated that ''obvious to try is not to be equated with obviousness.'' *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990). The Federal Circuit predecessor court, the Court of Customs and Patent Appeals, explained that ''there is usually an element of 'obviousness to try' in any research endeavor, that . . . is not undertaken with complete blindness but rather with some semblance of a chance of success.'' *In re Tomlinson*, 363 F.2d 928, 931 (CCPA 1966). The Supreme Court, however, stated that ''when there is a design need or a market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under [35 U.S.C. § 103].'' *KSR*, 127 S.Ct. at 1742. Thus, it appears that the themes of predictability versus unexpected results and routine testing versus technical difficulty have emerged as the primary focuses in the obviousness analysis.

In response to the Supreme Court's *KSR* decision, the United States Patent and Trademark Office issued new guidelines for examiners regarding the obviousness standard (72 Fed. Reg. 57526-35, 10/10/07). The guidelines articulate seven rationales for supporting an obviousness rejection under § 103, which can be distilled into the three basic concepts found in *KSR*: (1) predictable results; (2) obvious to try; and (3) a teaching, suggestion, or motivation to combine the references.

KSR has raised the patentability bar, and as a result, innovator companies must adapt to protect their patents, especially those for secondary pharmaceuticals. It means focusing on unexpected results or simply a lack of knowledge in the field to predict the outcome. It means focusing on the level of technical difficulty needed to obtain the results, whether that level is outside the realm of one of ordinary skill in the art, and whether others (including the patentee) failed before succeeding. It puts a new focus on who is a person of ordinary skill, what is the level of ordinary skill, how that person would have acted and why. Articulating the level of skill in the art can be a tactical decision—the higher the level of skill, the more likely that the invention is the result of ordinary experimentation rather than innovation. Defending against an obviousness challenge is not focused on the references themselves any longer; it is about the entire picture.

The Federal Circuit has decided a few pharmaceutical cases in the wake of *KSR*, with mixed outcomes. Nonetheless, some insight as to how the *KSR* decision will apply can be gleaned from these decisions, and some lessons can be learned—lessons that are critical to every innovator and generic company because patents are critical to the industry, and because as the Federal Circuit noted in *Pfizer v. Apotex*, ''the pharmaceutical industry may be particularly adversely impacted by application of an 'obvious to try' analysis.''

Establishing a Prima Facie Case of Obviousness

Every invalidity challenge under 35 U.S.C. § 103(a) begins with the establishment of a *prima facie* case of obviousness, by clear and convincing evidence. While the ultimate decision of obviousness is a question of law, it relies upon certain factual underpinnings, including the scope and content of the prior art, the differences between the prior art and the claimed invention at the time of the invention, and the level of ordinary skill in the art. Once a *prima facie* case of obviousness has been established, the patentee can rebut that finding with evidence of secondary considerations of non-obviousness such as failure of others, long felt but unsolved need for the invention, commercial success, or unexpected results. The Supreme Court's decision in *KSR* has not changed this overall framework for the obviousness analysis. What it has done, however, is made it easier to establish a *prima facie* case by relaxing the TSM test and espousing an ''obvious to try'' test, while reducing the impact of indicia of non-obviousness.

Post-*KSR* the Federal Circuit reiterated that certain threshold requirements must be met to establish a *prima facie* case of obviousness for structurally similar compounds. The patent challenger must identify a structurally similar compound (also called a ''lead compound'') in the prior art, and show that the ''prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.'' *Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1365 (5 PLIR 713, 7/13/07). There must be an identifiable reason ''that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new compound.'' *Id.* at 1357. That identifiable reason could be a reasonable expectation of success, a teaching in the prior art, or that it would it have been ''obvious to try.'' However, even if the *prima facie* case is established, it can be rebutted by secondary considerations of non-obviousness.

Selection of a Particular Lead Compound

In some cases, identification of the lead compound and the motivation to pursue modifications to it are

  PLIR ISSN 1542-9547

easy to establish. In *Pfizer v. Apotex,* 488 F.3d 1377 (Fed. Cir. 2007; 5 PLIR 317, 3/30/07), for example, the patent claimed a particular salt of amlodipine, a known compound with known beneficial properties. Thus, establishing amlodipine as the lead compound was simply a matter of course.

At the opposite end of the spectrum is *Takeda*. There, the patented compound, pioglitazone (an anti-diabetic drug), was based on a particular TZD compound referred to as ''Compound b.'' Because there were millions of potential TZD compounds and nothing in the prior art to suggest to a person of ordinary skill in the art that Compound b should be pursued (in fact, Compound b had negative indications including toxicity and increased brown fat production), defendant Alphapharm was unable to establish Compound b as the lead compound.

