

## **Pharmaceutical Salts and Obviousness – A View from an In-House Patent Attorney**

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With the most radical changes in patent prosecution practice from the United States Patent and Trademark Office in a generation coupled with a significant doctrinal shift in the courts, 2007 will surely be viewed as a significant inflection point for years to come. This paper focuses on one aspect of those changes, the law of obviousness, and analyzes some of the critical case law over the past year, concluding with thoughts on how the pharmaceutical industry might cope with the new patent landscape.

For background and context, I serve as chief patent counsel to Aptuit, Inc., a pharmaceutical development company employing approximately 2700 people worldwide. We do not market our own drug products. Rather, in this outsourcing world, we provide services to those who do market pharmaceuticals. A key part of those services includes improving the physical properties of discovery compounds. Much of this is done at SSCI, now a wholly-owned subsidiary of Aptuit, which has, over the past 15 years, developed a world-class expertise for improving the solid-state properties of drugs. SSCI also has tremendous experience in screening for new salts and crystalline forms of pharmaceuticals.

When given the choice between intravenous drug delivery and swallowing a tablet, most consumers will choose the tablet over the needle which is why pharmaceutical companies strongly prefer to develop oral drug delivery systems over all

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other possibilities. Likewise, oral drugs in the solid-state have advantages over liquid counterparts from the standpoint of stability, handling, and contamination. Accordingly, the pharmaceutical community consumes enormous resources converting promising pharmaceutically active molecules into effective solid-state oral formulations. The value of the solid-state properties of drugs, as opposed to their biological effects, has not been lost on the courts.

[C]ommercialization of [chemical and pharmaceutical] compounds may depend on their possession of unexpected properties. Such properties may be biological or physical. A failure to recognize all such properties that may be relevant to the value of such a compound may doom the compound being poured down the drain rather than becoming an important therapeutic.<sup>2</sup>

Over the past year, the courts have issued critically important opinions with tremendous consequences to the innovative process for bringing solid-state oral formulations to market in the United States.

***Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348 (Fed. Cir. 2007)**

In *Pfizer*, the court invalidated Pfizer's second-generation salt patent covering amlodipine besylate, the active ingredient in Norvasc®. Pfizer had filed two primary patents covering this drug product, U.S. Patent No. 4,572,909 ("the '909 patent") and U.S. Patent No. 4,879,303 ("the '303 patent"). The '909 patent claims amlodipine and its pharmaceutically acceptable acid-addition salts but does not specifically teach the besylate salt. The '303 patent specifically claims amlodipine besylate, amlodipine besylate in a pharmaceutical composition, and in a tablet. During prosecution, the application which matured into the '303 patent was originally rejected in view of the '909

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<sup>2</sup> *Pfizer, Inc. v. Apotex, Inc.*, 488 F.3d 1377, 1383 (Fed. Cir. 2007) (Lourie, J. dissenting from denial of *en banc* rehearing)

patent and several other references as being obvious, but issued after Pfizer submitted affidavit evidence from one of its inventors. At trial, the district court "concluded that Apotex failed to meet its burden of proving invalidity . . . by clear and convincing evidence."<sup>3</sup>

On appeal, however, the court reversed finding the claims obvious over the various references. The Court found several references particularly compelling especially an article by Berge listing "53 FDA-approved, commercially marketed anions, including benzene sulphonate, that are useful for making pharmaceutically-acceptable salts."<sup>4</sup> The Court found that the list of 53 possible anions could be whittled down to one, besylate, because of its "known acid strength, solubility, and other known chemical characteristics as reported in several other publications Pfizer has admitted are prior art."<sup>5</sup> Armed with these references, the Court ultimately concluded that "the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing."<sup>6</sup> The Court went on, however, with a sweeping generalization about the pharmaceutical development process using Norvasc® as an example.

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<sup>3</sup> *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1356 (Fed. Cir. 2007).

<sup>4</sup> *Id.* at 1355.

