No. 2006–1261

United States Court of Appeals

for the

Federal Circuit

PFIZER INC,

Plaintiff–Appellee,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.),

Defendant–Appellant.

Appeal from the United States District Court for the Northern District of Illinois in No. 03–CV–5289, Judge James M. Rosenbaum

ANSWER TO PETITION OF PLAINTIFF-APPELLEE PFIZER INC. FOR REHEARING AND REHEARING *EN BANC*

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CERTIFICATE OF INTEREST

Pursuant to FED. CIR. R. 47.4, counsel for Appellant Apotex, Inc. (formerly known as TorPharm, Inc.) certifies the following:

1. The full name of every party represented by me is:

Apotex, Inc. (formerly known as TorPharm, Inc.)

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

The party named in the caption is the real party in interest.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of the party represented by me are:

Apotex Pharmaceutical Holdings, Inc.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or agency or are expected to appear in this court are:

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April 27, 2007
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ANSWER

The panel correctly applied this Court's obviousness jurisprudence to the particular facts of this case under of the proper standard of review. The panel did not make new law, but instead explained and applied well-established law. The panel gave due regard to the clear error standard, but that standard did not protect the district court's errors of fact and law in this case. The panel properly used the inventor's testimony in the way precedent dictated it should, avoided an "obvious to try" test, and gave full consideration to the requirements of 35 U.S.C. § 103.

Predictability is not a surrogate for unexpected results in the obviousness analysis. That the chemical arts are by definition unpredictable does not make every result unexpected and patentable. Pfizer reacted a known acid, known to produce pharmaceutically acceptable, non-toxic salts, with a known base to produce a salt as suggested by the prior art. One of ordinary skill in the art would have expected results like those achieved. To merit a patent, Pfizer needed to be prepared to explain what one of ordinary skill in the art would have expected and why the results obtained were unexpected. Instead, the undisputed testimony was that while results in the chemical arts cannot be predicted with absolute certainty, this result, here, was not unexpected. That established, as a matter of law, that this claimed subject matter was **obvious**, as the court correctly held.

A petition for rehearing must state with particularity each point of law overlooked or misapprehended. FED. R. APP. PROC. 40. Petitioners do not identify a single incorrect statement of law in the opinion. Instead, petitioners state general principles the panel duly considered, about an inventor's expectations, about not applying an "obvious to try" test, about routine testing, and about equating absolute predictability with reasonable expectations. That is not an adequate basis for rehearing. Similarly, en banc rehearing is disfavored and ordinarily will not be ordered. FED. R. APP. PROC. 35(a). Case-specific decisions controlled by their unique facts (as this panel decision is) are rarely "enbancable." *See, Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1043, 80 USPQ2d 1944, 1948 (Fed. Cir. 2006) ("[W]hile the result may be of exceptional importance to the parties, it does not seem to be so to the law.") (Lourie, J., concurring in denial of *en banc*).

I. The Panel Considered and Properly Rejected the Points of Law and Fact That Pfizer Asserts Were Overlooked or Misapprehended.

In its petition Pfizer identifies six "points of law and fact" that it asserts were overlooked or misapprehended by the panel. In truth, the panel already carefully considered each of those points and rejected them, as explained hereinbelow.

A. The Panel Properly Rejected the District Court's Findings Concerning Amlodipine Besylate's Purported Unexpected Results Because They Were Factually and Legally Erroneous.

Petitioner has accused the panel of violating the "clear error" standard, but this case turns on the ultimate legal conclusion of obviousness, not disputes over

underlying facts. As the panel explained, "the parties stipulated to many of the facts, but disagree as to the ultimate legal outcome of obviousness based on those facts." (Slip op. 18.) As to the scope and content of the prior art, for example, the parties agreed that benzene sulphonate was known, was covered by the '909 patent, and was discussed in publications including the Berge article that were admittedly prior art. (Slip op. 18.) The Court did not overturn the trial court's finding as to the level of ordinary skill in the art and differences between the prior art and subject matter claimed. (Slip op. 18.) As to the ultimate legal conclusion of obviousness based on those facts — the trial court was entitled to no deference.

