

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 FRANCISCO C. PRATS, JACQUELINE WRIGHT BONILLA, and
JO-ANNE M. KOKOSKI, *Administrative Patent Judges*.

KOKOSKI, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Apotex Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”) to institute an *inter partes* review of claims 1–23 of U.S. Patent No. 7,879,828 B2 (Ex. 1001, “the ’828 patent”). Wyeth LLC (“Patent Owner”) did not file a preliminary response. We determined that the information presented in the Petition demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–23 as unpatentable under 35 U.S.C. § 103 as obvious over the combination of CN ’550,¹ Pawelczyk,² and Naggar.³ Pursuant to 35 U.S.C. § 314, we instituted this proceeding on April 21, 2014. Paper 10 (“Dec. to Inst.”), 2, 9.

Patent Owner filed a Patent Owner Response (Paper 36, “PO Resp.”), and Petitioner filed a Reply (Paper 60, “Reply”). Petitioner filed a Motion to Exclude (Paper 62) portions of the Declarations of Dr. Henry Grabowski (Ex. 2010) and Mr. Christian L. Ofslager (Ex. 2011), as well as a number of Patent Owner’s other exhibits. Patent Owner filed an Opposition to the Motion to Exclude (Paper 73), and Petitioner filed a Reply (Paper 75). Patent Owner filed a Motion to Exclude (Paper 66) CN ’550 and its accompanying translations and declarations (Exs. 1003–1005, 1046, 1047), and portions of the cross examinations of Dr. Lester Mitscher (Ex. 2175) and

¹ Chinese Patent Publication No. CN 1390550A, published January 15, 2003 (Ex. 1003 and Exs. 1004 and 1046 (English translations)).

² E. Pawelczyk et al., *Kinetics of Drug Decomposition. Part 74. Kinetics of Degradation of Minocycline in Aqueous Solution*, 34 POL. J. PHARMACOL. PHARMA. 409–421 (1982) (Ex. 1006).

³ V. Naggar et al., *Effect of Solubilizers on the Stability of Tetracycline*, 29(2) PHARMAZIE 126–129 (1974) (Ex. 1007).

Dr. Robert Williams (Ex. 2176). Petitioner filed an Opposition (Paper 70), and Patent Owner filed a Reply (Paper 76).

Petitioner supports its Petition with a Declaration by Mark L. Nelson, Ph.D. (Ex. 1002, “Nelson Decl.”). Patent Owner relies on Declarations by Lester A. Mitscher, Ph.D. (Ex. 2008, “Mitscher Decl.”), Robert O. Williams III, Ph.D. (Ex. 2009, “Williams Decl.”), Harry Grabowski, Ph.D. (Ex. 2010, “Grabowski Decl.”), and Christian L. Ofslager (Ex. 2011, “Ofslager Decl.”).

An oral hearing was held on January 23, 2015. A transcript of the hearing is included in the record. Paper 89 (“Tr.”).

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–23 of the ’828 patent are unpatentable.

A. *The ’828 Patent*

The ’828 patent relates generally 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, 11:15–12:53. 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.

Claims 1 and 12 of the '828 patent are independent. Claims 2–11 depend, directly or indirectly, from claim 1, which is reproduced below:

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. at 14:36–40.

Claims 13–23 depend, directly or indirectly, from claim 12, which is reproduced below:

12. A composition comprising tigecycline, lactose, and hydrochloric 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. at 14:62–65.

II. ANALYSIS

A. *Claim Interpretation*

In an *inter partes* review, “[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears.” 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC.*, 778 F.3d 1271, 1279–80 (Fed. Cir. 2015). Under this 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).

For purposes of our Decision to Institute, we determined that the terms in the challenged claims did not need to be construed expressly, and we see no reason to modify that determination in light of the record developed at trial.

B. *Obviousness of Claims 1–23 over CN ’550, Pawelczyk, and Naggar*

To prevail on its patentability challenge, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). We instituted review based upon Petitioner’s contention that the combination of CN ’550, Pawelczyk, and Naggar rendered claims 1–23 obvious under 35 U.S.C. § 103. Upon consideration of the parties’ arguments and evidence before us now, we determine that Petitioner has not demonstrated by a preponderance of the evidence that those claims would have been obvious over the combination of CN ’550, Pawelczyk, and Naggar for the reasons explained below.

