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Paper 10
Entered: April 21, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.
Petitioner

v.

WYETH LLC
Patent Owner

Case IPR2014-00115
Patent 7,879,828 B2

Before LORA M. GREEN, FRANCISCO C. PRATS, and JO-ANNE M. KOKOSKI, *Administrative Patent Judges.*

KOKOSKI, *Administrative Patent Judge.*

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

I. INTRODUCTION

Apotex Inc. ("Apotex") filed a Petition ("Pet.") to institute an *inter partes* review of claims 1-23 of U.S. Patent No. 7,879,828 ("the '828 patent"). Patent Owner Wyeth LLC ("Wyeth") waived filing a Preliminary Response. Paper 9. We have jurisdiction under 35 U.S.C. § 314.

The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a):

> THRESHOLD – The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

Upon consideration of the Petition, we conclude that Apotex has established a reasonable likelihood that it would prevail with respect to claims 1-23 of the '828 patent. Accordingly, we institute an *inter partes* review of claims 1-23 of the '828 patent.

A. Related Proceedings

Apotex indicates that the '828 patent was involved in *Wyeth Holdings Corp. v. Sandoz Corp.*, No. 09-955-LPS-CJB (D. Del.), to which Apotex was not a party. Pet. 2.

B. The '828 Patent (Ex. 1001)

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, 1:8-12. 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 of the '828 patent 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, 11:15-2:53. 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

Apotex 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

Apotex relies on the following prior art references:

Zhang et al., U.S. Patent App. Pub. No. 2005/0020610 A1, published January 27, 2005 ("Zhang"). (Ex. 1024).

Chinese Patent Publication No. 1390550A, published January 15, 2003 ("CN '550"). (Ex. 1003 and Ex. 1004 (English translation)).

Lawter et al., WO 01/19362 A2, published March 22, 2001 ("Lawter"). (Ex. 1019).

L. Kirsch et al., *Development of a Lyophilized Formulation for (R, R) Fomoterol (L)-Tartrate*, DRUG DEVEL. & INDUS. PHARM. 27(1):89-96 (2001) ("Kirsch"). (Ex. 1022).

B. 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) ("Herman"). (Ex. 1023).

E. 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) ("Pawelczyk"). (Ex. 1006).

V. Naggar et al., *Effect of Solubulizers on the Stability of Tetracycline*, PHARMAZIE 29(2) 126-129 (1974) ("Naggar"). (Ex. 1007).

B. Trivedi et al., *Stability Studies on Hamycin and Tetracycline Hydrochloride with Selected Diluents*, HINDUSTAN ANTIBIOTICS BULLETIN 16(4):175-184 (1974) ("Trivedi"). (Ex. 1011).

E. The Asserted Grounds of Unpatentability

Apotex challenges the patentability of claims 1-23 of the '828 patent on the following grounds:[1]

[1] Apotex supports its challenge with a declaration by Mark L. Nelson, Ph.D., executed on November 1, 2013 ("Nelson Declaration") (Ex. 1002).

Reference[s]	Basis	Claims challenged
CN ’550	§ 103(a)	1-23
CN ’550, Pawelczyk, and Naggar	§ 103(a)	1-23
CN ’550, Naggar, and Zhang	§ 103(a)	1-23
CN ’550 and Trivedi	§ 103(a)	1-23
CN ’550, Trivedi, Pawelczyk, and Naggar	§ 103(a)	1-23
CN ’550, Kirsch, and Herman	§ 103(a)	1-23
Lawter, CN ’550, and Trivedi	§ 103(a)	1-23

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under the broadest reasonable interpretation standard, claim terms are given their ordinary and customary meaning in view of the specification, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). The terms in the challenged claims need not be construed expressly for purposes of this decision.

B. Obviousness over CN '550 (Ex. 1004), Pawelczyk (Ex. 1006), and Naggar (Ex. 1007)

Apotex contends that claims 1-23 would have been obvious under 35 U.S.C. § 103 over the combination of CN '550, Pawelczyk, and Naggar. Pet. 40-44; *see also id.* at 31-40.

CN '550 is directed to lyophilized minocycline hydrochloride powder injections. Ex. 1004, 1:30-48.[2] The lyophilized powder is comprised of 0.05-10 parts minocycline hydrochloride, 0-100 parts excipient, and a suitable amount of a pH adjusting agent. *Id*. at 3:28-31. The excipient is selected from a group including lactose, mannitol, glucose, and dextran. *Id*. at 3:35-37. The pH adjusting agent is an inorganic acid, such as hydrochloric acid. *Id*. at 3:37-39. The pH of the lyophilized powder is 0-7.5, most preferably 2-3.5. *Id*. at 3:32-33. CN '550 discloses an embodiment in Example 1 that contains 108 g minocycline hydrochloride, 210 g mannitol, and a suitable amount of 0.1 M hydrochloric acid. *Id*. at 4:14-37. Example 2 in CN '550 discloses an embodiment containing 108 g of minocycline hydrochloride and 210 g of dextran. *Id*. at 4:38-46.

