

# PHARMACEUTICAL PATENTS AFTER KSR

## Withstanding the Obviousness Challenge

by Esther H. Steinhauer

In light of *KSR Int'l v. Teleflex, Inc.*,<sup>1</sup> patents are more vulnerable than ever to obviousness challenges under 35 U.S.C. § 103. In addition to rejecting the rigidity of the Federal Circuit's teaching-suggestion-motivation test,<sup>2</sup> *KSR* jettisoned the "obvious to try" rebuttal to obviousness challenges.<sup>3</sup> This article discusses several pharmaceutical cases decided in this new obviousness landscape and the guidance these decisions offer to patent practitioners.

*Alza Corp. v. Mylan Labs.*<sup>4</sup> is an example of the obviousness analysis endorsed by the Supreme Court in *KSR*.<sup>5</sup> Alza's patent for a once-daily extended release oxybutynin tablet, used in treating urinary incontinence and sold as Ditropan XL, was held invalid for obviousness.<sup>6</sup>

Relying on expert testimony<sup>7</sup> on lipophilic properties of oxybutynin and similar compounds, and on three prior art patents, Mylan argued that a person of ordinary skill in the art would have believed that a very slow release oxybutynin tablet could be therapeutically effective and would have been motivated to prepare such a composition.<sup>8</sup> The prior art included a sustained release composition of a highly water-soluble active ingredient (i.e., morphine), an extended-release oxybutynin composition with an enteric-coated polymer matrix similar to

Mylan's accused formulation but with a faster release rate than that claimed for Alza's formulation and a bilayer osmotic pump dosage form of several classes of active ingredients, including one of which oxybutynin is a member.<sup>9</sup>

Alza asserted that the physico-chemical properties of oxybutynin would prevent it from being absorbed in the colon, essential to effect the very slow release rate, and offered references suggesting that lipophilicity is not necessarily predictive of colonic absorption.<sup>10</sup> The court concluded that while colonic absorption of a lipophilic compound was not guaranteed, the evidence as a whole was clear and convincing that the person of ordinary skill in the art would have been motivated to combine prior art references to make the very slow release rate oxybutynin tablet.<sup>11</sup>

In a prelude to the Supreme Court's *KSR* decision, *Pfizer, Inc. v. Apotex, Inc.*<sup>12</sup> reversed the district court to hold that Pfizer's patent for amlodipine besylate tablets, sold as Norvasc and used in treating hypertension and certain types of angina, was obvious.<sup>13</sup> The court below had upheld the patent as nonobvious on the ground that there was no expectation of success because the prior art taught and the experts agreed that "[t]here is no reliable way of predicting

the influence of a particular salt species on the behavior of a parent compound." Moreover, the besylate salt of amlodipine was found to be unexpectedly superior to the other amlodipine salts in the prior art, including those disclosed in an earlier Pfizer patent covering a genus of certain dihydropyridine compounds and their pharmaceutically acceptable acid addition salts.<sup>14</sup>

Because Pfizer's earlier patent did not expressly disclose the besylate salt or the anions required to make it, and because the anions that were disclosed did not have a chemical structure analogous to that of the besylate, Pfizer argued that its earlier patent neither suggested nor motivated the person of ordinary skill in the art to make amlodipine besylate. Moreover, at the time of the invention the besylate salt was rarely used in pharmaceutical formulations.<sup>15</sup>

Although the earlier Pfizer patent did not expressly disclose amlodipine besylate or the specific anions required



**Ms. Steinhauer** is Counsel in the New York office of Hunton & Williams LLP. The views expressed here are her personal views.

to make it, the court found that “neither do they exclude” them. It also rejected Pfizer’s argument that “unpredictability” in an art was sufficient to overcome an obviousness challenge, pointing to the testimony of Pfizer’s scientists who tested various amlopidine salts, including the besylate, with an expectation of improved physicochemical properties over the maleate.<sup>16</sup> Pfizer’s invention was analogized “to the optimization of a range or other variable within the claims that flows from the ‘normal desire’ of scientists to improve upon what is already generally known.”<sup>17</sup>

