NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

APOTEX INC.,
Appellant

v.

WYETH LLC,
Appellee

2015-1871

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2014-00115.

Decided: August 16, 2016

JOHN J. MOLENDA, Steptoe & Johnson, LLP, New York, NY, argued for appellant. Also represented by ROBERT GREENFELD; KATHERINE H. JOHNSON, Chicago, IL.

DAVID I. BERL, Williams & Connolly LLP, Washington, DC, argued for appellee. Also represented by STANLEY E. FISHER, ADAM D. HARBER, THOMAS H.L. SELBY, SARA KAISER CREIGHTON.

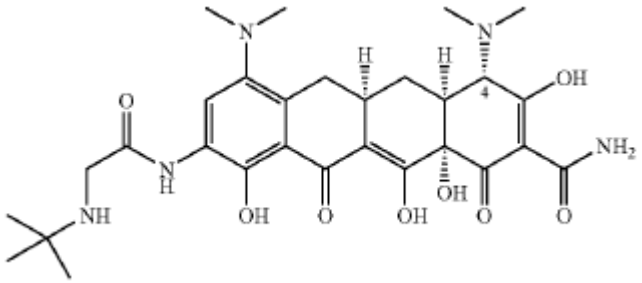
Before LOURIE, WALLACH, and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Apotex Inc. appeals from the U.S. Patent and Trademark Office Patent Trial and Appeal Board ("the Board") final written decision in an *inter partes* review concluding that claims 1–23 of U.S. Patent 7,879,828 ("the '828 patent") are not unpatentable as obvious. *See Apotex Inc. v. Wyeth LLC*, No. 2014-00115, 2015 WL 1848261, at *14 (P.T.A.B. Apr. 20, 2015). For the reasons that follow, we affirm.

BACKGROUND

Wyeth LLC owns the '828 patent, directed to a composition comprising tigecycline, a suitable carbohydrate, and an acid or buffer. '828 patent col. 1 ll. 10–11. Tigecycline is a known antibiotic in the tetracycline family, *id.* col. 1 ll. 22–23, with the following structure:



see, e.g., *id.* col. 2 (formula 1). "It may be used as a treatment against drug-resistant bacteria," and often "work[s] where other antibiotics have failed." *Id.* col. 1 ll. 23–25.

In solid and solution form, tigecycline experiences two significant forms of degradation. At basic pH, tigecycline primarily undergoes oxidation. *See id.* col. 2 ll. 25–27; *id.* col. 2 ll. 31–33 ("[Tigecycline] possesses a phenol moiety, and it is well known in the art of organic chemistry that phenols are particularly prone to oxidation."). As the pH decreases, however, oxidation slows down, and epimeriza-

tion emerges as the "predominant degradation pathway." *See id.* col. 2 ll. 45–50. Tigecycline and its epimer differ in one respect: "[i]n tigecycline, the N-dimethyl group at the 4 carbon is cis to the adjacent hydrogen," whereas in the epimer, the "N-dimethyl group" and the adjacent hydrogen are trans to one another. *See id.* col. 3 ll. 16–19. Because of that structural difference, the epimer lacks the antibacterial efficacy of tigecycline, and is thus "an undesirable degradation product." *See id.* col. 3 ll. 19–22.

The invention of the '828 patent lessens both of the above-mentioned degradation pathways, and provides for a stable tigecycline composition in solid and solution form. *Id.* col. 1 ll. 7–10; *id.* col. 4 ll. 49–51. In particular, "[t]he inventive compositions" comprise tigecycline, an acid or a buffer, and a suitable carbohydrate. *See, e.g.*, *id.* col. 1 ll. 10–13. According to the specification, the acid minimizes oxidative degradation, and the carbohydrate stabilizes the tigecycline against epimer formation at acidic pH. *See id.* col. 4 ll. 56–59.

The '828 patent contains 23 composition claims. *See id.* col. 14 l. 35–col. 16 l. 10. For purposes of this appeal, independent claim 1 is representative:

> 1. A composition comprising tigecycline, lactose, and an acid selected from hydrochloric acid and gentisic acid, wherein the molar ratio of tigecycline to lactose is between about 1:0.2 and about 1:5 and the pH of the composition in a solution is between about 3.0 and about 7.0.

Id. col. 14 ll. 35–39. Claim 12 is identical to claim 1 but is limited to hydrochloric acid. *See id.* col. 14 ll. 62–65. The remaining dependent claims further require a lyophilized composition (claim 2); a solid form composition (claims 3 and 18–22); narrower pH ranges (claims 4, 5, 10, 11, and 14–17); and narrower molar ratios of tigecycline to lactose (claims 9 and 13). *See, e.g.*, *id.* col. 14 l. 35–col. 16 l. 10.

In March 2013, Apotex filed a petition to institute *inter partes* review of the '828 patent. The Board instituted review based on one ground: that claims 1–23 would have been obvious over the combination of Chinese Patent Publication No. 1390550A ("CN '550"); V. Naggar et al., *Effect of Solubilizers on the Stability of Tetracycline*, 29 PHARMAZIE 126 (1974) ("Naggar"); and E. Pawelczyk et al., *Kinetics of Drug Decomposition: Part 74: Kinetics of Degradation of Minocycline in Aqueous Solution*, 34 POL. J. PHARMACOL. PHARM. 409 (1982) ("Pawelczyk").