Takeda teaches an important lesson to both innovator and generic companies: the obviousness analysis may never get past the preliminary stages, depending on the facts presented. As is always true, the key issues in establishing the lead compound are the scope and content of the prior art and the level of skill in the art. But the application of those facts to the lead compound analysis can be critical. Were there numerous potential lead compounds or only a few? Too many options weighs against a conclusion of obviousness. Was there any reason to select the lead compound as opposed to another compound? A teaching that the lead compound was more promising weighs in favor of obviousness, but a teaching that another compound was more promising weighs against. Were there reasons *not* to pursue the lead compound? That weighs against finding obviousness because there was no reasonable expectation of success. Or, is there simply no evidence on whether one skilled in the art would have pursued that compound? A generic company should not assume that structural similarity alone is sufficient to establish a lead compound. As the Federal Circuit reiterated in *Takeda,* ''generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from another.'' *Takeda,* 492 F.3d at 1361.

Modification of the Lead Compound

Establishing the lead compound is the first step. The patent challenger then must prove that the specific chemical modifications made to the lead compound to arrive at the patented compound were either taught or suggested by the prior art, or were ''obvious to try,'' and that there was a reasonable expectation of success. *KSR* and subsequent Federal Circuit cases indicate that no matter which route to obviousness is pursued by the patent challenger, certain types of evidence become critical to the analysis, such as evidence of failure of others (or the patentee); evidence that there were numerous ways to modify the lead compound other than the one ultimately chosen and patented; evidence that obtaining the patented compound required more than routine verification testing; evidence of unexpected results; or evidence of teaching away in the prior art or other facts showing there was no reasonable expectation of success. Innovator companies should seek to find and retain such evidence, while generics will want to counter it with evidence that the methods and results were routine and expected.

The outcome of any particular case will of course depend on the facts presented, the arguments made, the credibility of witnesses, and myriad other variables that play into any litigation. But recent Federal Circuit decisions do provide some guidance as to how things may play out for particular categories of compounds.

New Chemical Entities

The Federal Circuit continues to express its willingness to uphold patents on new chemical compounds, stating that experiments ''to verify the physiochemical characteristics'' of a particular compound ''are not equivalent to the trial and error procedures employed to *discover* a new compound. . . .'' *Pfizer v. Apotex*, 480 F.3d at 1367.

As mentioned above, *Takeda* involved the TZD compound pioglitazone, which is the active ingredient in Actos. Pioglitazone differed structurally from Compound b (a prior art TZD compound selected as the lead compound) in two respects: (1) it replaced a methyl group of Compound b with an ethyl group; and (2) that ethyl group was in position 5 of the pyridine ring rather than position 6. Alphapharm argued these modifications to Compound b were obvious, but the Federal Circuit disagreed. Not only did Alphapharm fail to establish Compound b as the lead compound (see *supra*), but the court held that even if Compound b had been established as the lead compound, there was insufficient evidence to prove that one of ordinary skill in the art would have made the particular modifications made by Takeda.

In particular, the evidence established that the methyl group in Compound b could have been replaced with any number of groups, such as a chloride or halide. There was nothing in the prior art to indicate that an ethyl group was superior to any other group in reducing the unwanted side effects of Compound b, nor was there anything in the prior art to indicate that moving the ethyl group from the 5 position to the 6 position would have any beneficial effect. Thus, there was no teaching, suggestion, or motivation to make the particular modifications; there was no reasonable expectation of success that the modifications would work; and because there were many potential modifications and no teaching as to which would be most promising, the particular modifications were not obvious to try.

Innovator companies should consider responding to an obviousness challenge by identifying drawbacks of the lead compound, especially if the prior art offers no solution to overcome those drawbacks. And again, the identification of options is critical. The more potential paths that could have been taken, the less obvious the path chosen. Finally, evidence of trial and error can be important. Evidence that other modifications to the lead compound were considered or attempted may show that the patented compound was not the result of mere verification of a predicted outcome, but was actually the result of the trial and error needed to discover a new compound.

Purified Components of a Mixture

The Federal Circuit has decided two cases on purified enantiomers and stereoisomers since *KSR*, which reach opposite results and demonstrate the importance of the level of skill in the art to the post–*KSR* obviousness analysis. In *Forest Laboratories v. Ivax Pharmaceuticals,* 501 F.3d 1263 (Fed. Cir. 2007; 5 PLIR 900, 9/7/07), a claim to a substantially pure (+)-enantiomer of citalopram (Lexapro) was upheld as patentable. Although the

racemate was disclosed in the prior art, the claim was non-obvious primarily because at the time of the invention, resolving the racemate was difficult and unpredictable. In fact, many others had failed in their attempts to do so.

In *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007; 5 PLIR 929, 9/14/07), on the other hand, a claim to the all-S stereoisomer of an ACE inhibitor was found to be obvious in view of the prior art which disclosed related ACE inhibitors and the fact that the all-S configuration was more potent. In addition, separating the stereoisomers was described in the prior art and, at the time of the invention, was simply a matter of course. Thus, the all-S stereoisomer of the particular compound was predicted to have improved properties, and all that needed to be done was routine experimentation to verify that expectation.

