Trials@uspto.gov
571-272-7822

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

Case IPR2015-00873
Patent 7,879,828 B2

Before JACQUELINE WRIGHT BONILLA, CHRISTOPHER L. CRUMBLEY, and JO-ANNE M. KOKOSKI, *Administrative Patent Judges.*

KOKOSKI, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Apotex Inc. ("Petitioner") filed a Petition ("Pet.") to institute an *inter partes* review of claims 1–23 of U.S. Patent No. 7,879,828 B2 ("the '828 patent," Ex. 1001). Paper 1. Wyeth LLC ("Patent Owner") filed a Preliminary Response ("Prelim. Resp."). Paper 6. We have jurisdiction under 35 U.S.C. § 314.

Upon consideration of the Petition, the Preliminary Response, and the evidence of record, we determine that Petitioner has not established a reasonable likelihood of prevailing with respect to claims 1–23 of the '828 patent. Accordingly, we deny the Petition and do not institute an *inter partes* review.

A. Related Proceedings

The parties indicate that the '828 patent is involved in at least four pending district court actions. Pet. 4; Paper 5, 3. Petitioner states that it is not a party to any of the pending actions. Pet. 4. The '828 patent was the subject of IPR2014-00115 ("the '115 IPR"), also filed by Petitioner, a proceeding in which a Final Written Decision ("the '115 Final Decision," Ex. 2002) issued on April 20, 2015 (*Apotex Inc. v. Wyeth LLC*, Case IPR2014-00115, slip op. at 26 (PTAB April 20, 2015) (Paper 94)), and IPR2014-01259, in which institution was denied on February 13, 2015 (*Initiative for Responsibility in Drug Pricing LLC v. Wyeth LLC*, Case IPR2014-01259, slip op. at 7 (PTAB Feb. 13, 2015) (Paper 8)).

B. The '828 Patent

The '828 patent, titled "Tigecycline Compositions and Methods of Preparation," is directed to compositions comprising tigecycline, a suitable carbohydrate, and an acid or buffer. Ex. 1001, 1:8–11. Tigecycline, a

chemical analog of minocycline, is a tetracycline antibiotic used to treat drug-resistant bacteria. *Id*. at 1:22–25. Due to poor oral bioavailability, tigecycline typically is formulated as an intravenous solution that is prepared from a lyophilized tigecycline powder immediately prior to administration. *Id*. at 1:45–50. In solution, tigecycline undergoes oxidation at slightly basic pH, causing the tigecycline to degrade relatively rapidly. *Id.* at 2:24–26, 33–40. When the pH of the solution is lowered, however, oxidative degradation decreases, and degradation by epimerization predominates. *Id*. at 2:43–49. The tigecycline epimer lacks antibacterial effect, and is, thus, an undesirable degradation product. *Id*. at 3:19–22. According to the '828 patent, the claimed compositions reduce tigecycline degradation, because the acidic pH of the solution comprising tigecycline and a suitable carbohydrate minimizes oxidative degradation, while the carbohydrate stabilizes the tigecycline against epimerization in the acidic solution. *Id.* at 4:49–59.

The Specification discloses various embodiments, such as compositions comprising tigecycline, lactose, and hydrochloric acid, at pH values between 3.0 and 7.0. *Id.* at 7:63–10:35, 11:15–12:53. The Specification further discloses embodiments where the molar ratio of tigecycline to lactose varies between 1:0.24 and 1:4.87. *Id*. at 13:40–14:33.

C. Illustrative Claim

Petitioner challenges claims 1–23 of the '828 patent. Claims 1 and 12 are independent claims. Claim 1 is illustrative, and reads as follows:

> 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.

D. The Prior Art

Petitioner applies the following references in its asserted grounds:

Name	Description	Date	Exhibit No.
CN '550	Chinese Patent Publication No. 1390550A	Jan. 15, 2003	1003 1004 (English translation)
Kirsch et al.	*Development of a Lyophilized Formulation for (R, R)- Formoterol (L)-Tartrate*, DRUG DEVEL. & INDUS. PHARM. 27(1):89–96	2001	1007
Herman et al.	*The Effect of Bulking Agent on the Solid-State Stability of Freeze-Dried Methylprednisolone Sodium Succinate*, PHARM. RES. 11(10):1467–1473	1994	1006
Pawelczyk et al.	*Kinetics of Drug Decomposition. Part 74. Kinetics of Degradation of Minocycline in Aqueous Solution*, POL. J. PHARMACOL. PHARMA. 34:409-421	1982	1008
Remmers et al.	*Some Observations on the Kinetics of the C·4 Epimerization of Tetracycline*, J. PHARMA. SCI. 52(8):752–756	1963	1009

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–23 of the '828 patent on the following grounds:

References	Basis	Claims challenged
CN ’550, Kirsch, and Herman	§ 103(a)	1–3, 6–9, 12, 13, 18, 19
CN ’550, Kirsch, Herman, Pawelczyk, and Remmers	§ 103(a)	4, 5, 10, 11, 14–17, 20–23

II. ANALYSIS

A. Claim Interpretation

We interpret claims of an unexpired patent using the “broadest reasonable construction in light of the specification of the patent in which [the claims] appear[].” 37 C.F.R. § 42.100(b). For purposes of this Decision, based on the record before us, we determine that none of the claim terms requires an explicit construction.

