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 Civil Action No. 03-CV-5289
Judge James M. Rosenbaum

BRIEF OF *AMICUS CURIAE* PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF THE COMBINED PETITION OF PLAINTIFF-APPELLEE PFIZER INC. FOR REHEARING AND REHEARING *EN BANC*

Christopher N. Sipes
Richard L. Rainey
Scott C. Weidenfeller
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
202-662-6000

Counsel for Amicus Curiae
Pharmaceutical Research and
Manufacturers of America

Dated: April 12, 2007

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel for *Amicus Curiae* Pharmaceutical Research and Manufacturers of America ("PhRMA") certifies the following:

1. The full name of every party or *amicus curiae* represented by me is:

Pharmaceutical Research and Manufacturers of America ("PhRMA").

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:

Pharmaceutical Research and Manufacturers of America.[1]

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the *amicus curiae* represented by me are:

None.

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

PhRMA did not appear in the trial court. Before this Court, PhRMA is represented by Covington & Burling LLP, Washington, D.C. and the following attorneys with that firm:

Christopher N. Sipes
Richard L. Rainey
Scott C. Weidenfeller

Christopher N. Sipes

Dated: April 12, 2007

[1] PhRMA members are listed at http://www.phrma.org/about_phrma/member_company_list/members. Plaintiff-Appellee Pfizer Inc. is a member of PhRMA.

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STATUTE

INTEREST OF THE *AMICUS CURIAE*

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies. PhRMA's members, which invested an estimated $43 billion toward the discovery and development of new medicines in 2006, rely on strong and clear patent rights to protect their research investments. A meaningful part of that research is directed toward discovering new formulations for pharmaceutical compounds, as opposed to new compounds themselves.

The patent at issue relates to an important improvement in the formulation of the drug amlodipine. Although it was known that amlodipine could be made in a pharmaceutically acceptable salt form, the inventor in this case found that common pharmaceutically acceptable salts of amlodipine, such as the maleate salt, lack certain important characteristics needed to make their manufacture and use commercially acceptable. For example, the amlodipine maleate salt form is sticky and exhibits poor shelf stability, so it cannot be marketed in tablet form. After testing many of the 53 known pharmaceutically acceptable salt anions, the inventor found one salt, amlodipine besylate, that unexpectedly solved those problems, *see* slip op. at 5-6, providing a "unique combination of good formulation properties," U.S. Patent No. 4,879,303, col. 1, ll. 33-34. The result is a product

that has benefited millions of people suffering from high blood pressure, and which no doubt has saved countless lives. As three district courts, including the one below, have properly recognized, this improvement invention was not obvious, and indeed, laborious testing of numerous anions was required to find it.

The panel nonetheless disregarded the district court's findings of fact and erroneously held that the claimed formulation was obvious because the salt "has no effect on the therapeutic effectiveness of the active ingredient" and because the particular anion used to form the salt was known in the prior art to form pharmaceutically acceptable salts with other active pharmaceutical ingredients used for other purposes. Slip op. at 32. This holding inappropriately requires that patentability in the pharmaceutical field must be derived from improvements in therapeutic effects, rather than on improvements in other important properties, such as safety, stability, and ease of use. *See, e.g., In re Ruschig*, 343 F.2d 965, 977 (CCPA 1965) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing.") (quoting *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963)).

In the pharmaceutical and chemical arts, many valuable inventions lie in the recognition that a particular chemical entity within a known class of compounds has unique properties particularly suited to a given application. Such inventions should not be denigrated, as the panel does, merely because the entity

was found, and its unexpected properties identified, by "routine" experimentation. Not surprisingly, the panel recognized that "the pharmaceutical industry may be particularly adversely impacted by application of" its standard in this case. Slip op. at 29. We agree, and urge immediate reversal of the panel's decision.

ARGUMENT

I. THE PANEL IMPROPERLY IGNORED THE INNOVATION NECESSARY FOR SUCCESSFUL DRUG FORMULATION.

A. The Panel's Focus On The Effectiveness Of The Active Ingredient Was Too Narrow.

The panel "h[e]ld that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where . . . the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt." Slip op. at 32. The panel further held that, in this case, "the prior art heavily suggest[ed]" the besylate acid addition salt because (1) a prior art reference "clearly pointed the skilled artisan to 53 anions that, as of 1974, were pharmaceutically acceptable," *id.* at 29; (2) another prior art reference and an inventor's testimony showed that the list could be further narrowed, *id.*; and (3) several prior art references taught the besylate salt forms of other pharmaceutical compounds, *id.*; *see also id.* at 37.