In *Aventis,* the Federal Circuit provided guidance on when purified compounds are patentable over the prior art mixture: ''Such a purified compound is not always prima facie obvious over the mixture; for example, 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.'' *Aventis,* 499 F.3d at 1031. On the other hand, the court observed that ''[o]rdinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compounds is a mainstay of the chemist's art. If it is known how to perform such an isolation, doing so is likely the product not of innovation but of ordinary skill and common sense.'' *Id.* at 1302. Thus, these cases are another variation on the same theme—unexpected results and failure of others show non-obviousness; verification of a predictable outcome through routine methods is fatal to a patent claim.

Salts of Known Compounds

The final category of compounds recently addressed by the Federal Circuit is salts of known compounds. Although decided one month prior to the Supreme Court's *KSR* decision, the Federal Circuit's decision in *Pfizer v. Apotex* is entirely consistent with *KSR,* even applying an ''obvious to try'' standard.

Pfizer dealt with a claim to amlodipine besylate, a particular salt of the known compound amlodipine. Despite expert testimony that the number of potential salts of amlodipine was ''unlimited,'' the Federal Circuit held that the claim was obvious. The court reasoned that a skilled chemist would start with the known anions rather than experiment with new ones. The court found that at the time, there were 53 pharmaceutically acceptable salts that had been approved by the Food and Drug Administration, one of which was the besylate. It was likely that a chemist, in developing a pharmaceutical drug, would begin with that list. But even among those 53, the besylate would have stood out to one of ordinary skill because of its known strength, solubility, and its use in promoting stability. Thus, the Federal Circuit concluded, this was a case where it was obvious to try. Although there may have been some unpredictability in whether the particular salt would work, ''obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.'' *Pfizer,* 480 F.3d 1363. The court concluded that this case was ''analogous to the optimization of a range or other variable within the claims that flows from the 'normal desires of scientists or artisans to improve upon what is already generally known.' '' *Id.* at 1368 (quoting *In re Peterson,* 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

The *Pfizer* decision indicates that evidence showing that one skilled in the art could have pursued a number of different avenues of investigation is important, but that *reasonable* avenues should be the focus, not every possibility under the sun. Just because one of ordinary skill in the art could make a new salt does not mean that such a path would be pursued. Moreover, had there been evidence of unexpected results, or that the besylate salt was considered undesirable, the results may have been different.

Secondary Considerations of Non-Obviousness

A *prima facie* case of obviousness can be rebutted by a showing of secondary considerations of non-obviousness. In its post-*KSR* decisions, the Federal Circuit has focused in particular on unexpected results and failure of others as evidence of non-obviousness, although it has acknowledged that commercial success and long felt but unsolved need are still factors to be considered.

Recently the Federal Circuit reversed a Board of Patent Appeals decision of obviousness and remanded for further consideration because the Board failed to consider the secondary considerations of non-obviousness presented in expert affidavits. *In re Sullivan,* 498 F.3d 1345 (Fed. Cir. 2007). *Sullivan* involved patent claims to an antivenom composed of Fab fragments. The expert affidavits submitted by the applicant indicated that the prior art taught away from using Fab fragments, there was no reasonable expectation that Fab fragments would work as an antivenom, and the fact that Fab fragments were effective as an antivenom was an unexpected result. The Federal Circuit also mentioned in passing that there was a long felt but unsolved need for a new antivenom. Similarly, in *Forest Labs. v. Apotex,* the Federal Circuit focused the crux of its analysis on the failure of others to separate the enantiomers, while mentioning in passing that evidence of commercial success and copying by others also supported a finding of non-obviousness.

In *Pfizer,* on the other hand, the Federal Circuit rejected Pfizer's argument that unexpected results overcame the *prima facie* case of obviousness. The court emphasized that any superior properties must be *unexpected*, which requires consideration of evidence as to what *would* be expected. But, ''because the record [was] devoid of *any* evidence of what the skilled artisan would have expected,'' Pfizer's evidence of unexpected results failed. It also held that even if Pfizer had established unexpected results, it was still insufficient to overcome the ''strong case of obviousness'' established. The court also affirmed the district court's use of evidence of a high volume of commercial sales as indicative of improved properties of the drug, and not as a secondary consideration of non-obviousness.

Every innovator company thus should put forth any facts it has of non-obviousness, as well as facts necessary to give the evidence context, such as what would have been expected or what constitutes commercial

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success in the field. And generics of course should be ready to rebut those facts and to do so in creative ways. For example, one district court recently found evidence of commercial success unpersuasive because the drug was marketed under the well-known trade name ''Pepcid.'' *McNeil-PPC, Inc. v. Perrigo Co.* (S.D.N.Y. July 3, 2007).

The Future of Secondary Pharmaceutical Patents

Secondary pharmaceutical patents still have a future. But to prevail against an obviousness challenge, innovator companies must shift their focus and tactics in each element of the analysis, from identifying the person of skill in the art, to collecting the key facts from their scientists (including evidence of failures or other courses pursued), to finding experts qualified to testify about the reasonable courses of action a person of skill in the art would have pursued and what was both expected and unexpected. On the flip side, the generic companies now have more leeway in combining prior art references, but should focus on retaining experts who will testify that the invention was ''obvious to try'' and the mere verification of an expected result, as opposed to true innovation.