NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

ICOS CORPORATION,
Appellant

v.

ACTELION PHARMACEUTICALS LTD,
Appellee

2017-1017, 2017-1018

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2015-00561, IPR2015-00562.

Decided: April 18, 2018

MARK J. FELDSTEIN, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for appellant. Also represented by JASON LEE ROMRELL, YIEYIE YANG; CHARLES E. LIPSEY, J. DEREK MCCORQUINDALE, Reston, VA; MARK STEWART, Eli Lilly and Company, Indianapolis, IN.

MARK EDWARD WADDELL, Loeb & Loeb LLP, New York, NY, argued for appellee. Also represented by

KATHLEEN GERSH, WARREN K. MACRAE; ALEXANDRA CAVAZOS, Los Angeles, CA.

Before MOORE, LINN, and CHEN, *Circuit Judges*.

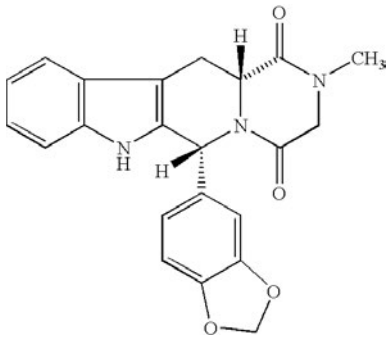
MOORE, *Circuit Judge*.

ICOS Corporation appeals the Patent Trial and Appeal Board's inter partes review ("IPR") decisions holding claims 1–32 of U.S. Patent No. 7,182,958 and claims 1–11 of U.S. Patent No. 6,821,975 would have been obvious over PCT Application WO 97/03675 ("Daugan"), PCT Application WO 96/38131 ("Butler"), U.S. Patent No. 4,721,709 ("Seth"), and Wadke, et al., *Preformulation Testing*, *in* Pharmaceutical Dosage Forms (Herbert A. Lieberman, et al., eds., 1989) ("Wadke"). Because the Board did not err in its obviousness analysis and substantial evidence supports its underlying fact findings, we affirm.

BACKGROUND

The '958 patent is directed to pharmaceutical formulations containing micronized tadalafil. Claim 1, which is representative, reads:

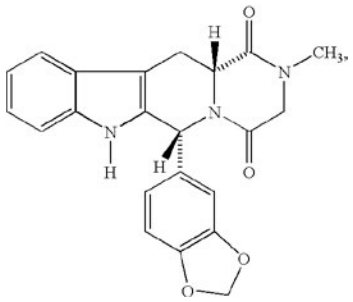
> 1. A pharmaceutical formulation comprising an active compound having the structural formula



> wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles of the said compound have a particle size of less than about 40 microns; about 50% to about 85%, by weight, of a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

The '975 patent is directed to micronized tadalafil in a free-drug particulate form. Claim 1, which is representative, recites:

> 1. A free drug particulate form of a compound having a formula



> or pharmaceutically acceptable salts and solvates thereof, comprising particles of the compound wherein at least 90% of the particles have a particle size of less than about 40 microns.

Actelion Pharmaceuticals Ltd. ("Actelion") filed two petitions for inter partes review. The first, IPR2015-00561, alleged claims 1–32 of the '958 patent would have been obvious over the combination of Daugan, Butler, Seth, and the common pharmaceutical knowledge reflected in Wadke and two other references. The second, IPR2015-00562, alleged claims 1–11 of the '975 patent would have been obvious over Daugan, Butler, Seth, and

Wadke, and additionally in view of U.S Patent No. 4,344,934. The Board instituted IPR of all claims.

Daugan discloses a compound having the structural formula depicted in the claims, i.e., tadalafil, and the excipients included in claim 1 of the '958 patent. J.A. 3811. Butler discloses that tadalafil is poorly water soluble and teaches a process of preparing a solid dispersion of tadalafil and a pharmaceutically acceptable carrier or excipient. J.A. 3873-74. Seth discloses that when poorly soluble hydrophobic drugs are used in solid dosage forms, their rate of dissolution is often slow, and a "frequently used method to overcome such problems is to finely grind or 'micronize' drug substances to reduce their particle-size." J.A. 3918. Wadke discloses that "[i]t is now generally recognized that poorly soluble drugs showing a dissolution-rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided state than as coarse material," and "[g]rinding should reduce coarse material to, preferably, the 10- to 40- [micron] range." J.A. 4004–05.