In its final written decision, the Board evaluated the relevant prior art of record and made the following factual findings. First, the Board found that CN '550[*] discloses a minocycline-based powder injection, acknowledging that minocycline is a tetracycline antibiotic. *Apotex*, 2015 WL 1848261, at *4. The powder injection comprises "minocycline hydrochloride, . . . [a] lyophilized powder supporting agent, and a suitable amount of a pH adjusting agent." *Id.* The powder supporting agent can be lactose, and the "pH adjusting agent is an inorganic acid, such as hydrochloric acid." *Id.* The composition is stable against "degradation by light, heat, oxygen, and water." *See id.* at *8.

Next, the Board found that Pawelczyk addresses the stability of minocycline in solutions over a broad range of pHs, specifically "teach[ing] that oxidation is the predominant minocycline degradation process above pH 5." *Id.* at *5. Last, the Board found that Naggar addresses the rate

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[*] In its decision to institute, the Board relied on an incorrect translation of CN '550. *See Apotex*, 2015 WL 1848261, at *3–4. Apotex submitted a corrected translation in response to Wyeth's objections, and the Board relied on that corrected translation in its final written decision. *See id.* at *4. Discrepancies between the two translations are not relevant to this appeal. *See* Appellant's Br. 11 n.4.

of tetracycline epimerization, specifically teaching that "at a pH of 2–6, tetracycline undergoes a reversible epimerization at the C4 dimethylamino group." *Id.* Further, the Board found that Naggar teaches that such epimerization occurs "most rapidly at a pH of 3–4," and that solubilizers, such as polysorbate 20, urea, and thiourea, help stabilize tetracycline against epimerization. *Id.*

After making those factual findings, the Board concluded that the combination of CN '550, Naggar, and Pawelczyk did not render the claims of the '828 patent unpatentable as obvious. It first reasoned that Apotex failed to explain why a skilled artisan "would have substituted tigecycline for minocycline in the CN '550 composition for any reason, much less in an attempt to make a lyophilized tigecycline composition that was stable against epimerization." *Id.* at *7. It then reasoned that Apotex failed to establish why a skilled artisan would have been motivated to combine CN '550, Pawelczyk, and Naggar, and use lactose, as a means for stabilizing tigecycline against epimerization. *Id.* at *9.

Apotex timely appealed; we have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review the Board's legal determinations *de novo*, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), and the Board's factual findings underlying those determinations for substantial evidence, *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). Obviousness is a question of law based on underlying factual findings, *In re Baxter Int'l, Inc.* 678 F.3d 1357, 1361 (Fed. Cir. 2012), such as what a reference teaches, *In re Beattie*, 974 F.2d 1309, 1311 (Fed. Cir. 1992), and whether a skilled artisan would have had a reason to combine references, *see In re Hyon*, 679 F.3d 1363, 1365–66 (Fed. Cir. 2012).

Apotex challenges the Board's conclusion regarding obviousness in two respects. First, it contends that the Board imported an epimeric stability limitation into the claims, and thereby wrongly relied on the failure of CN '550 to teach the epimeric stability of its composition. Second, Apotex argues that the Board failed to consider any motivation to combine the prior art of record beyond the problem the patentee was trying to solve, in contravention of *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), and cases from this court. We address and reject each challenge in turn.

Regarding the first challenge, an obviousness inquiry must focus on the limitations in the claims, *see Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 16 (1966) (noting that under § 103, an obviousness inquiry involves an assessment of "the differences between the prior art and the claims at issue"); *see also Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1346 (Fed. Cir. 2015) ("[T]he district court properly found that corneal permeability is not relevant in the discussion of composition claims 12–16 because these claims do not contain the corneal permeability limitation found in method claim 6."), and here, the challenged claims do not require epimeric stability.

The Board noted that "the claims do not recite epimeric stability," and therefore stated that the purported "obviousness of the claims [could] be demonstrated *without* a showing of epimeric stability in the prior art," *Apotex*, 2015 WL 1848261, at *9 (emphasis added), but in the Board's view, Apotex failed to do so. In any event, it is hard to see how, in view of that statement, the Board imported an epimeric stability limitation into the claims. To the extent the Board considered epimeric stability during its obviousness analysis generally, it did so in the context of assessing whether a skilled artisan would have been motivated to combine references. That is not the same as importing a limitation into the claims.

Turning to Apotex's second argument, the Board correctly considered several purported motivations to combine the prior art beyond epimeric stability. *See KSR*, 550 U.S. at 419–20; *see Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367–68 (Fed. Cir. 2012). In its brief to us, Apotex argues that the Board failed to consider specific motivations to combine the prior art references. Apotex first contends that that the structural similarity of tigecycline and minocycline would have motivated a skilled artisan to replace minocycline with tigecycline in the CN '550 composition. Appellant's Br. 20. To that end, Apotex invokes *Senju*, arguing that a skilled artisan necessarily would have been motivated to "make the simple substitution of generational drugs." *See* Oral Arg. at 4:35–4:43.