The court concluded that a person of ordinary skill in the art would have been motivated to prepare amlopidine besylate because: 1) Pfizer’s scientists wanted an anion structurally different than the maleate so as to avoid the degradation of the amlopidine in the maleate formulation, 2) a limited number of pharmaceutically acceptable salts were then available, including besylate, and 3) the prior art taught the favorable properties of besylate salts of other pharmaceutical compositions, although unrelated to amlopidine.<sup>18</sup>

In a display of candor, the court acknowledged that the “[p]harmaceutical industry may be particularly adversely impacted by an application of ‘an obvious to try analysis.’” And “optimization” inventions were distinguished from “the trial and error procedures often employed [by scientists] to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success.”<sup>19</sup>

“Routine optimization” was also the basis for obviousness invalidity in *PharmaStem Therapeutics, Inc. v. Viacell, Inc.*<sup>20</sup> Prior art showing that human umbilical cord blood contained

progenitor cells was held sufficient to suggest the presence of high concentrations of stem cells thereby motivating the “routine research” that led to two patents for compositions and method relating to treating humans with stem cells.<sup>21</sup> Rejecting PharmaStem’s argument that novelty of invention resided in the proof of presence of stem cells (not just progenitor cells) in fetal blood, the court found the patents invalid because there was no novelty in the claimed methods to collect, cryopreserve or transplant the cord blood.<sup>22</sup>

In contrast, evidence of “trial and error” discovery in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*<sup>23</sup> was sufficiently persuasive to rebut an obviousness challenge. Takeda’s patent for pioglitazone, sold as ACTOS and used in controlling the blood sugar of diabetes Type 2 patients, was challenged by Alphapharm based on a prior art compound, “compound b,” disclosed in an earlier patent for a genus of thiazolidinediones, and structurally similar to pioglitazone.<sup>24</sup>

Agreeing with the district court that Alphapharm had failed to make out a *prime facie* case of obviousness, the panel majority concluded that a person of skill in the art would not have selected to modify “compound b” from the millions of prior art compounds disclosed in the earlier patent because there was no evidence that it was the most therapeutically effective.<sup>25</sup> Likewise, nothing in the prior art suggested to modify “compound b” by homologization or ring-walking.<sup>26</sup> In fact, the prior art taught away from the invention as “compound b” was shown in a contemporaneous publication to be toxic and to have other side effects.<sup>27</sup> In addition, pioglitazone exhibited unexpectedly superior properties over the prior art thiazolidinediones.<sup>28</sup>

The *Takeda* panel squarely distinguished *KSR* and *Pfizer* decisions; *KSR* on the basis that in *Takeda* the invention was not obvious to try, and *Pfizer* on the basis that nothing in the prior art would have led the person of ordinary skill in the art to choose to modify prior “compound b” over the numerous other compounds.<sup>29</sup> The court emphasized that “in cases involving new chemical compounds it remains necessary to identify some reason . . . to modify a known compound in a particular manner to establish *prime facie* obviousness . . .,” citing to several earlier decisions on obviousness and “structural similarity.”<sup>30</sup>

## District Court Decisions

This distinction between “optimization” versus “trial and error” inventions also runs through recent district court decisions concerning pharmaceutical patents. In *McNeil-PPC, Inc. v. Perrigo Co.*,<sup>31</sup> a patent for a composition containing aluminum or magnesium hydroxide (antacids) plus famotidine, a bitter tasting guanidinothiazole that inhibits acid secretion in the stomach was invalidated for obviousness. The granulated famotidine was coated with an impermeable membrane to protect it from antacid degradation.<sup>32</sup>

The invalidating prior art included tablets combining uncoated famotidine plus magnesium or aluminum hydroxide but without reference to famotidine’s bitter taste or its masking, a method for coating granulations of other active ingredients to mask their taste in chewable tablets and methods for tastemasking active granulated ingredients such as famotidine.<sup>33</sup>