The panel thus narrowly focused on the anion's effect only on "the therapeutic effectiveness of the active ingredient," not the anion's effect on other

properties of the formulation, such as solubility, nonhygroscopicity, stability, and ability to be formed into tablets on a commercial scale tablet press, and the salt's combination of properties that make it suitable for a safe, effective, and commercializable drug product. As a result, the panel failed to credit those additional properties that could make a formulation non-obvious, and failed to follow clear precedent. *See, e.g.*, *In re Cescon*, 474 F.2d 1331, 1334 (CCPA 1973) ("It has long been our position that a compound and its properties are inseparable and that no property can be ignored in determining patentability over the prior art."); *Ruschig*, 343 F.2d at 977; *Papesch*, 315 F.2d at 391.

Indeed, as the panel itself noted, this Court has recently recognized the unpredictability of salt formation, *id.* at 28 (citing *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed. Cir. 2006)), and a long line of precedent holds that mere disclosure of a genus of pharmaceutical compounds does not render obvious the selection of a particular species within that genus that has beneficial properties, where, as in this case, there is no disclosure in the prior art directing a person of ordinary skill in the art to select that species, *see* Pfizer Pet. Reh'g & Reh'g *En Banc* at 16. *See, e.g.*, *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 350-51 (Fed. Cir. 1992); *see also Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985). The panel's decision to the contrary here was thus improper and should be reconsidered to make clear that other

superior properties, as well as the combination of properties as a whole, of a formulation can render a claim to an improved formulation non-obvious.

B. The Panel Improperly Treated The Experimentation Involved In Formulating A Pharmaceutical Product As Routine "Verification" Of The Product's Properties.

The panel also improperly failed to recognize the important innovation necessary to drug product formulation and design, holding that experimentation to determine which formulation of a pharmaceutical product is superior is "routine testing" that merely verifies expected results. *See* slip op. at 29-31. Creating a drug formulation does not consist merely of verifying that a particular salt will form from the combination of a free base and an anion. Rather, the process involves (among other things) substantial investigation to discover which form of an active moiety has superior properties. By focusing only on the question whether the particular salt of the active moiety could be formed and would be bioavailable, the panel ignored the innovation necessary to develop a superior drug product from a compound.[2] Indeed, that Plaintiff-Appellee Pfizer Inc. ("Pfizer"), an established and successful drug pioneer, itself in this case initially developed a different salt and felt the need to switch in mid-course, shows

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[2] For example, the panel did not take into account in its obviousness analysis the inventor's testimony that the outcome of salt formation is unpredictable and that he did not believe that any of the alternative acids would necessarily solve the problem with the maleate salt. *See* Pfizer Pet. Reh'g & Reh'g *En Banc* at 9.

the difficulty in pharmaceutical development—an indication of non-obviousness (failure) erroneously rejected by the panel. *Id.* at 34-35.

The panel itself noted that "one skilled in the art would expect [a range of 53 anions] to provide salts having a range of properties, some of which would be superior, and some of which would be inferior," to those of a known salt. *Id.* at 38. Thus, faced with a variety of anions from which to choose, inventors must experiment to determine which anion forms a salt with superior properties for formulation as a pharmaceutical product and could not be sure that a salt with the right combination of properties even existed. Whether it might be obvious to try formulations of salts based on known anions, the mere disclosure of a particular compound and a variety of anions that might form salts with that compound is insufficient to render a new salt formulation obvious because that "disclosure itself does not contain a sufficient teaching of how to obtain the desired result," *i.e.*, the salt formulation with superior properties. *In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990); *see also In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Moreover, the panel's reliance on the "routine testing" required to "verify" the properties of particular salt formulations (even if that were a proper characterization) is inconsistent with both 35 U.S.C. § 103(a), which states that "[p]atentability shall not be negatived by the manner in which the invention was made," and precedent holding that the fact that an invention is obtained through

"routine testing" or "routine experimentation" does not render the invention obvious. *See, e.g., In re Yates*, 663 F.2d 1054, 1056 n.4 (CCPA 1981); *In re Saether*, 492 F.2d 849, 854 (CCPA 1974); *In re Fay*, 347 F.2d 597, 602 (CCPA 1965).

Although the panel attempted to avoid this precedent by stating that, "on the *particularized facts of this case*, consideration of the 'routine testing' performed by Pfizer is appropriate," slip op. at 31 (emphasis in original), citing *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989), *Merck* is inapposite. In *Merck*, this Court held that a claimed combination of two compounds known to be effective as diuretics was obvious. *See id.* The inventor testified that an increase in the amount of sodium excretion was expected from that combination; only the amount of that increase was unknown. *See id.* To the contrary, in this case, the panel erroneously put weight on its conclusion that some salt formulations would be superior and others would be inferior to the known amlodipine maleate. Even were this true, Pfizer had to perform testing to determine whether a particular salt formulation was superior, not merely the extent to which it was superior. Accordingly, the testing at issue here was of a very different kind and quality than the testing at issue in *Merck*.

II. THE PANEL ENGAGED IN IMPROPER FACT FINDING.

A. The Panel Improperly Engaged In *De Novo* Appellate Review Of The Fact Findings Underlying The District Court's Judgment.