<sup>5</sup> *Id.* at 1363.

<sup>6</sup> *Id.* at 1367.

The evidence shows that, upon making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type[s] of experiments used by Pfizer scientists to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed 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>7</sup>

Pfizer filed for a rehearing *en banc* which was denied. In dissent, Judge Rader opined that the implications of the panel's decision would reach far beyond the facts the case.

Many if not most pharmaceutical inventions are discovered through a routine screening protocol or through an established trial and error process. Pharmaceutical inventions discovered by these routine screening methods include not only new formulations and salt forms, but also include the active pharmaceutical compounds themselves. Thus, this decision calls into question countless pharmaceutical patents, which in turn could have a profoundly negative impact on investments into the design and development of new life-saving pharmaceuticals.<sup>8</sup>

***Sanofi v. Apotex*, 470 F.3d 1368 (Fed. Cir. 2006) & 492 F.Supp.2d 353 (S.D.N.Y. 2007)**

In a case that has made international news, Sanofi sued Apotex for infringing U.S. Patent No. 4,847,265 ("the '265 patent) which claims the d-enantiomer of clopidrogel bisulfate, the active ingredient in Plavix®. In an appeal from a preliminary injunction issued by Judge Stein in the Southern District of New York on August 31, 2006, the Federal Circuit upheld the preliminary injunction issued by the district court. The court found that all the usual requirements for issuing such an injunction, such as likelihood of

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<sup>7</sup> *Id.*

<sup>8</sup> *Pfizer, Inc. v. Apotex, Inc.*, 488 F.3d 1334, 1384 (Fed. Cir. 2007) (Rader, J. dissenting from denial of *en banc* rehearing).

success on the merits, were met. Judge Stein conducted a bench trial in early 2007 and delivered his opinion on June 19 of this year.

In the appellate case, Apotex argued that the claim covering the d-enantiomer of the bisulfate salt of clopidrogel was invalid over a prior art reference, U.S. Patent No. 4,529,596 ("the '596 patent") which teaches the racemate of clopidrogel as a free base. Apotex's arguments were based both on inherency and obviousness. The Federal Circuit found that although there was a general teaching of bisulfate salts in the '596 patent, that disclosure was "insufficient to disclose a single enantiomer of a compound a bisulfate salt,"<sup>9</sup> and it agreed with the district court that the patent was not invalid for being inherently anticipated.

With respect to obviousness, the Court reached a similar conclusion. It found no error in the lower court's findings that there was nothing in the prior art to suggest that making the d-enantiomer of the bisulfate salt would result in the beneficial properties now associated with Plavix®.

At the subsequent bench trial, these issues came into even sharper focus. Citing testimony from Sanofi's expert,<sup>10</sup> the court differentiated the formation of salts in solution with the formation of solid-state salts having particular physical properties. Furthermore, the court found it generally desirable to prepare crystalline solid-state salts. "Formation of a crystalline salt is important for an orally administered drug such as clopidrogel, and the salt form of a drug can affect a drug's pharmacological properties because of its effect on solubility, which influences absorption in the body and

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<sup>9</sup> *Sanofi-Synthelabo, Inc. v. Apotex, Inc.*, 470 F.3d 1368, 1376 (Fed. Cir. 2006).

<sup>10</sup> In the interest of full disclosure, Sanofi's expert, Professor Stephen Byrn, is a founder of SSCI, Inc. and chairs Aptuit's scientific advisory board.

bioavailability."<sup>11</sup> A critically important aspect of crystalline forms is that their existence, structure, and properties cannot be predicted in advance.