B. 35 U.S.C. § 315(e)(1)

Patent Owner contends that Petitioner is estopped, by 35 U.S.C. § 315(e)(1), from requesting *inter partes* review because the asserted grounds are based on prior art that Petitioner “was aware of, cited, and relied on in the ’115 IPR,” and therefore “could have been raised in the ’115 IPR.” Prelim. Resp. 9–10. 35 U.S.C. § 315(e)(1) provides:

> (e) Estoppel.–
>
> (1) Proceedings before the Office.—The petitioner in an inter partes review of a claim in a patent under this chapter that results in a final written decision under section 318(a), or the real party in interest or privy of the petitioner, *may not request or maintain a proceeding before the Office with respect to that claim on any ground that the petitioner raised or reasonably could have raised during that inter partes review*.

(Emphasis added).

The preconditions for applying § 315(e)(1) estoppel are in place here because the Petitioner here and in the '115 IPR are the same, and the '115 IPR resulted in a final written decision. For the reasons that follow, we determine Petitioner could have raised its second asserted ground—obviousness of claims 4, 5, 10, 11, 14–17, and 20–23 over the combination of CN '550, Kirsch, Herman, Pawelczyk, and Remmers ("Ground 2")—in the '115 IPR.

What a petitioner "could have raised" was broadly described in the legislative history of the America Invents Act ("AIA") to include "prior art which a skilled searcher conducting a diligent search reasonably could have been expected to discover." 157 Cong. Rec. S1375 (daily ed. Mar. 8, 2011) (statement of Sen. Grassley). In this case, however, we do not need to determine what such a search may have uncovered, because the record demonstrates that Petitioner was aware of the prior art references asserted in Ground 2 when it filed the '115 IPR.

In the '115 IPR Petition (Ex. 2001), Petitioner challenged claims 1–23 of the '828 patent on seven obviousness grounds based on a number of different references, including CN '550, Kirsch, Herman, and Pawelczyk. Ex. 2001, 3. Although Remmers was not included in any of the asserted grounds, in a section of the '115 IPR Petition describing the chemistry and degradation of tetracycline antibiotics, Petitioner states:

> Remmers also discloses that C4 epimerization of tetracycline occurs at a pH from 2.4 to 6.0, and that the equilibrium concentration of the C4 epimer is a function of the pH of the solution. Remmers studied C4 epimerization of tetracycline at pH 2.4, 3.2, 4.0, 5.0 and 6.0, and concluded that the rate at which epimerization occurs is essentially identical at pH 3.2, 4.0 and 5.0.

Id. at 16 (citations omitted). Petitioner cites Remmers for the same teaching in the instant Petition. *See* Pet. 54 ("Remmers studied C4 epimerization of tetracycline at pH 2.4, 3.2, 4.0, 5.0, and 6.0, and determined the equilibrium concentrations of C4 epimer as a function of pH."). Petitioner, therefore, had knowledge of Remmers and what it discloses when it filed the '115 IPR.

Petitioner argues that it could not have raised Ground 2 in the '115 IPR. Pet. 3. Petitioner states:

> Ground 2 could not have been raised during the '115 IPR because in its Decision instituting IPR, the Board indicated that the then-presented grounds of unpatentability were redundant. However, to the extent Patent Owner has based its arguments on the theory that CN '550, Naggar, and Pawelczyk do not provide motivation because CN '550 does not expressly mention epimerization, it is clear that the present grounds are not cumulative. [Petitioner] could not have raised Ground 2 in the '115 IPR because of the Board's view at the time that such grounds were redundant with the ground upon which the '115 IPR was instituted.

Id. (citation omitted). It is unclear, however, how the Board's determination that several grounds in the '115 IPR Petition were redundant to the ground upon which trial was instituted in the '115 IPR is relevant to determining whether Petitioner could have raised Ground 2 in the '115 IPR Petition. Petitioner did not know, at the time it filed the '115 IPR Petition, that the Board would find the grounds proposed therein to be redundant. Petitioner cannot argue that it could not have raised Ground 2 in the '115 IPR Petition because the Board found different grounds to be redundant to each other, after Petitioner had already made the decision not to raise Ground 2 in its prior petition.