From the Board's opinion, it is clear that it fully considered that potential motivation to combine and found it wanting. In its first paragraph of analysis, the Board acknowledged Apotex's assertion that one of skill in the art "would find reason to substitute tigecycline for minocycline" in CN '550 because it "was known to work where other antibiotics have failed," and because "minocycline and tigecycline are tetracycline antibiotics" with "identical A and B rings." *Apotex*, 2015 WL 1848261, at *5. In addressing that assertion, the Board rejected Apotex's proffered expert testimony on this point as unpersuasive. *Id.* at *7 ("Dr. Nelson does not explain . . . why the knowledge that tigecycline is effective 'where other antibiotics have failed' would lead a person having ordinary skill" to substitute tigecycline for minocycline in CN '550). And Apotex did not establish that minocycline was known to "have failed."

Moreover, the Board found that no evidence suggested that tigecycline would be as stable in the CN '550 composition, as the notion of "identical A and B rings" alone was insufficient to show that. *See id.* at *8; *cf.* Joint App. 1729–34 (Wyeth's expert noting that the oxidation rates for tigecycline and minocycline differ because of their

differing structures); '828 patent col. 3 ll. 32–34 ("[T]he rate of degradation may vary depending upon the tetracycline"; "the epimerization rate of tigecycline is particularly fast."); *id.* col. 4 ll. 4–6 ("[E]pimerization is a more serious problem with tigecycline than with other tetracyclines[,] such as minocycline."). Thus, there can be no question that the Board considered the structural similarities between tigecycline and minocycline as a potential motivating factor for a skilled artisan to substitute tigecycline for minocycline in the CN '550 composition. The Board simply found that the record did not support that finding, and we decline to disturb its decision on appeal. Moreover, there is not necessarily a motivation to substitute one antibiotic for a structurally related one when the prior-art antibiotic has a favorable stability profile, and there is nothing in the record here to show that the substitution would solve any other problem.

We further find Apotex's invocation of *Senju* unpersuasive. As an initial matter, *Senju* does not stand for the general proposition that a skilled artisan would always be motivated to try later generation compounds in an old composition. Rather, the conclusion of obviousness in *Senju* turned on the very specific factual findings made by the district court about the teachings of the prior art and the similarities across the quinolone family of compounds. *See, e.g.*, *Senju*, 780 F.3d at 1343 ("The '470 patent also teaches that each of the disclosed quinolones have 'similar substituents,' and that pharmaceutical formulations of gatifloxacin follow 'the routes well known' with respect to 'oral[] and parenteral[]' administration." (internal citation omitted)). Factual findings of that nature in *Senju*, favorable to a conclusion of obviousness, are noticeably absent here.

In addition to addressing the structural similarities of tigecycline and minocycline, the Board addressed epimeric stability, and found that a skilled artisan would not have been motivated to combine Pawelczyk, Naggar, and CN

'550, and use lactose, to stabilize tigecycline against epimer formation. *See Apotex*, 2015 WL 1848261, at *7, *9–13. In particular, the Board found that (1) none of the references discloses tigecycline; (2) Naggar and Pawelczyk do not disclose lactose, much less disclose it as a stabilizing means against epimer formation; (3) CN '550 teaches lactose as a "powder supporting agent," but does not teach that it makes a composition stable against epimerization; and (4) Apotex failed to show why a skilled artisan would have been motivated to use lactose in view of Naggar, when Naggar teaches a different polysaccharide, polysorbate 20, as the least effective solubilizer in a larger list of solubilizers, such as urea. *Id.* at *9, *13. Moreover, the Board rejected Apotex's expert testimony as "not supported by objective evidence or analysis," instead relying on Wyeth's evidence as persuasive. *Id.* at *10–11. Apotex does not now meaningfully challenge any of those factual findings; we likewise decline to disturb them.

Apotex lastly argues that the Board failed to consider whether a skilled artisan (1) would have been motivated to combine the art of record to optimize the pH ranges in CN '550, or (2) would have modified the pH ranges in CN '550 to the ranges recited in the dependent claims of the '828 patent "because those ranges were commonly used in conventional injection solutions." *See* Appellant's Br. 20, 29. Apotex correctly asserts that the Board did not expressly address those motivations, but we find no reversible error in that omission in view of Apotex's ultimate failure to establish why a skilled artisan would have been motivated to substitute tigecycline for minocycline, the dispositive issue here.

In sum, while tigecycline is closely related to minocycline structurally and in terms of benefit, the Board did not err in concluding that there was insufficient basis in the record to show that it would have been obvious to a skilled artisan to substitute tigecycline in the prior art minocycline composition.

CONCLUSION

We have considered all of Apotex's remaining arguments, but conclude that they are without merit. The Board's decision was supported by substantial evidence and not erroneous as a matter of law. For the reasons set forth above, we affirm the Board's decision.

AFFIRMED