However, the prior art teaches and both parties' experts agreed and the Court finds-that whether a crystalline material will form in a particular reaction of acid and base, the type of crystalline material that will form, and the properties that the crystalline material will have, are all unpredictable.<sup>12</sup>

The court also tied the unpredictability of crystalline forms to the formation of salts and their properties. Quoting from the infamous Berge reference, the court found:

Choosing the appropriate salt . . . can be a very difficult task, since each salt imparts unique properties to the parent compound . . . . Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound.<sup>13</sup>

The court held that clopidrogel bisulfate possesses "a highly favorable combination of properties" that were unexpected and therefore not obvious to one of ordinary skill in the art.<sup>14</sup> Of course, the court had to confront the *Pfizer v. Apotex* decision and did so by distinguishing the case on the "particularized facts" of the Pfizer case.<sup>15</sup>

### ***Pfizer and Sanofi in view of KSR.***

I will not repeat the facts of KSR here, assuming they are well known to the reader. There is little doubt that KSR changed the way, at least in theory, we consider obviousness. The TSM test, while not eliminated, has been removed as the *sine qua non* of obviousness leaving us instead with standards including "common sense." Perhaps the

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<sup>11</sup> *Sanofi-Synthelabo, Inc.*, 470 F.3d at 1374.

<sup>12</sup> *Id.*

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

<sup>14</sup> *Id.* at 391.

<sup>15</sup> *Id.* at 392.

most applicable and instructive portion, at least to the pharmaceutical industry, of the Court's opinion is its discussion of the "obvious to try" standard.

[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.<sup>16</sup>

The United States Patent and Trademark Office has recently embraced new "obviousness to try" standards which were published on October 10, 2007.<sup>17</sup> Section E of the guidelines, illustrates how the Office views the new "obvious to try" method of invalidating patents as articulated by *KSR*. The Office presents three examples from recent cases, two dealing with pharmaceuticals, one of which being the decision in *Pfizer, Inc. v. Apotex, Inc.* According to the Office's interpretation of the *Pfizer* case, by narrowing down the list of possible salt formers to 53 (from the Berge reference), the court was able to conclude that this would lead to a "reasonable expectation of success."<sup>18</sup> With this reasoning and interpretation of case law, it will be virtually impossible to obtain patents on pharmaceutical salts as they are commonly claimed today. This calculus assumes, however, that the salt selection process leads to an "anticipated success." In that assumption, perhaps, one may find a way to draft claims to avoid rejections and judicial holdings of obviousness.

### **Salts in the New Age of Obviousness – Where Do We Go From Here?**

A potential response to the purported death knell of pharmaceutical salts lies in the inherent properties of the solid-state. It is well settled among solid-state scientists

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<sup>16</sup> *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007).

<sup>17</sup> Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526 (Oct. 10, 2007).

<sup>18</sup> *Id.* at 57532.

that it is not possible to predict what chemical entities will crystallize, under what conditions they will crystallize, how many different crystalline forms are possible, and what the physical properties of those forms will be.<sup>19</sup> In other words, the solid-state is filled with unpredictability, much more unpredictability than in the synthetic organic chemistry schemes found in patents covering new chemical entities.

Imagine a claim that is directed to "crystalline compound sulfate" or "crystalline compound sulfate having x-ray powder diffraction peaks at about 10.0, 11.1, 12.2, and 13.3 degrees two-theta." Such a claim could never be predicted in advance and it would be impossible to know how many experiments it would take to prepare a compound covered by such a claim or even if it would be possible to do so. Furthermore, pharmaceutically relevant physical properties such as solubility, dissolution, hygroscopicity, etc. of the compound would have to be measured experimentally and could not be accurately predicted. Thus, a claiming strategy to escape an obviousness determination, especially in second-generation patents, could include drafting salt claims as if they were polymorph claims to take advantage of the unpredictable nature of the solid state. A downside, of course, would likely be a sacrifice in claim scope which comes from attempting to enable broad claims in an unpredictable art. Nevertheless, in circumstances where the marketed product has already been identified, such a strategy is better insulated against an obviousness rejection from the Patent Office or an adverse obviousness holding from the court than traditional pharmaceutical salt claim strategies.

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<sup>19</sup> See e.g., Angelo Gavezzotti, *Are Crystal Structures Predictable?*, 27 **Accounts of Chemical Research** 309-14 (1994).