In the '958 IPR, the Board found a motivation to combine Butler's teaching that tadalafil has poor solubility with Seth's teaching that compounds with low solubility generally also have a slow dissolution rate, and with Seth and Wadke's teachings that reducing particle size through micronization can increase dissolution rate. It found ICOS had not shown that a preformulation analysis would have deterred an ordinarily skilled artisan from pursuing micronization. It found that, while Seth recognizes disadvantages to micronization, those disadvantages would not have stopped ordinarily skilled artisans from using the technique. It found there was a reasonable expectation of success in combining the teachings of these references, and rejected ICOS' claim of unexpected results. It found Daugan teaches the specific required excipients in claim 1 in a limited number of examples.

In the '975 IPR, the Board found Daugan, Butler, Seth, and Wadke disclose every limitation of the challenged claims. It found the general knowledge that tadalafil is poorly water soluble would have motivated an ordinarily skilled artisan to micronize it to improve its absorption and an ordinarily skilled artisan would have had a reasonable expectation of success in doing so. It found Daugan, Butler, Seth, and Wadke do not teach away from micronization.

Based on these facts, in each instance, the Board concluded that the claims would have been obvious. ICOS appeals. It argues the Board improperly substituted its own obviousness arguments for those in the petition and improperly shifted the burden to ICOS to show nonobviousness. It argues the references do not provide a motivation to combine or a reasonable likelihood of success. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review the Board's determination of obviousness de novo and its underlying factual findings for substantial evidence. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Board decisions must be set aside if they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706.

I

As discussed above, the Board made several fact findings in support of its conclusions of obviousness. On appeal, ICOS challenges the Board's findings that there was a motivation to micronize tadalafil, that a skilled artisan would have had a reasonable expectation of success in doing so, and that Daugan teaches the claimed combination of excipients. Substantial evidence supports each of these findings.

Substantial evidence supports the Board's findings that the prior art discloses the compound tadalafil, the

micronization of drugs to less than about 40 microns, and a motivation to combine these teachings. Daugan discloses tadalafil. Wadke teaches the micronization of drug particles, stating, "[g]rinding should reduce coarse material to, preferably, the 10- to 40- [micron] range." J.A. 4004–05. Butler teaches tadalafil is poorly water soluble, and Seth teaches that poorly water soluble drugs often also have slow dissolution. Both Seth and Wadke further disclose that micronization solves dissolution problems. J.A. 3918 (A "frequently used method to overcome such problems is to finely grind or 'micronize' drug substances to reduce their particle-size."); J.A. 4004–05. In light of this prior art, substantial evidence supports the finding that one of ordinary skill would have been motivated to micronize tadalafil to less than about 40 microns.

Substantial evidence also supports the Board's findings that a skilled artisan would have had a reasonable expectation of success in combining these teachings to micronize tadalafil. Actelion's expert testified that even if tadalafil's absorption was solubility-limited, a skilled artisan would still have considered particle size reduction useful for increasing dissolution rate and improving absorption.

While ICOS argues the prior art taught away from micronization, substantial evidence supports the Board's finding that it did not. Although Butler discloses coprecipitation as a solution to tadalafil's poor solubility, the Board credited Actelion's expert's testimony that Butler does not suggest that micronization would not work but instead simply chooses another possible solution. While Seth recognized problems with agglomeration when micronizing, the Board similarly credited Actelion's expert's testimony that there were recognized solutions in the art. The Board determined Wadke does not teach a sequential approach that favors coprecipitates over micronization but instead describes two alternative ap-

proaches and recognizes particle size reduction was the "most commonly employed practice." J.A. 4022.