Additionally, famotidine in combination still tasted bitter and plaintiffs’ internal documents and witness testimony showed that coating was selected over other tastemasking technologies because

of its superior results. The court held, therefore, that a person of ordinary skill in the art would have been motivated to coat famotidine used in combination with antacids.<sup>34</sup> The unexpectedly superior results of decreased famotidine degradation in the composition could not overcome the clear and convincing evidence of obviousness.<sup>35</sup>

Also invalidated for obviousness was a patent for a composition of the analgesics tramadol and acetaminophen combined at a range of weight ratios in *Ortho-McNeil Pharm., Inc. v. Kali Labs., Inc.*<sup>36</sup> The prior art taught combinations of acetaminophen plus other analgesics, including opioids.<sup>37</sup> Although the claimed range was not identically disclosed in any single reference, the court held that together the references created a range fully overlapping that claimed,<sup>38</sup> and that a person of ordinary skill in the art would have been motivated to seek the optimum values for this variable.<sup>39</sup> Little weight was accorded the evidence of unexpected synergy because similar prior art formulations also showed synergy.<sup>40</sup>

In contrast, *Sanofi-Synthelabo et al. v. Apotex*<sup>41</sup> upheld a patent for clopidogrel, a dextrorotatory enantiomer<sup>42</sup> of a compound in a class of known thienopyridines. Clopidogrel bisulfate is sold as Plavix and used in reducing heart attacks and strokes.<sup>43</sup> Rejecting Apotex's argument that the enantiomer was obvious in view of an earlier Sanofi patent disclosing a genus of thienopyridine compounds in racemate form, and their various salts, the court concluded that a person of ordinary skill in the art would not have reasonably expected an enantiomer of any prior art racemate to possess all of the racemate's therapeutic activity and none of its toxicity.<sup>44</sup> The *Pfizer* decision was distinguished on the

basis that no evidence or prior art taught the favorable properties of pharmaceutically acceptable bisulfate salts.<sup>45</sup>

## Conclusion

From this rapidly evolving caselaw, practitioners can expect that improvement or "optimization" claims for pharmaceuticals with different salt forms, different excipients, adjusted dosages, release rates or formulations of known active ingredients, or optimized variables for known combinations, are very vulnerable to invalidation or rejection for obviousness, even when supported by unexpected results.

On the other hand, new compound/active pharmaceutical ingredient claims are more likely to withstand an obviousness challenge. And somewhere in the middle are claims for new administration forms of a known active ingredient, or new combinations showing unexpected synergy, superior therapeutic efficacy or other improved properties, which are heavily dependent on the teachings of the prior art and its understanding by the person of ordinary skill in the art. ▲

years of experience in controlled release technology or a Bachelor's degree with five years of experience. *Id.* at 1293.

<sup>8</sup> *Id.* at 1292.

<sup>9</sup> *Id.* at 1292-93.

<sup>10</sup> *Id.* at 1292; 1293-95.

<sup>11</sup> *Id.* at 1294-95.

<sup>12</sup> 480 F.3d 1348 (Fed. Cir. 2007).

<sup>13</sup> *Id.* at 1352.

<sup>14</sup> *Id.* at 1353; 1356-57.

<sup>15</sup> *Id.* at 1361-62.

<sup>16</sup> *Id.* at 1364-66. Because the unexpected results relied on below were those expected from any besylate salt composition and because *Pfizer* had decided against using the amlodipine maleate formulation, in part, as difficult to manufacture and not because of the besylate's superior physicochemical properties, secondary considerations of nonobviousness were found unpersuasive. *Id.* at 1370-71.

<sup>17</sup> *Id.* at 1368 (citations omitted).

<sup>18</sup> *Id.* at 1361-63.

<sup>19</sup> *Id.* at 1367.

<sup>20</sup> 2007 U.S. App. LEXIS 16245 (Fed. Cir. July 9, 2007).