As the panel noted, the district court discussed prima facie obviousness in the patent office but **did not make** its own findings about whether a skilled artisan would have been motivated to combine the prior art. (Slip op. 19.) Findings never made are entitled to no deference. Instead, the panel concluded as a matter of law that no reasonable finder of fact could have failed to find such motivation. (Slip op. 19–20.) If the trial court **had** found an absence of motivation to combine (and it did not), such a finding would have been clearly erroneous. Thus, contrary to Pfizer's Point #1, the panel did not violate the clear error standard, nor did it improperly reject the district court's findings.

B. The Panel Properly Considered the Inventors' Own Testimony As Corroborating What Was Already Known In the Prior Art, As This Court Has Done On Numerous Other Occasions.

Pfizer and others complain that the panel cited to the testimony of named inventors Wells and Davison to corroborate its obviousness conclusion. First, it should be noted that Pfizer chose to call both Dr. Wells and Mr. Davison as witnesses and thereby opened the door for cross examination and their admissions about what was known and expected in the art. Second, the subject of their testimony relied on by the panel was not their own insight but instead an indication of what those of ordinary skill in the art already knew. For example, Mr. Davison admitted that it "would have been a mistake" to try novel anions before ones that the FDA had previously approved (Slip Op. 22). However, the panel did not rely on just Mr. Davison's testimony to establish this point, and also relied on the testimony of Pfizer's expert, Dr. Anderson, who "similarly admitted in his testimony that it would have been logical to use Berge's list of [53] FDA-approved anions to produce a drug formulation." (Slip Op. 22). Elsewhere in its decision, the panel relied on Dr. Wells' testimony **and** the prior art **Carabateas** patent to demonstrate that one of ordinary skill in the art was capable of further narrowing the list of known pharmaceutically acceptable anions to "a much smaller group including benzene sulphonate, with a reasonable expectation of success." (Slip op. 29.)

The panel also cited to Dr. Wells' admissions on cross examination that there was a reasonable expectation, although no guarantee, that besylate would form a successful amlodipine salt with improved physicochemical properties over the maleate salt, including improved stability and non-stickiness. (Slip op. 26; A833.) However, the panel also cited to the prior art '909 patent and its "strong suggestion that any and all pharmaceutically acceptable anions would form non-toxic acid addition salts and work for their intended purpose — that is, to improve bioavailability of the active ingredient amlodipine and to improve handling and storage of amlodipine." (Slip op. 26.) The panel also relied on Pfizer's own admissions to the FDA that it was known that the besylate salt of amlodipine would work for its intended purpose: "We feel that the change in salt form [from maleate to besylate] is justified since benzene sulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine (Serentil)." (Slip op. 26.) In other words, the panel did not use only inventor testimony to support its obviousness conclusions. Instead, abundant evidence from the experts on both sides and from the prior art references compelled the panel's obviousness conclusion.

Furthermore, as this Court's precedent makes clear, there is nothing wrong, unfair, or improper about applying the inventors' own admissions of what was known and expected in the art to find obviousness. This court has previously relied on similar testimony by inventors in a number of other of cases, so this repre-

sents no departure from precedent. For example, in *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164, 77 USPQ2d 1865, 1871 (Fed. Cir. 2006), the Court relied on similar testimony that the inventor picked a particular compound because "the literature said that it might be possible to use tertiary amines [in the reaction] . . . and [it was] habitual [under the] circumstances to try various options until you get the reaction to work." *Id.* Like Dr. Wells, the inventor in *Medichem* tried to qualify that response by asserting that "she had no reason to say that there were grounds for expecting anything from the addition of tertiary amine." *Id.* However, the Court there explained that a prior art teaching that the addition of a particular compound works some of the time is sufficient to provide a motivation to use it. *Id.* at 1166–67, 77 USPQ2d at 1871 ("We wish to emphasize that this is not a case where the prior art's lack of definiteness or certainty about the result of using a tertiary amine in a specific reaction system renders the inventive subject matter 'obvious to try' but not obvious.")

The Court further explained reliance on this type of testimony in *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989):

> When [the inventor was] asked: "Isn't it also normal when you administer a potassium sparing compound along with hydrochlorothiazide a period of time, that there would be some increase in the amount of sodium excretion?", he responded: "That is a possibility. That is not an assured consequence." But, "absolute predictability of success" is not the criterion; "for obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903.