1. *Overview of CN '550*

CN '550 is a Chinese-language patent application. Ex. 1003. In support of the Petition, Petitioner relied on a certified English translation of CN '550 (Ex. 1004,⁴ “the first translation”) that described lactose, and other ingredients, as excipients. *See, e.g.*, Ex. 1004, 1:32–33 (“[The formulation] is made of minocycline hydrochloride, an excipient, and a pH adjusting agent.”), 3:35–37 (“The excipient is . . . selected from mannitol, glucose, NaCl, dextran, lactose, and hydrolyzed gelatin.”); Pet. 26–30. After the Decision to Institute issued, but before the Patent Owner Response was filed, Patent Owner objected to the first translation on the basis that “excipient” should have been translated as “lyophilized powder supporting agent,” and that lactose was included in a list of excipients on page 3 of the translation, when it did not appear in the original text. Transcript of Teleconference, Ex. 2172, 16:6–22; Paper 66, 3.

In response to Patent Owner’s objections, Petitioner submitted a corrected certified translation of CN '550 (Ex. 1046,⁵ “the corrected translation”). In the corrected translation, the characters originally translated as “excipient” are translated as “lyophilized powder supporting agent,” and lactose no longer appears in the list on page 3. *See, e.g.*, Ex. 1046, 1 (“[The formulation] is made of minocycline hydrochloride, a lyophilized powder supporting agent, and a pH adjusting agent.”), 3 (“The lyophilized powder supporting agent is . . . selected from mannitol, glucose, NaCl, dextran, and

⁴ The cited page numbers in Exhibit 1004 refer to the numbers at the bottom of each page, rather than those at the top.

⁵ The cited page numbers in Exhibit 1046 refer to the numbers at the bottom of each page, rather than those at the top.

hydrolyzed gelatin.”). Patent Owner does not object to the content of the corrected translation, but did file a motion to exclude both translations, which we address below. Ex. 2172, 28:5–15; Paper 66, 1–13.

Although we relied upon the first translation in the Decision to Institute, we rely on the corrected translation in rendering this Final Decision. As such, the following discussion of CN ’550 with respect to Petitioner’s contention that the ’828 patent would have been obvious over the combination of CN ’550, Pawelczyk, and Naggar is based on the corrected translation.

CN ’550 is directed to lyophilized minocycline hydrochloride powder injections. Ex. 1046, 1. The lyophilized powder is comprised of 0.05–10 parts (by weight) minocycline hydrochloride, 0–100 parts lyophilized powder supporting agent, and a suitable amount of a pH adjusting agent. *Id.* at 3. The lyophilized powder supporting agent can be selected from mannitol, glucose, sodium chloride, dextran, lactose, and hydrolyzed gelatin. *Id.* at 2 (claim 5), 3. The pH adjusting agent is an inorganic acid, such as hydrochloric acid. *Id.* at 3. The pH of the lyophilized powder is 0–7.5, most preferably 2–3.5. *Id.* 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. Example 2 discloses an embodiment containing 108 g of minocycline hydrochloride, 210 g of dextran, and a suitable amount of acetic acid. *Id.* Example 3 describes an embodiment containing 108 g minocycline hydrochloride, 210 g hydrolyzed gelatin, and a suitable amount of phosphoric acid. *Id.* at 5.

2. *Overview of Pawelczyk*

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.

3. *Overview of Naggar*

Naggar details an investigation of the rate of tetracycline epimerization under various experimental conditions. Ex. 1007, 126. Naggar teaches that, at a pH of 2–6, tetracycline undergoes a reversible 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 a pH of 3–5 is “chemically stable over a long period of time.” *Id.*

4. *Analysis*

Petitioner contends that CN '550 discloses a lyophilized composition that is stabilized against light, heat, oxygen, and water, and contains (1) minocycline (an analog of tigecycline), (2) lactose, glucose, or dextran, and (3) hydrochloric acid. Pet. 31–40. Petitioner contends that a person skilled in the art “would find reason to substitute tigecycline for minocycline in the lyophilized formulation of CN '550” because tigecycline was known to work where other antibiotics, including other tetracyclines had failed, and 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. *Id.* at 31–32. Petitioner also contends that because Naggar teaches that tetracyclines are stabilized against epimerization by hydrogen bonding between a saccharide (such as lactose) and a tetracycline, “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.” *Id.* at 44.