On this record, we determine that Ground 2 constitutes a ground that Petitioner could have raised in the '115 IPR. Petitioner was aware of, and cited, all of the Ground 2 prior art in the '115 IPR Petition, and therefore reasonably could have raised it during that proceeding. Accordingly, Petitioner is estopped under 35 U.S.C. § 315(e)(1) from asserting Ground 2 now.

Patent Owner also contends that Petitioner is estopped from asserting its first ground based on CN '550, Kirsch, and Herman ("Ground 1") in this proceeding. *See* Prelim. Resp. 9–16. Petitioner asserted Ground 1 in the '115 IPR Petition (where it was identified as Ground 6), and the Board found it to be redundant to the ground upon which trial was instituted. Ex. 2001, 51–55; Ex. 2003, 9. Because the Board did not reach the merits of the challenge presented in Ground 1 when deciding whether to institute a trial in the '115 IPR, we determine that Petitioner is not estopped from asserting Ground 1 in this proceeding.

As discussed above, the estoppel provisions of 35 U.S.C. § 315(e)(1) apply only to grounds that petitioner "raised or reasonably could have raised *during* [the] inter partes review." (emphasis added). An *inter partes* review does not begin until the Office decides to institute review; prior to that point, our Rules refer to a "preliminary proceeding" that begins with the filing of a petition and ends with a decision whether to institute trial. 37 C.F.R. § 42.2; *accord Intellectual Ventures II LLC v. JPMorgan Chase & Co.*, 781 F.3d 1372, 1376 (Fed. Cir. 2015) ("[The AIA] . . . suggests that a petition is a request for a [covered business method review] proceeding, not that the petition itself is part of the proceeding" and "the Director decides whether to 'institute,' or begin, a [] proceeding"). Therefore, grounds raised during the

preliminary proceeding, but not made part of the instituted trial, are not raised "during" an *inter partes* review and cannot be the basis for estoppel under 35 U.S.C. § 315(e)(1). Nor are such grounds ones that "reasonably could have been raised during" the review, because once denied, the Board's decision on institution prevents Petitioner from raising that ground during the trial. *See* 77 Fed. Reg. 48,680, 48,689 (Aug. 14, 2012) ("[a]ny claim or issue not included in the authorization for review is not part of the review").

Ground 1 in the instant Petition was never raised *during* the '115 IPR, because the Board denied institution of Ground 6 as redundant, and Petitioner could not have raised Ground 6 again once institution was denied as to that ground. Estoppel under 35 U.S.C. § 315(e)(1), therefore, does not bar Petitioner from maintaining a proceeding before the Office on Ground 1.

C. 35 U.S.C. § 325(d)

Patent Owner requests that the Board exercise its discretion under 35 U.S.C. § 325(d) and decline to institute *inter partes* review of the '828 patent because Petitioner "asserts both substantially the same art and substantially the same arguments as the Board considered in the '115 IPR proceeding." Prelim. Resp. 16. Specifically, Patent Owner contends the Petition "presents no new prior art, and asserts CN '550 and the secondary references for the same purposes it did in the '115 IPR." *Id.* at 20.

The permissive language of 35 U.S.C. § 325(d) does not prohibit instituting *inter partes* review based on arguments previously presented to the Office. *See* 35 U.S.C. § 325(d) ("In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director *may take into account* whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were

presented to the Office.") (emphasis added). While we are mindful of the burden on Patent Owner and the Office to rehear the same or substantially the same arguments that have been considered by the Office in other proceedings, we note that we did not reach the merits of Petitioner's arguments with respect to Ground 1 when considering the '115 IPR. Therefore, we do not exercise our authority to decline an *inter partes* review of the '828 patent under § 325(d).

D. Obviousness over CN '550, Kirsch, and Herman

Petitioner contends that claims 1–3, 6–9, 12, 13, 18, and 19 would have been obvious under 35 U.S.C. § 103(a) over the combination of CN '550, Kirsch, and Herman. Pet. 32–51. Petitioner relies on a Declaration by Raj Suryanarayanan, Ph.D. (Ex. 1002) in support of its contentions.

Petitioner contends that CN '550 describes all of the limitations of independent claims 1 and 12, except that it discloses minocycline, not tigecycline. Pet. 41–42. Petitioner contends that "[i]t was known in the art that tetracyclines, including minocycline and tigecycline, oxidize in neutral or basic solutions and epimerize in acidic solutions," and, "[a]lthough they proceed along two different pathways, oxidation and epimerization present the same ultimate problem: they reduce the amount of tetracycline present to exert its desired antibiotic effect." *Id.* at 39. Petitioner further contends that "[a] person of ordinary skill in the art would have found motivation to use lactose to improve the stability of a lyophilized tigecycline composition against degradation caused by oxygen, water, heat, and light as taught by CN '550," because "[d]egradation of tigecycline caused by oxygen, water, and heat were also problems with the original, unstable tigecycline formulation." *Id.* at 40.