Substantial evidence also supports the Board's finding that an ordinarily skilled artisan would have combined the claimed excipients recited in claim 1 of the '958 patent. Claim 1 requires: (1) about 50% to about 85%, by weight, of a water-soluble diluent; (2) a lubricant; (3) a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and (4) a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof. Each of these limitations is present in Daugan. Examples A1 and B2 in Daugan disclose oral formulations of tadalafil containing lactose, which Actelion's expert testified is a water-soluble diluent and is present in the examples at 59.3% and 70.5%, by weight. Examples A1, A2, B1, and B2 all disclose the use of forms of magnesium stearate, which Actelion's expert testified was a commonly used lubricant. Example B1 discloses the use of polyvinyl pyrollidone, which Actelion's expert testified is another name for providone. Daugan specifically discloses tadalafil in combination with the disintegrant croscamellose sodium in example B1 and with the disintegrant crosprovidone in examples A1 and A2. In short, example B1 discloses all of the claimed excipients except the diluent, which is disclosed in examples A1 and B2, and which Actelion's expert testified was commonly used in oral tablets. The Board's finding that one of skill in the art would have combined the claimed excipients with micronized tadalafil is, therefore, supported by substantial evidence.

II

ICOS argues the Board improperly substituted its own obviousness arguments in place of Actelion's arguments. For example, ICOS argues that in the '958 IPR, the Board improperly relied on Lawrence X. Yu, *An*

Integrated Model for Determining Causes of Poor Oral Drug Absorption, 16 Pharmaceutical Research 1883 (1999) ("Yu"), a reference that is not in the prior art, to conclude that one of skill in the art would not necessarily have engaged in rational formulation and preformulation testing. ICOS argues this violates 35 U.S.C. § 316(e), which places the burden on the petitioner to establish unpatentability, because Actelion never cited this portion of Yu and did not argue one skilled in the art would have acted irrationally. It also argues this violates due process under the APA because the Board relied on a new theory of obviousness for the first time in its final written decision. The record, however, indicates that ICOS introduced Yu as rebuttal evidence to support its theory of rational design. The Board's determination that, read in its entirety, Yu does not clearly support the position for which ICOS introduced it in rebuttal was not in error. The Board did not use Yu to teach elements of the claim or to supply the motivation to combine. Its findings regarding Yu are limited to its rejection of ICOS' arguments regarding this reference.

While ICOS argued Wadke implied a sequential practice of first trying to increase solubility and then, if that fails, trying micronization, Actelion argued Wadke taught micronization as a solution. The Board did not err in resolving the parties' dispute as to the teaching of Wadke. The Board's factual determination as to which interpretation to adopt does not constitute improperly raising a new argument.

Likewise, in the '958 IPR, the Board did not err in citing Modern Pharmaceutics (Gilbert S. Banker & Christopher T. Rhodes eds., 3d ed.) ("Banker") in its discussion of micronization during formulation. ICOS first raised at the hearing the argument that Wadke is irrelevant to formulation design because it is titled "Preformulation Testing." Unlike in *Honeywell Int'l Inc. v. Mexichem Amanco Holding SA*, 865 F.3d 1348, 1358 (Fed. Cir.

2017), here, the Board did not rely on a new ground of rejection not previously raised. Although Actelion cited Banker for a different proposition, the Board relied on Banker to support a finding responding to ICOS' late-raised interpretation of Wadke.

ICOS argues the Board raised new arguments to side-step Seth's teaching away from micronization. In this case, the Board did not err in considering the testimony of ICOS' expert Dr. Byrn in determining that read as a whole, Seth did not teach away. The Board was free to consider this rebuttal evidence.

CONCLUSION

Based on the Board's findings that each limitation was in the prior art, the prior art provided a motivation to combine these elements in the manner claimed, and there was a reasonable expectation of success in doing so, we see no error in the Board's conclusions of obviousness. We have considered ICOS' remaining arguments and find them unpersuasive. We therefore affirm the Board's conclusion that claims 1–32 of the '958 patent and claims 1–11 of the '975 patent would have been obvious over Daugan, Butler, Seth, and Wadke. The judgments of the Board are affirmed.

AFFIRMED