Patent Owner asserts that CN ’550 does not teach or suggest the use of lactose to minimize or prevent epimerization. PO Resp. 24–27. Patent Owner asserts that CN ’550 describes lactose as a “lyophilized powder supporting agent,” which “provides physical support to a lyophilized powder formulation” so that it does not collapse, not as “an ingredient that engages in chemical interactions such as deprotonating the active ingredient to avoid epimerization.” *Id.* at 24. Therefore, according to Patent Owner, a person having ordinary skill in the art would have understood that lyophilized powder supporting agents “play a very specific role in maintaining physical structure,” and “would never have looked” at the disclosure of lactose in CN ’550 to enhance chemical stability of a tigecycline formulation. *Id.* at 26. Patent Owner notes that other lyophilized powder supporting agents named in CN ’550, such as mannitol, sodium chloride, and hydrolyzed gelatin, do not “suggest a common chemical interaction or bonding potential” or have similar structures that would suggest, to a person having ordinary skill in the art, a common interaction between each named lyophilized powder supporting agent and a tetracycline derivative. *Id.* at 25. Patent Owner also asserts that there is no indication, in any event, that the compositions described in CN ’550 were epimerically stable. *Id.* at 28–30.

Patent Owner further asserts that Naggar does not teach an ordinary artisan that lactose can be used to stabilize tetracyclines against epimerization. PO Resp. 31–36. Patent Owner notes that Naggar does not disclose lactose, and the disclosed compound noted by Petitioner— polysorbate 20—is not as effective against epimerization as other disclosed solubilizers, such as PEG 6000 and thiourea. *Id.* at 31–32. There is therefore no reason, Patent Owner asserts, for a person having ordinary skill in the art to choose lactose to stabilize tigecycline against epimerization based on the disclosures in Naggar. *Id.* at 32–36.

We agree with Patent Owner that Petitioner has not shown, by a preponderance of the evidence, that a person having ordinary skill in the art would have had reason to substitute tigecycline for minocycline in the lyophilized formulation of CN '550, or to make the compositions recited in the challenged claims in particular in any event. Pet. 31–33. As discussed in more detail below, none of CN '550, Pawelczyk, or Naggar discloses or discusses tigecycline. PO Resp. 19. Petitioner does not explain adequately why an ordinary artisan, reading such references, would have had reason to use tigecycline in the formulation of CN '550 when the references themselves lack any teaching or suggestion about the use or specific chemistry of tigecycline in particular. In addition, we also agree with Patent Owner that Petitioner has not shown sufficiently that a person having ordinary skill in the art would have considered it obvious to include lactose in a tigecycline composition in the amounts recited in the '828 patent claims, for example, to stabilize the composition against epimerization.

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such

that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Prior art references must be “considered together with the knowledge of one of ordinary skill in the pertinent art.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Moreover, an obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418. A patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was known, independently, in the prior art. *Id.* A party that petitions the Board for a determination of obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

a. Substituting Tigecycline for Minocycline

Petitioner states that a person of 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. 31. Petitioner cites Dr. Nelson's testimony in support of this contention:

A person of ordinary skill in the art in 2005 would find reason to substitute tigecycline for minocycline in the lyophilized formulation of CN '550, because the '828 Patent states that it was known that tigecycline “has been shown to work where 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.”

Nelson Decl., Ex. 1002 ¶ 84 (citing Ex. 1001, 1:23–44).

Dr. Nelson 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 CN '550 compositions. Neither Petitioner nor Dr. Nelson 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 any evidence or explanation why a person having ordinary skill in the art would have expected reasonably that the substitution 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 for any reason, much less in an attempt to make a lyophilized tigecycline composition that was stable against epimerization on this basis, as Petitioner contends.

