

Think *KSR v. Teleflex* Does Not Impact Pharmaceutical Patent Validity? Think Again

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On April 30, 2007, the Supreme Court rejected in *KSR Int'l Co. v. Teleflex Inc.* the “rigid approach” of the Court of Appeals for the Federal Circuit in favor of an “expansive and flexible approach” on the question of whether a patent claim was obvious in view of prior art. The *KSR* decision will make it more difficult to procure and defend all patents, not just mechanical patents like the one at issue in *KSR*. In fact, the effect of the *KSR* case began soon after the Supreme Court agreed to hear the *KSR* case, including two different pharmaceutical cases wherein 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). These cases make clear that no technology is immune from *KSR*.

In *Alza*, a generic drug maker (Mylan) sought to market a once-a-day controlled-release formulation of oxybutynin, a drug used to treat urinary incontinence. Once-a-day dosing provided the usual benefits of convenience, steady-dosing, and in addition, possibly reduced absorption of a metabolite that leads to side-effects. *Alza* sued for infringement, asserting the following claim:

2. A sustained-release oxybutynin formulation for oral administration to a patient in need of treatment for urge incontinence comprising a therapeutic dose of an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that delivers from 0 to 1 mg in 0 to 4 hours, from 1 mg to 2.5 mg in 0 to 8 hours, from 2.75 to 4.25 mg in 0 to 14 hours, and 3.75 mg to 5 mg in 0 to 24 hours for treating urge incontinence in the patient.

The district court held the claim obvious, anticipated, and not infringed. The Federal Circuit affirmed the holdings of obviousness and non-infringement, and stated that it need not decide the anticipation issue because of its invalidity holding on obviousness grounds. The Federal Circuit began its discussion on obviousness on 35 U.S.C. 103, and its case law, and the Supreme Court’s seminal decision in *Graham*:

As for obviousness, a claimed invention is unpatentable if the differences between it and the prior art are “such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.” 35 U.S.C. § 103(a) (2000); *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 13-14, 86 S. Ct. 684, 15 L. Ed. 2d 545, (1966)). Obviousness is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial. 464 F.3d at 1289.

The Federal Circuit noted that in *Graham*, the Court “recognized the importance of guarding against hindsight, as is evident in its discussion of the role of secondary considerations as ‘serv[ing] to guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue.’” 464 F.3d at 1290. The Federal Circuit stated that its “‘motivation to combine’ requirement [also called the “motivation-suggesting-teaching test”] likewise prevents statutorily proscribed hindsight reasoning when determining the obviousness of an invention.” *Id.* This is important because the obviousness inquiry must be conducted “‘at the time the invention was made’ 35 U.S.C. § 103.” *Id.*

The Federal Circuit stated that “[t]here is flexibility in our obviousness jurisprudence because a motivation may be found implicitly in the prior art” and that it does “not have a rigid test that requires an actual teaching to combine before concluding that one of ordinary skill in the art would know to combine references.” *Id.* at 1291.

Alza's principal argument on appeal was that "no one of ordinary skill in the art would have been motivated to adapt the [technology of three references] to oxybutynin in the first place, because a person of ordinary skill in the art would have had no reason to expect that such an extended release oxybutynin formulation would have therapeutic value." *Id.* at 1294.

The Federal Circuit held far from teaching away or detracting from the weight of the testimony of Mylan's expert's, the prior art references relied upon by Alza, taken as a whole, were "entirely consistent with the finding that in 1995 a person of ordinary skill in the art would have expected a general, albeit imperfect, correlation between a drug's lipophilicity and its colonic absorptivity." *Id.* at 1295 [Emphasis added]. Accordingly, the Federal Circuit held there was "no clear error in the district court's factual findings that while colonic absorption was not guaranteed, the evidence, viewed as a whole, is clear and convincing that a person of ordinary skill in the art would nonetheless have perceived a reasonable likelihood of success and that she would have been motivated to combine prior art references to make the claimed invention." *Id.*

After the Supreme Court heard argument (but prior to its decision) in *KSR*, the Federal Circuit found another pharmaceutical patent invalid for obviousness. In *Pfizer*, the district court found that the besylate salt of amlodipine was unexpectedly superior to the amlodipine salts of the prior art. 480 F.3d at 1356. Specifically, the district court found that "while amlodipine besylate was not superior to amlodipine maleate 'in every category,' it nonetheless 'clearly and unexpectedly illustrates a superior combination of properties when compared to what was suggested in the preferred preparation--ostensibly

the amlodipine maleate disclosed as the preferred embodiment of [Pfizer's own prior art] '909 patent." *Id.* at 1357.