The panel engaged in a "de novo assessment of the determination below on obviousness in view of all of the evidence," slip op. at 40, rather than limiting its review to determining whether the district court's fact findings regarding obviousness were clearly erroneous. In doing so, the panel did not merely reverse the district court's ruling that the claims at issue were not obvious, it went further and made its own fact findings regarding at the very least *prima facie* obviousness. *See, e.g., id.* at 34 ("[W]e hold that Apotex introduced clear and convincing evidence that a skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine at the time the invention was made."); *see also id.* at 20-22, 24, 28 (finding evidence "clear and convincing").

However, as the Supreme Court has held, that is not the proper route for an appellate court to take in such a situation: "If the Court of Appeals believed that the District Court had failed to make findings of fact essential to a proper resolution of the legal question, it should have remanded to the District Court to make those findings." *Icicle Seafoods, Inc. v. Worthington*, 475 U.S. 709, 714 (1986); *see also Zenith Corp. v. Hazeltine*, 395 U.S. 100, 123 (1969) ("In applying the clearly erroneous standard to the findings of a district court sitting without a

jury, appellate courts must constantly have in mind that their function is not to decide factual issues de novo.").

Moreover, the Supreme Court has held that this Court must properly apply the clearly erroneous standard of Federal Rule of Civil Procedure 52(a) to district courts' obviousness inquiries, rather than "substituting its view of factual issues for that of the District Court." *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 809-11 (1986). The panel's *de novo* fact finding on appeal was therefore inappropriate, and the panel should have remanded the case to the district court for further analysis in accordance with the panel's standard.[3]

B. The Panel Improperly Used The Insight Of One Of The Inventors To Determine What Would Have Been Obvious To A Person Of Ordinary Skill In The Art.

Moreover, the panel improperly relied on the inventors' insight to show what a person of ordinary skill in the art would have expected about the properties of the amlodipine besylate salt. *See, e.g.*, slip op. at 25 ("Dr. Wells readily compiled a list of seven alternative anions—including the besylate—each of which he expected would form an amlodipine acid addition salt."); *id.* at 38

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[3] The misguided nature of such fact finding on appeal is demonstrated by the fact that the panel found that a "reasonable fact-finder" could only conclude that the skilled artisan would have had a motivation to combine and a reasonable expectation of success, slip op. at 20, 24, even though three district courts have found the claims not obvious after holding trials, *see Pfizer, Inc. v. Mylan Labs*, No. 02-CV-1628, slip op. at 38-41 (W.D. Pa. Feb. 27, 2007); *Pfizer Inc. v. Synthon Holdings, B.V.*, No. 05-CV-0039, slip op. at 25-26 (M.D.N.C. Aug. 31, 2006); *Bench Order Tr.*, No. 03-CV-5289, at 23:7-9 (N.D. Ill. Jan. 18, 2006).

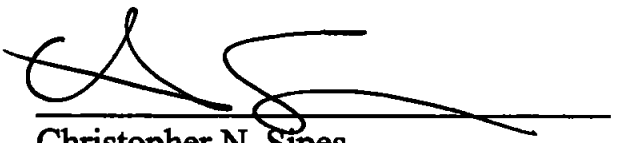
("Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate."); *id.* at 39 ("Amlodipine besylate is obvious on the facts of this case because the '909 patent suggested—and Dr. Wells expected—that every other potential salt form of amlodipine would be adequate for its intended purpose . . . .").

Such reliance on the inventor's teachings and knowledge is directly contrary to established precedent. *See Interconnect Planning*, 774 F.2d at 1138 ("The invention must be evaluated not through the eyes of the inventor, who may have been of exceptional skill, but as by one of 'ordinary skill.'"); *In re Shuman*, 361 F.2d 1008, 1012 (CCPA 1966) ("It is impermissible to first ascertain factually what [the inventors] did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants' invention from such prior art."); *see also In re Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002) ("It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to '[use] that which the inventor taught against its teacher.'") (alteration in original). The panel's decision was thus improper.

CONCLUSION

For the foregoing reasons, *amicus curiae* PhRMA respectfully requests that the Petition for Rehearing and Rehearing *En Banc* be granted.

Respectfully submitted,



Christopher N. Sipes
Richard L. Rainey
Scott C. Weidenfeller
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
202-662-6000
Counsel for Amicus Curiae Pharmaceutical Research and Manufacturers of America

CERTIFICATE OF COMPLIANCE

This brief complies with the page limitations of Federal Circuit Rules 35(g) and 40(g) because this brief does not exceed ten (10) pages, excluding the parts of the brief exempted by Federal Circuit Rules 35(c)(2) and 40(c)(1). This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2003 in fourteen-point Times New Roman font.

Christopher N. Sipes
Counsel for Amicus Curiae
Pharmaceutical Research and
Manufacturers of America