Petitioner also argues that a person having ordinary skill in the art “would understand and expect that lactose would be effective to stabilize minocycline and tigecycline against C4 epimerization in a solution having a pH from 0.1–7.5, including an acid pH of 2.0–3.5, as taught by CN ’550, based on the exact structural identity of the A and B rings in these analogs.” Pet. 32 (citing Nelson Decl., Ex. 1002 ¶ 88). Petitioner goes on to conclude:

A person of ordinary skill in the art would expect each of the saccharide excipients disclosed in CN ’550 to be effective to stabilize minocycline and tigecycline against C4 epimerization in a solution having a pH from 0.1–7.5, including an acid pH of 2.0–3.5, because of the structural similarities of glucose (a monosaccharide), lactose (a disaccharide), and dextran (a polysaccharide). It was known in the prior art, including CN ’550, that suitable carbohydrates including disaccharides such as lactose, monosaccharides such as glucose, and polysaccharides such as dextran, are effective to stabilize tetracyclines against epimerization at acid pHs.

Id. (citing Nelson Decl., Ex. 1002 ¶¶ 42–50, 56–59, 86–87).

Petitioner’s contentions in this regard are insufficient because they presume that a person of ordinary skill in the art would have recognized that the compositions disclosed in CN ’550 were stable against epimerization. As is discussed below, Petitioner has not established that a person of ordinary skill in the art would have known from the CN ’550 disclosure that the described minocycline compositions were stable against epimerization.

In its Reply, Petitioner argues that whether a person having ordinary skill in the art would have recognized that the CN ’550 compositions were epimerically stable is irrelevant to the obviousness inquiry:

Contrary to [Patent Owner]’s fundamental argument, the ’828 patent claims do not relate to a method for stabilizing tigecycline against epimerization, or indeed, any method of stabilizing tigecycline. The claims recite a lyophilized

composition, containing tigecycline, lactose and hydrochloric acid, having a specified pH “in a solution” that is not limited to any one of the 3 solutions that are disclosed in the specification. The issue is whether a [person having ordinary skill in the art] would have found it obvious to make the claimed composition, by substituting tigecycline for minocycline in the composition disclosed in CN ’550, for **any** reason, not just to reduce epimerization.

Reply 3 (citations omitted).

Petitioner also argues that a person having ordinary skill in the art would have expected, from CN ’550’s disclosure of minocycline compositions that are stabilized against degradation by light, heat, oxygen, and water that also have good therapeutic effectiveness, that similar benefits would result if tigecycline were simply substituted for minocycline. *Id.* at 4; *see also* Pet. 39 (“[a] person of ordinary skill in the art would recognize that the technique for stabilizing minocycline disclosed in CN ’550 by using lactose, would similarly stabilize and improve a composition containing the analog antibiotic tigecycline”). As noted above, however, Petitioner does not establish adequately that an ordinary artisan would have had reason to believe that tigecycline, rather than minocycline, would have been similarly stable in the formulation disclosed in CN ’550.

Petitioner is correct that the claims do not recite epimeric stability and therefore obviousness of the claims can be demonstrated without a showing of epimeric stability in the prior art. We are not persuaded, however, that Petitioner has established that a person having ordinary skill in the art would have found it obvious to substitute tigecycline for minocycline in the composition disclosed in CN ’550.

*b. Using Lactose to Stabilize a
Lyophilized Tigecycline Composition*

Petitioner relies on CN '550's disclosure of "stable" minocycline compositions as motivation for a person having ordinary skill in the art to combine CN '550 with Pawelczyk and Naggar to address the problem of tigecycline's instability due to epimerization. Pet. 40. In urging that a person having ordinary skill in the art would have used lactose to stabilize a lyophilized tigecycline composition against epimerization, Petitioner also points to Naggar's teaching that (1) tetracycline antibiotics undergo epimerization at pH conditions between 2 and 6, (2) the epimerization occurs at the C4 dimethylamino group, and (3) polysorbate 20 stabilizes tetracycline against epimerization. Pet. 42–44. Based on these disclosures in CN '550 and Naggar, and Pawelczyk's teaching that "a pH range below 5 is preferable to avoid oxidative degradation of minocycline," Petitioner concludes 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 in solutions having a pH in the range from 4 to 6 taught as optimal by Naggar." *Id.* at 41, 44.