Id. at 809, 10 USPQ2d at 1847. The inventor's testimony here, that there is an expectation but no guarantee (A833), is substantially the same as that testimony used in *Merck*. Far from departing from precedent regarding an inventor's testimony, the panel was bound by precedent to decide the case as it did. Thus, contrary to Pfizer's Point #2, the panel did not improperly rely on the inventor's expectations.

C. The Panel Properly Analyzed the Scope and Content of the Prior Art In Determining Amlodipine Besylate Was Obvious.

Pfizer argues that the panel should have limited its determination of obviousness to a comparison of the properties of amlodipine besylate to those of amlodipine maleate, which Pfizer asserts was the "closest prior art." The panel expressly considered and properly rejected this argument, noting that "there was precious little evidence" to support the district court's "implicit finding" that amlodipine maleate was the closest prior art. (Slip op. 37.) The panel went on to explain that "the prior art of Schmidt, Spiegel, Carabateas, and Barth . . . evidences that one skilled in the art would expect an acid addition salt made from benzene sulphonate to have good physicochemical properties." (*Id.*) Thus, the panel properly compared amlodipine besylate to the prior art as a whole, including the numerous other instances of prior uses of the besylate salt form to enhance physicochemical characteristics of an active drug compound, to reach its obviousness conclusion.

It also is instructive to compare what Pfizer says now about the expectations for such salts with what it has said before. Now, Pfizer insists that the desirability

of the benzene sulphonate salt "cannot be determined with the salts of other drug compounds." But Pfizer **stipulated** that those references are prior art. (A250.) Pfizer itself relied on the known safety and non-toxic characteristics of those prior art besylate salts of other drug compounds besides amlodipine when it tried to justify its change from maleate to besylate to the FDA: "We feel that the change in salt form is justified since benzenesulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine." (A7687; Slip op. 26.) Pfizer also downplayed the difference between the maleate and the besylate salts to this Court, when describing the prior art '909 patent's teachings about amlodipine salts in *Pfizer v. Dr. Reddy's Labs.*, 359 F.3d 1361, 1366, 69 USPQ2d 2016, 2018 (Fed. Cir. 2004). (Slip op. 26.) There, Pfizer argued "the besylate part of the molecule has no therapeutic effect; the addition salt part of the molecule (i.e., the besylate or the maleate) is a means of delivering the amlodipine part of the molecule, which provides the therapeutic value." (A15419–20.) Thus, contrary to Pfizer's Point #3, the panel did compare the claimed subject matter to the closest prior art.

D. Whatever Practical Value Amlodipine Besylate May Have Does Not Overcome Apotex's Clear and Convincing Proof That The Compound Was Obvious and Would Be Expected To Exhibit Good Physico-Chemical Properties.

Pfizer complains that the panel failed to take into consideration the "practical value" of amlodipine besylate. But "practical value" does not impart patentability. Many inventions have practical value, but are nonetheless obvious. *See*

DyStar Textilfarben BmbH v. C.H. Patrick Co., 464 F.3d 1356, 1368, 80 USPQ2d 1641, 1651 (Fed. Cir. 2006) (creating a "product or process that is more desirable, for example, because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient . . . to enhance commercial opportunities . . . is universal— and even common-sensical."). Here, unexpectedly superior results, not just practical value, were required to overcome Apotex's strong showing that amlodipine besylate was obvious. "Pfizer has simply failed to prove that the results are unexpected." (Slip op. 38.) As the panel explained: "[a]nother defect in the district court's reasoning is its failure to recognize that by definition, any superior property must be unexpected to be considered as evidence of non-obviousness." (Slip op. 37.) The panel went on to explain that "we do not see the trial court's finding that amlodipine besylate had adequate physicochemical characteristics as sufficient to uphold the court's ultimate holding of unexpected superiority." (Slip op. 38 (emphasis in original).) Thus, contrary to Pfizer's Point #4 the panel considered Pfizer's practical value argument and properly rejected it, finding that the properties of amlodipine besylate were neither unexpected ("the '909 patent suggested – and Dr. Wells expected -- that every other potential salt form of amlodipine would be adequate for its intended purpose") nor sufficiently superior to overcome obviousness. (Slip op. 39.)

E. The Panel Correctly Applied, and Did Not Violate, the Express Language of the 35 USC § 103(a) to Find Claims 1-3 Obvious.