<sup>21</sup> *Id.* at \*43-65.

<sup>22</sup> *Id.* at \*57-58. In her dissent, Judge Newman railed against the panel majority's "judicial hindsight" and disregard of the evidence of long-felt need and other secondary considerations of nonobviousness. *Id.* at \*88-98.

<sup>23</sup> 2007 U.S. App. LEXIS 15349 (Fed. Cir. June 28, 2007).

<sup>24</sup> *Id.* at \*3-6.

<sup>25</sup> *Id.* at \*7-17 (citations omitted).

<sup>26</sup> *Id.* at \*24-26.

<sup>27</sup> *Id.* at \*18-20.

<sup>28</sup> *Id.* at 27-29.

<sup>29</sup> *Id.* at \*20-23.

<sup>30</sup> *Id.* at \*11-13 (citations omitted).

<sup>31</sup> 2007 U.S. Dist. LEXIS 40476 (S.D.N.Y. June 5, 2007).

<sup>32</sup> *Id.* at \*2-4.

<sup>33</sup> *Id.* at \*17-20.

<sup>34</sup> *Id.* at \*21-30. Evidence of commercial success was negated by plaintiffs' heavy expenditures to market the commercial product and by the brand strength of their other famotidine products. *Id.* at \*32-36.

<sup>35</sup> *Id.* at \*35-39.

<sup>36</sup> 2007 U.S. Dist. LEXIS 25459 (April 4, 2007).

<sup>37</sup> *Id.* at \*91-102.

<sup>38</sup> *Id.* at \*102-103.

<sup>39</sup> *Id.* at \*116-122. Because there was no nexus between the involved patent claims and the commercial product, plaintiffs' commercial success evidence was also unpersuasive. *Id.* at \*144-148.

<sup>40</sup> *Id.* at \*125-136.

<sup>41</sup> 2007 U.S. Dist. LEXIS 44033 (S.D.N.Y. June 19, 2007).

<sup>42</sup> Enantiomers are molecules with identical chemical substituents and an asymmetric carbon, but differing in their spatial arrangements. They are optically active, rotating light either to the right (dextrorotatory) or left (levorotatory). A racemate is composed of equal amounts of levo- and dextrorotatory molecules and has no optical activity. *Id.* at \*11-12 (citation omitted).

<sup>43</sup> *Id.* at \*3-21.

<sup>44</sup> *Id.* at \*28-54.

<sup>45</sup> *Id.* at \*54-64; \*67; \*99-114.

<sup>1</sup> 127 S.Ct. 1727, 550 U.S. \_\_\_\_ (2007).

<sup>2</sup> *Id.* at 1734-1735; 1739. *KSR* emphasized that the *Graham* factors define the inquiry under 35 U.S.C. § 103. *Id.* at 1734. *Graham v. John Deere Co.*, 383 U.S. 1 (1966) sets forth four relevant factors as follows: (1) scope and content of prior art; (2) skill level of a person of ordinary skill in the art, (3) differences between claimed invention and the prior art, and (4) objective *indicia* of nonobviousness such as commercial success, long felt need, *etc.*

<sup>3</sup> *Id.* at 1740-42. Under *KSR*, the level of ordinary skill in the art becomes a crucial determinant of whether the creative steps of such a person would have resulted in an obvious invention. *Id.* at 1745-46. *See e.g., Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 2007 U.S. App. LEXIS 16576 (Fed. Cir. July 11, 2007, unpublished) (patent directed to a compound for treating ear infections without damaging a patient's hearing held obvious where level of ordinary skill in the art erroneously decided below).

<sup>4</sup> 464 F.3d 1286 (Fed. Cir. 2006).

<sup>5</sup> *KSR*, 127 S.Ct. at 1743.

<sup>6</sup> *Alza*, 464 F.3d at 1288; 1290-91; 1294-95.

<sup>7</sup> The person of ordinary skill in the art was agreed to have an advanced degree in pharmacy, biology, chemistry or chemical engineering with at least two