As Patent Owner points out, however, neither CN '550, Pawelczyk, nor Naggar discloses tigecycline, Naggar and Pawelczyk do not disclose lactose, and CN '550 only discloses lactose as one of a list of lyophilized powder supporting agents in a dependent claim. PO Resp. 19–20. In addition, although CN '550 states that the disclosed formulations are stable against light, heat, oxygen, and water (Ex. 1046, 1, 3), there are no statements from which a person skilled in the art would understand that the CN '550 formulations were epimerically stable. PO Resp. 23–24. Indeed,

neither CN '550 nor Pawelczyk mention epimerization at all. As discussed above, the '828 patent, but none of the cited prior art references, discloses that compositions having the claimed ingredients and pH are stabilized against oxidative degradation and epimerization of tigecycline.

In support of its contention regarding the epimeric stability of the compositions disclosed in CN '550, Petitioner relies on Dr. Nelson's testimony in which he asserts that "CN '550 discloses that the lyophilized powder is stabilized under acidic conditions, and a person of ordinary skill in the art would readily appreciate that stabilization would include prevention of C4 epimerization in an acidic solution by the disclosed excipients, which include the carbohydrates lactose, glucose and dextran." Nelson Decl., Ex. 1002 ¶ 78. Dr. Nelson concedes that CN '550 does not mention epimerization explicitly (Complete Deposition Transcript of Mark L. Nelson, Ph.D., Ex. 2012, 38:6–39:15), but argues that a person skilled in the art would understand that because epimerization affects stability, and CN '550 discloses stable formulations, those formulations must be epimerically stable. *Id.* at 47:11–23.

Dr. Nelson's statements regarding what a person skilled in the art would have understood about the epimeric stability of the CN '550 compositions, however, are not supported by any objective evidence or analysis. Dr. Nelson simply states the skilled artisan would "readily appreciate" that the CN '550 compositions are epimerically stable, without providing any explanation as to why that would be the case. Dr. Nelson relies on CN '550's teaching that the disclosed compositions feature stable light, thermal, oxygen, and water properties, but does not expound upon the reasons why a person skilled in the art would understand that statement to

include epimeric stability. *See, e.g.*, Nelson Decl., Ex. 1002 ¶ 78.

Dr. Nelson's unsupported and unexplained opinions are not persuasive. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (stating a lack of objective support for an expert opinion "may render the testimony of little probative value in [a patentability] determination").

Patent Owner, in contrast, provides reasoning as to why a person having ordinary skill in the art would not have understood CN '550 to address epimeric stability. PO Resp. 22–24. For example, Patent Owner notes that CN '550 does not include data, studies, or any explicit indication that epimeric stability was a part of the disclosure. *Id.* at 23; *see also* Williams Decl., Ex. 2009 ¶ 69 ("A [person of ordinary skill in the art] simply would not believe that a reference solves an epimerization problem if it neither mentions epimerization, nor provides any analytical data relating to epimerization."). Dr. Mitscher also testified that a person having ordinary skill in the art would not understand that the compositions described in CN '550 reduced epimerization:

Nor does the bare statement that CN '550 that the goal of the study was "to provide a lyophilized minocycline hydrochloride powder injection that features stable light, thermal, oxygen, and water properties; is non-polluting and easy to manipulate, transport, and store" teach or suggest that the formulations reduced epimerization. To the contrary, if the invention were targeted at preventing epimerization as well, a [person of ordinary skill in the art] would have expected epimerization to be included in this list or otherwise mentioned. The fact that it is absent would lead a [person of ordinary skill

in the art] to believe that either the formulations do not work to solve an epimerization problem, or that the authors did not test or otherwise have reason to believe that the disclosed formulations were solutions to the epimerization problem.