It is in this context that Petitioner contends that a person having ordinary skill in the art would have found reason to substitute tigecycline for minocycline in the CN '550 compositions because it was known to work where other antibiotics failed, and that it was active against specific viruses that show tetracycline resistance. Pet. 41–42. Petitioner cites Dr. Suryanarayanan's testimony in support of this contention:

> A person of ordinary skill in the art in 2005 would find reason to substitute tigecycline for its known chemical analog minocycline in the lyophilized formulation of CN '550. Ex. 1001, 1:23–24. Further, a person of ordinary skill in the art would have been motivated to substitute tigecycline for minocycline because it was known that tigecycline "has been shown to work other antibiotics have failed" and "it has been active against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, vancomycin resistant enterococci…and against organisms carrying either of the two major forms of tetracycline resistance: efflux and ribosomal protection". *Id.* at 1:23–44.

Ex. 1002 ¶ 73.

Dr. Suryanarayanan does not explain, however, why the knowledge that tigecycline is effective "where other antibiotics have failed" would lead a person having ordinary skill in the art to substitute tigecycline for minocycline in the compositions disclosed in CN '550, a reference addressing the stability of lyophilized minocycline compounds. Neither Petitioner nor Dr. Suryanarayanan provides information demonstrating that a person of ordinary skill in the art would correlate the therapeutic effectiveness of tigecycline as an antibiotic to the properties of tigecycline that must be considered when preparing a lyophilized formulation of tigecycline. Moreover, Petitioner does not provide adequate evidence or explanation why a person having ordinary skill in the art reasonably would

have expected that the substitution of tigecycline for minocycline in the CN '550 compositions would have resulted in a stabilized tigecycline composition. Petitioner, therefore, has not provided sufficient rationale to explain why a person having ordinary skill in the art would have substituted tigecycline for minocycline in the CN '550 compositions.[1]

None of CN '550, Kirsch, or Herman discloses or discusses tigecycline, and CN '550 does not include any examples in which the disclosed minocycline compositions are stabilized with lactose. Prelim. Resp. 26. Petitioner does not adequately explain why a person having ordinary skill in the art, reading such references, would have had reason to use tigecycline in the compositions described by CN '550 when the references themselves lack any teaching or suggestion about the use or specific chemistry of tigecycline in particular. Petitioner, relying on Dr. Suryanarayanan's testimony, argues that "[a] person of ordinary skill in the art would recognize [that the] technique for stabilizing minocycline disclosed in CN '550 by using lactose, would improve a composition containing the similar antibiotic tigecycline," and "would be encouraged by Herman and Kirsch to select lactose rather than mannitol as a lyophilization excipient for minocycline and tigecycline in order to reduce the amount of residual water in the solid cake that comes into contact with the active pharmaceutical ingredient." Pet. 42 (citing Ex. 1002 ¶¶ 73–74), 48 (citing Ex. 1002 ¶ 88).

[1] Petitioner made this argument in the '115 IPR, and our conclusions here are consistent with those set forth in the '115 Final Decision. *See* Ex. 2002, 12.

Dr. Suryanarayanan's statements regarding what a person skilled in the art would have understood about the stability of tigecycline and lactose in the CN '550 compositions, however, are not supported by sufficient objective evidence or analysis. Dr. Suryanarayanan simply states that the skilled artisan "would recognize" from CN '550 that lactose would stabilize tigecycline, and "would be encouraged" by Kirsch and Herman to use lactose, instead of the mannitol described in the CN '550 examples, in the CN '550 compositions, without providing adequate explanation as to why that would be the case. Dr. Suryanarayanan's unsupported and unexplained opinions are not persuasive.

Accordingly, we determine that the record before us does not establish a reasonable likelihood that Petitioner would prevail in showing claim 1 and claims 2, 3, and 6–9 that depend therefrom, and claim 12 and claims 13, 18, and 19 that depend therefrom, would have been obvious over the combination of CN '550, Kirsch, and Herman.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that Petitioner has demonstrated a reasonable likelihood that at least one of the challenged claims of the '828 patent is unpatentable based on the asserted grounds.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*.

PETITIONER:

Kenneth J. Burchfiel
Travis B. Ribar
Grant S. Shackelford
SUGHRUE MION, PLLC
kburchfiel@sughrue.com
tribar@sughrue.com
gshackelford@sughrue.com

PATENT OWNER:

Stanley E. Fisher
David I. Berl
Galina I. Fomenkova
WILLIAMS & CONNOLLY LLP
sfisher@wc.com
dberl@wc.com
gfomenkova@wc.com