Pfizer ascribes error to the panel's recognition that picking the besylate salt was a matter of routine experimentation. (A943 at 675:15; A957.) However, the panel was well aware of the statutory language of § 103(a) that "[p]atentability shall not be negatived by the manner in which the invention was made," and was sensitive to "the fact that reference to 'routine testing' or 'routine experimentation' is disfavored." (Slip op. 30.)

The choice of the besylate salt was obvious before any of the test were run. Pfizer's routine testing merely **verified** the obvious choice and did not show any unexpected results from the besylate salt. As the panel explained: "However, on the particularized facts of this case, consideration of the 'routine testing' performed by Pfizer is appropriate because 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." (Slip op. 31 (underlining in original, bolding supplied).) This Court expressed a similar view in *Merck*:

> The evidence at trial showed that, though requiring time and care, the **experimentation** needed to arrive at the claimed dosages was **nothing more than routine**. "Patentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103. But 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**, viewed in light of the prior art."

874 F.2d at 809, 10 USPQ2d at 1847 (citation omitted, emphasis added).

This is not a case where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988). (Slip op. 29, *see also* A944 at 679:20–24; A964; A968–69.) Here, the prior art and nature of the problem faced provided a motivation to try the besylate and the prior art and science provided a reasonable expectation of success. As discussed above, besylate was in the genus of pharmaceutically acceptable amlodipine salts that the '909 patent taught would work. There was testimony at trial that one of ordinary skill in the art would have considered besylate as a salt candidate for amlodipine because of its acid strength, solubility, and known chemical characteristics. (A964; A968–69.) A host of other references (*e.g.*, A15239–40 (Schmidt); A15257 (Barth); A7519–20 (Berge)) taught to use the besylate salt to improve solubility and stability. This prior art provides a reasonable expectation that the besylate would be an effective amlodipine salt. *O'Farrell*, 853 F.2d at 904, 7 USPQ2d at 1680 ("For obviousness under § 103, all that is required is a reasonable expectation of success."); *In re Corkill*, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985) ("Although Uytterhoeven declared that it **cannot be predicted** how any candidate will work in a detergent composition, but that it **must be tested**, this **does not overcome Corey's teaching that hydrated zeolites will**

work.") (emphasis added). The routine testing discussed in the panel decision simply confirmed what already would have been expected from the prior art. This same testing verified that other amlodipine salts tested, most notably, the toluene-sulphonate (tosylate) also would result in a commercially viable amlodipine salt. (A8095 "the besylate **and tosylate** salts match up to the basic criteria for a pharmaceutically acceptable salt of Amlodipine. **(Good solubility and stability, non–hygroscopic and low sticking propensity.)**" [emphasis added].) "These types of experiments used by Pfizer's 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." (Slip op. 31, underlining in original.) Thus, this is not a case like the folklore about Edison methodically and exhaustively testing thousands upon thousands of potential materials from which to make a light filament. Here, the prior art and nature of the problem faced provided a motivation to try the besylate and the prior art and science provided a reasonable expectation of success. Contrary to the petitioner's Point 5, the panel did not ignore the language of § 103 regarding the manner of invention.

F. The Panel Correctly Held That Amlodipine Besylate Was Obvious, Not Merely Obvious to Try.

Pfizer also accuses the panel of applying an "obvious to try" rather than an obviousness standard. The panel did no such thing. Presumably the panel was

aware of that principal, because it devoted eight pages of its opinion to and cited some eighteen cases in explaining why the subject matter here was not just obvious to try, but instead obvious. (Slip op. 27–34.) As this court has previously cautioned, the "meaning of this maxim is sometimes lost." *O'Farrell*, 853 F.2d at 903, 7 USPQ2d at 1680. Any subject matter that is obvious under § 103 "would also have been, in a sense, obvious to try." *Id.* That does not impart patentability.