Mitscher Decl., Ex. 2008 ¶ 110 (internal citations omitted). We find Patent Owner's arguments, that a person having ordinary skill in the art would not have looked to a reference that does not mention epimerization in order to solve the problem of epimeric instability of tigecycline compositions, to be persuasive. PO Resp. 22–24; *see Yorkey v. Diab*, 601 F.3d 1279, 1284 (Fed. Cir. 2010) (holding that Board has discretion to give weight to one item of evidence over another “unless no reasonable trier of fact could have done so”).

Dr. Nelson also relies on the following statement in CN '550 regarding the therapeutic effectiveness of the disclosed lyophilized minocycline compositions as further support of Petitioner's contention that the disclosed lyophilized powder supporting agents are stabilizing the formulations against epimerization (Ex. 2012, 91:3–93:16; PO Resp. 26–27):

This disclosure is a lyophilized powder for injection with a pH level of 0–7.5, with the most suitable level being 2–3.5. Its uses are as follows: It has a very good therapeutic effect on a variety of infections caused by drug-resistant *Staphylococcus aureus*, *Chlamydia*, and *Acinetobacter*, and can be administered extravascularly. The lyophilized powder supporting agent is a soluble support easily dissolved in water and fast-dissolving in clinical applications, selected from mannitol, glucose, NaCl, dextran, and hydrolyzed gelatin.

Ex. 1046, 3.

Dr. Nelson does not provide any objective evidence explaining how the stated therapeutic effectiveness of the compositions in CN '550 correlates to epimeric stability. The mere fact that the CN '550

compositions are therapeutically effective does not necessarily mean that they are stable against epimerization. Patent Owner, however, provides evidence that stability testing does not correlate to the activity of a compound, which is determined using different testing methods. PO Resp. 29. Dr. Mitscher testified that “*stability* testing is distinct from the test of the *activity* of a compound, typically performed by assessing the minimum inhibitory concentration (‘MIC’) at which a compound inhibits growth of bacteria,” and that “an MIC test is not intended to convey information regarding a compound’s stability and does not do so.” Mitscher Decl., Ex. 2008 ¶ 65 (emphasis in original).

Dr. Mitscher also explained that a person of ordinary skill in the art would not have relied on MIC testing to reach a conclusion about the degree of a compound’s stability for a number of reasons, including that (1) MIC testing is performed on the active pharmaceutical ingredient, not on the formulation, and (2) there is no standard or accepted way of substituting MIC test results for stability test results. *Id.* ¶ 123. Dr. Williams agrees with Dr. Mitscher, and points out that a person of ordinary skill in the art “in 2005 would not have interpreted a statement about microbiological activity as indicative of the stability of a formulation, particularly a statement involving an active ingredient in the tetracycline class that is known to be susceptible to degradation.” Williams Decl., Ex. 2009 ¶ 39.

Moreover, Dr. Nelson’s testimony regarding the therapeutic effectiveness of the CN ’550 compositions and the ability of lactose to stabilize minocycline against epimerization is based on an admittedly incorrect translation of CN ’550. PO Resp. 25. Dr. Nelson’s reliance on the statement of therapeutic effectiveness in CN ’550 was premised on the first

translation's erroneous inclusion of lactose in the sentence "[t]he lyophilized powder supporting agent is a soluble support easily dissolved in water and fast-dissolving in clinical applications, selected from mannitol, glucose, NaCl, dextran, and hydrolyzed gelatin" that immediately followed the sentence describing therapeutic effectiveness. *Id.* at 26–27. According to Dr. Nelson, it was important that lactose appeared in the same paragraph as the statement of therapeutic effectiveness of the disclosed embodiments because "I would try the same experiment, just supplanting lactose for hydrolyzed gelatin because they'd mentioned that it works the same as the hydrolyzed gelatin." Ex. 2012, 91:3–25. Dr. Nelson further testified that this disclosure would provide motivation for a person skilled in the art to use lactose. *Id.* at 93:5–16. Although Dr. Nelson also testified that his conclusions are not changed by the corrected translation, neither he nor Petitioner provide any analysis or evidence as to why this is the case. *Id.* at 426:17–23.