Pawelczyk reports the results of studies investigating the stability of minocycline in aqueous solutions over a broad pH range. Ex. 1006, 409. Pawelczyk discloses aqueous minocycline solutions at pH 4.38, 4.86, and 5.42. *Id*. at 413, Table 1. Pawelczyk teaches that oxidation is the predominant minocycline degradation process above pH 5. *Id.* at 417.

Naggar details an investigation of the rate of tetracycline epimerization under various experimental conditions. Ex. 1007, 126. Naggar teaches that, at pH 2-6, tetracycline antibiotics undergo a reversible

[2] The cited page numbers in Exhibit 1004 refer to the numbers at the bottom of each page, rather than those at the top.

epimerization at the C4 dimethylamino group. *Id*. The epimerization occurs most rapidly at a pH of 3-4. *Id*. Naggar teaches that solubilizers (such as polysorbate 20, PEG 6000, urea, and thiourea) interact with tetracycline and act as deprotonating agents, thus inhibiting epimerization by deterring the rearrangement of tetracycline ring A. *Id*. at 127. Naggar reports that tetracycline and a solubilizer in solution with pH of 3-5 is "chemically stable over a long period of time." *Id*.

Apotex asserts that CN '550 discloses almost all of the limitations of the '828 patent claims (Pet. 31-40), and provides a detailed claim chart setting forth where each of the limitations may be found (*id*. at 26-30). Apotex concedes that CN '550 does not disclose tigecycline, but states that CN '550 does disclose minocycline. *Id*. at 31. Apotex asserts that because minocycline and tigecycline are tetracycline antibiotics that have identical A and B rings, and undergo epimerization at the C4 dimethylamino group by the same reaction, a person skilled in the art "would find reason to substitute tigecycline for minocycline in the lyophilized formulation of CN '550." *Id*. at 31-32.

Further, because Naggar teaches that tetracyclines are stabilized against epimerization by hydrogen bonding between a saccharide (such as lactose) and a tetracycline, Apotex contends that "a person of ordinary skill in the art would understand and expect that lactose disclosed in CN '550 would also be effective to stabilize tigecycline against epimerization." Pet. 44. Apotex also contends that a person skilled in the art would reduce the pH of an aqueous solution of minocycline, tetracycline, or tigecycline to below about 5 to avoid oxidative degradation, as taught by Pawelczyk, and specifically would have adjusted the pH of the solution to about 4-5, as

taught by Naggar, to limit degradation by epimerization. *Id.* at 42-43. According to Apotex, substituting tigecycline for minocycline in the CN '550 composition containing lactose is a "predictable variation" that "a person of ordinary skill in the art could easily implement." *Id*. at 39 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007)).

Regarding the recited molar ratios of tigecycline to lactose, Apotex asserts that because "[t]he molar ratio would vary widely for the same weight ratios of components," a person skilled in the art would consider "the weight ratio of minocycline hydrochloride to mannitol disclosed in Example 1 of CN '550, and the same weight ratio of minocycline hydrochloride to dextran in Example 2," and would use the same weight ratio of minocycline to lactose to stabilize minocycline. Pet. 37. According to Apotex, a person skilled in the art would consider the weight ratio of minocycline to the polysaccharide dextran in CN '550 Example 2, and "would find it obvious to stabilize a composition containing tigecycline and the disaccharide lactose" in the same approximate weight ratio. *Id*. at 38.

We have considered the arguments and evidence presented by Apotex, and we are persuaded that Apotex has demonstrated a reasonable likelihood that independent claims 1 and 12 would have been obvious based on the combination of CN '550, Pawelczyk, and Naggar. We also have considered Apotex's arguments and evidence as to dependent claims 2-11 and 13-23, and likewise are persuaded that Apotex has demonstrated a reasonable likelihood that it would prevail as to those claims as well. Accordingly, we institute *inter partes* review of claims 1-23 for obviousness over CN '550, Pawelczyk, and Naggar.

C. Other Grounds

Upon review of the other challenges asserted by Apotex against claims 1-23, we conclude that they are redundant in light of the grounds on which we institute review.

III. CONCLUSION

Based on the arguments in the Petition and the evidence of record, we determine that Apotex has demonstrated a reasonable likelihood that it would prevail on its challenge of claims 1-23 of the ’828 patent.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *granted* as to claims 1-23 of the ’828 patent with respect to the following ground:

Claims 1-23 under 35 U.S.C. § 103 as obvious over the combination of CN ’550, Pawelczyk, and Naggar;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the ’828 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial;

FURTHER ORDERED that all other grounds presented in Apotex’s Petition are *denied*, and no ground other than those specifically granted above is authorized for the *inter partes* review as to claims 1-23; and

FURTHER ORDERED that an initial conference call with the Board

is scheduled for 1:00 PM Eastern Time on May 22, 2014. The parties are directed to the Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,765-66 (Aug. 14, 2012), for guidance in preparing for the initial conference call, and should be prepared to discuss any proposed changes to the Scheduling Order entered herewith and any motions the parties anticipate filing during the trial.

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