The Federal Circuit reversed the district court's holding of non-obviousness. It was undisputed that the claims of Pfizer's prior art '909 patent literally encompassed amlodipine besylate. *Id.* at 1361. The Federal Circuit held that a suggestion, teaching or motivation does not have to be found explicitly in the prior art references sought to be combined, but rather "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *Id.* at 1362. The Federal Circuit stated that the record shows that "one skilled in the art would have been motivated to choose an anion having a different structure than that of maleate," and that "compelling" testimony from Apotex's expert "supports an inference that the skilled artisan actually would have been encouraged, rather than discouraged, to choose an anion without the same double bond [as the maleate salt ion], such as benzene sulphonate, in order to avoid [an] addition reaction." *Id.*

The Federal Circuit stated that "clear and convincing evidence establishes that, out of the list of 53 anions [in secondary reference Berge], one of ordinary skill in the art would have favorably considered benzene sulphonate because of its known acid strength, solubility, and other known chemical characteristics as reported in several other publications." *Id.* at 1363.

Hence, the "evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that an acid addition salt of besylate would form and would work for its intended purpose." *Id.* at 1364. Indeed, as soon as tablet processing problems arose with the amlodipine maleate form tablet

formulations, Pfizer “readily compiled a list of seven alternative anions—including the besylate—each of which he expected would form an amlodipine acid addition salt.” *Id.*

The Federal Circuit stated that this is not the case where there are “numerous parameters” to try, but rather “the only parameter to be varied is the anion with which to make the amlodipine acid addition salt.” *Id.* at 1366. The Federal Circuit cited three facts that weighed in favor of the obvious determination: (1) reasonable (although not guaranteed) expectation that amlodipine besylate would form; (2) Pfizer conceded in prior litigation that the type of salt had no effect on the therapeutic effect of the active ingredient, amlodipine, and was practically interchangeable, and (3) numerous other publications clearly directed the skilled artisan to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate, including, significantly, one patent that taught the besylate acid addition salt form of another dihydropyridine pharmaceutical compound. *Id.*

Thus, “this is not the case where the prior art teaches merely to pursue a ‘general approach that seemed to be a promising field of experimentation’ or ‘gave only general guidance as to the particular form of the claimed invention or how to achieve it.’” *Id.* Rather, it was admitted that (1) “in selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry;” (2) “Berge clearly pointed the skilled artisan to 53 anions that, as of 1974, were pharmaceutically acceptable;” and (3) as demonstrated by testimony by Pfizer and the Carabateas patent, “one of ordinary skill in the art was capable of further narrowing that

list of 53 anions to a much smaller group, including benzene sulphonate, with a reasonable expectation of success.” *Id.*

The Federal Circuit stated that while patentability of an invention is not negated by the manner in which it was made, “the converse is equally true: patentability is not imparted where ‘the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.’” *Id.* at 1369. The Federal Circuit stated that Pfizer failed to prove that the properties of amlodipine besylate over the prior art would have been unexpected to the skilled artisan, and that even if Pfizer made such a showing, “this secondary consideration does not overcome the strong showing of obviousness in this case.” *Id.* at 1371.

In *KSR*, Supreme Court set forth reasoning similar to the Federal Circuit reasoning in *Pfizer*:

When there is a design need or 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 § 103.

After *KSR*, the Federal Circuit denied Pfizer’s request rehearing en banc (with Newman, Lourie, Radar, dissenting).

In sum, patents claiming new forms of known drugs will likely be subjected to increased challenges. Similarly, applicants can no longer expect to obtain easy allowance of new forms of known drugs without also showing unexpected results. As *Pfizer* illustrates, even a showing of unexpected results will not necessarily rebut a strong *prima facie* case of obviousness.