Additionally, to the extent that Petitioner argues that a person having ordinary skill in the art would have been motivated to combine CN '550, Pawelczyk, and Naggar because they each teach stabilization of tetracyclines by saccharides (Tr. 31:4–7), that argument is similarly unpersuasive.

Specifically, Petitioner argues that Naggar's disclosure of the saccharide polysorbate 20 as being effective to stabilize tetracycline against epimerization "informs a person skilled in the art that the stabilization of tetracyclines including minocycline and tigecycline by saccharides involves a hydrogen bond between an excipient such as lactose and a tetracycline such as minocycline or tigecycline that may result from hydrogen bonding." Pet. 44. Dr. Nelson then explains that "polysorbate is a carbohydrate based

polymer having primary and secondary hydroxyl groups that are characteristic of saccharides,” and further describes that “[c]arbohydrates including monosaccharides such as glucose and mannose; disaccharides exemplified by lactose and sucrose; and poly-saccharides such as dextran, have the ability” to stabilize epimerization “via an intramolecular interaction.” Nelson Decl., Ex. 1002 ¶¶ 43, 45. At no point does Dr. Nelson or Petitioner explain adequately, however, why a person having ordinary skill in the art would have focused on Naggar’s disclosure of polysorbate 20 over other solubilizers disclosed therein (when Naggar indicates that other solubilizers worked better), nor why one would have used lactose instead of polysorbate 20 in any event, when the reference does not mention other polysaccharides, much less lactose in particular.

Dr. Nelson’s testimony is unpersuasive. Dr. Nelson opines that all of the elements of the claims disparately existed in the prior art, but fails to provide sufficient reason why one of ordinary skill in the art at the time of filing would have combined the different elements, some disclosed and some not, in the different references. *See, e.g., InTouch Techs., Inc. v. VGO Commc’ns, Inc.*, 751 F.3d 1327, 1348–49 (Fed. Cir. 2014) (holding expert testimony to be impermissible hindsight for failing to explain what reason or motivation one of ordinary skill in the art at the time of the invention would have had to place the prior art together).

In an obviousness determination, we must avoid analyzing the prior art through the prism of hindsight. Instead, we must “cast the mind back to the time the invention was made” and “occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.” *W.L. Gore & Assoc., Inc. v. Garlock*,

Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983). Here, Petitioner attempts to imbue one of ordinary skill in the art with knowledge of the claimed invention, when no prior art reference or references of record conveys or suggests that knowledge. Rather, Petitioner’s argument that CN ’550 is combinable with Pawelczyk and Naggar appears to be premised on Petitioner’s knowledge of the ’828 patent’s disclosure of lyophilized compositions of tigecycline and lactose that are stable against epimerization. *See, e.g.*, Tr. 28:6–12 (“The same saccharides are disclosed in the claims of the Chinese ’550 patent The ’828 patent says all disaccharides are expected to work. Saccharides are generally expected to work. And here are three that are expected to work. One of them is lactose, one of them is glucose, and one of them is dextran.”).

c. Conclusion

Petitioner bears the burden of showing by a preponderance of the evidence that an ordinary artisan would have had reason to combine elements in the asserted prior art references to achieve the recited compositions. On the record before us, we find that Petitioner has not shown that the combination of CN ’550, Pawelczyk, and Naggar renders the challenged claims unpatentable. Therefore, we conclude Petitioner has not demonstrated by a preponderance of the evidence that claims 1–23 of the ’828 patent would have been obvious over the combination of CN ’550, Pawelczyk, and Naggar.

C. Secondary Considerations of Non-Obviousness

Patent Owner contends that Petitioner fails to meet its burden of showing unpatentability because objective indicia of nonobviousness indicate that the claimed subject matter would not have been obvious. PO

Resp. 57–60. As discussed above, we find that Petitioner has not demonstrated that claims 1–23 would have been obvious over the combination of CN ’550, Pawelczyk, and Naggar. Thus, we need not address Patent Owner’s evidence regarding secondary considerations of nonobviousness.