The panel already discussed the perceived tension between the principles that "obvious to try" is not enough, but "absolute predictability" is not required. (Slip op. 27.) As the court correctly concluded, the proper way to determine obviousness in any particular case, including this one, is not blind adherence to an artificial list of rules and exceptions. (*See* Slip op. 30, *citing In re Yates*, 663 F.2d 1054, 1056 n.4, 211 USPQ 1149, 1151 n.4 (C.C.P.A. 1981). Instead, the correct analysis is to apply the proper, approved analytical framework to the unique facts of each case as was done here, with due consideration first to (i) scope and content of the prior art, (ii) level of ordinary skill in the art, (iii) differences between the claimed subject matter and the art, and (iv) secondary factors, and also to (i) motivation to combine and (ii) reasonable expectation of success. Where, as here, the panel has scrupulously followed that analytical framework, cries of "obvious to try" offer no principled distinction between this case and any other. Thus, contrary

to Pfizer's Point #6, the panel did not apply or rely on an impermissible "obvious to try" standard.

II. Even If Apotex Had Not Proven Amlodipine Besylate Was Obvious, and It Did, the Patent Is Unenforceable Because Pfizer Misled The PTO.

The panel determined that Apotex's inequitable conduct arguments were moot as a result of its obviousness determination. (Slip op. 3.) However, if Pfizer's petition for rehearing or rehearing en banc is granted, then unenforceability must be revisited.

As demonstrated in the record below and in Apotex's briefing to this Court, Pfizer lied to the PTO about every criteria on which it based its claimed patentability. Pfizer's false statements and misrepresentations to the PTO go to the very heart of what it asserts are the unexpected results supporting patentability. In its patent application, Pfizer identified "four physicochemical criteria" that it said a pharmaceutically acceptable salt "must satisfy" "to be suitable" for commercialization. (A1795 col. 2:10–14.) Pfizer claimed that **only** besylate satisfied all four criteria, (A1795 col. 2:6–21), but Pfizer misled the PTO about every single one of those criteria and about its ultimate conclusion, as summarized below.

What They Told the PTO	What They Told Management	What We Know Now
Besylate is unique, and the "only" salt satisfying four stated criteria for a commercially suitable	Tosylate also satisfies each of the criteria and is also suitable for a commercial drug product.	Besylate is not uniquely suitable, but instead is one of several pharmaceutically acceptable salts

drug product. (A1795)	(A8095)	Pfizer could have commercialized.
Besylate's solubility is 4.6 mg/ml, giving a pH of 6.6, even higher than maleate's 4.5 mg/ml giving a pH of 4.8. (A1795)	Besylate's solubility is 3.6 mg/ml, giving a pH of 4.5, not as high as the maleate's solubility of 4.5 mg/ml giving pH of 4.8. (A1928)	Besylate is slightly soluble, which is no better than other salts and Pfizer says pH does not really matter.
Stability tests on actual tablets and capsules with specific formulations. (A1795)	Stability testing on compacts and blends. (A855)	Pfizer never did stability testing on tablets or capsules or use those formulations.
Short term, high-temperature tests proved besylate's stability. (A1796)	Short-term, high temperature studies may not be predictive of longer term storage at realistic temperatures. (A1921)	More reliable, longer term testing which Pfizer withheld showed that other amlodipine salts, including tosylate and mesylate, were just as stable as besylate.
Besylate is not hygroscopic, based on three days of testing. (A1796)	Besylate is hygroscopic, as shown in testing beyond three days reported to management but not the patent office. (A15035)	Besylate does take on water and tends to form a hydrate (i.e. is hygroscopic under Pfizer's definition).
Pfizer tested stickiness for 1050 tablets in batches of 50, 100, 150, 200, and 250. (A1796)	Pfizer used one batch of 50 tablets, testing every 10th tablet — or at most 150 tablets total. (A837, A880)	Pfizer did not test 1050 tablets, but instead only 50.

CONCLUSION

For the foregoing reasons, Apotex requests that the Court deny Pfizer's petition for rehearing and rehearing en banc and that it issue its mandate issue on an expedited basis.

Respectfully Submitted,

Date: April 27, 2007

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CERTIFICATE OF SERVICE

United States Court of Appeals
Federal Circuit
No. 2006-1261
----------)
PFIZER, INC.,
Plaintiff-Appellee,
v.
APOTEX INC.,
Defendant-Appellant.
----------)

I, John C. Kruesi, Jr., being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

I am retained by WELSH & KATZ, LTD., Attorneys for Amicus Curiae, Generic Pharmaceutical Association.

That on the **27th Day of April, 2007** I served the within **ANSWER TO PETITION OF PLAINTIFF-APPELLEE PFIZER INC. FOR REHEARING AND REHEARING EN BANC** upon:

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April 27, 2007