III. MOTIONS TO EXCLUDE

A. *Petitioner’s Motion to Exclude*

Petitioner moves to exclude Exhibits 2010 (Grabowski Declaration), 2011 (Ofslager Declaration), 2026, 2037–2151, and 2153–2168. Paper 62, 1, 4, 5, 8, 11. Because our Decision does not rely on any of the challenged exhibits, we dismiss Petitioner’s Motion to Exclude as moot.

B. *Patent Owner’s Motion to Exclude*

Patent Owner moves to exclude CN ’550 and its accompanying translations and declarations (Exs. 1003–1005, 1046, 1047), and portions of the cross examinations of Dr. Mitscher and Dr. Williams (Exs. 2175, 2176). Paper 66, 1.

1. *Exhibits 1004, 1005, 2175, and 2176*

Because we do not rely on Exhibits 1004, 1005, nor Dr. Mitscher’s or Dr. William’s testimony on cross-examination in reaching the Final Written Decision, we dismiss as moot Patent Owner’s Motion to Exclude as to Exhibits 1004, 1005, 2175, and 2176.

2. *Exhibits 1003, 1046, and 1047*

Patent Owner argues that Exhibit 1047 (Declaration of Jennifer Brooks filed in support of the corrected translation of CN ’550 (Ex. 1046)) includes materially inaccurate statements regarding the errors in the first translation of CN ’550 (Ex. 1004). Paper 66, 11–13. According to Patent

Owner, the declaration cannot support the corrected translation of CN '550 (Ex. 1046) because it does not comply with 37 C.F.R. § 42.63(b), and in the absence of a properly supported translation, CN '550 (Ex. 1003) is inadmissible. *Id.* at 13. Patent Owner does not object to the content of the corrected translation (Ex. 1046). *See* Paper 70, 1–2.

Rule 42.63(b) states:

When a party relies on a document or is required to produce a document in a language other than English, a translation of the document into English and an affidavit attesting to the accuracy of the translation must be filed with the document.

37 C.F.R. § 42.63(b); *see also* § 42.2 and §1.68 (defining “affidavit”). The Brooks Declaration (Ex. 1047) was signed by the translator of CN '550, states that the translation is true and accurate, and includes an acknowledgement that the statements are made of the declarant’s own knowledge and with the “knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the involved patent/application.” Ex. 1047 ¶ 11. Therefore, Exhibit 1047 complies with § 42.63(b), and Exhibit 1046 is supported by a proper declaration.

Patent Owner further argues that the Brooks Declaration is misleading because it states that the inclusion of lactose in the first translation was an inadvertent error, and “that ‘excipient’ is merely a less literal translation, and there is no mention of the first declaration being submitted under Ms. Brooks’ name without her knowledge or consent.” Paper 66, 11–12. Patent Owner argues that Petitioner submitted the misleading declaration in order

to comply with Rule 42.123 regarding the filing of supplemental information. *Id.* at 10–11, 13.

Rule 42.123(b) states:

A party seeking to submit supplemental information more than one month after the date the trial is instituted, must request authorization to file a motion to submit the information. The motion to submit supplemental information must show why the supplemental information reasonably could not have been obtained earlier, and that consideration of the supplemental information would be in the interests-of-justice.

37 C.F.R. § 42.123(b). According to Patent Owner, Petitioner could not show that the corrected translation could not have been obtained earlier without including the alleged misleading statements in the declaration. Paper 66, 13.

Here, the record reflects that Petitioner provided the corrected translation in response to Patent Owner's objections to the first translation, and that Patent Owner does not object to the translation itself. Patent Owner does not identify any reason why we would be unable to weigh this evidence without prejudice or confusion.

In addition, as the moving party, Patent Owner does not persuade us that Exhibit 1047 does not comply with § 42.63(b). Accordingly, we deny Patent Owner's Motion to Exclude in relation to Exhibits 1003, 1046, and 1047.

IV. CONCLUSION

For the reasons given, we are not persuaded that Petitioner has shown by a preponderance of the evidence that claims 1–23 of the '828 patent would have been obvious over the combined teachings of CN '550, Pawelczyk, and Naggar.

V. ORDER

In consideration of the foregoing, it is

ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 1–23 of the '828 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 62) is *dismissed*;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 66) is *dismissed-in-part* and *denied-in-part*; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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