IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.
Petitioner

v.

WYETH LLC
Patent Owner

Patent No. 7,879,828

PETITION FOR INTER PARTES REVIEW
OF U.S. PATENT NO. 7,879,828
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## OTHER AUTHORITIES

- 37 C.F.R. § 42.104(a) ................................................................................................. 1
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EXHIBITS CITED

Ex. 1001 U.S. Patent No. 7,879,828 ("‘828 patent")
Ex. 1002 Expert Declaration of Raj Suryanarayanan, Ph.D.
Ex. 1003 Chinese Patent Publication No. 1390550A
Ex. 1004 Translation of Chinese Patent Publication No. 1390550A (Ex. 1003) ("CN ’550")
Ex. 1005 Declaration of Jennifer Brooks ("Brooks Decl.") (translator)
Ex. 1010 U.S. Patent No. 5,122,519 ("Ritter")


Ex. 1019  Original Tygacil® Label

Ex. 1020  Declaration of Christian L. Ofslager, filed in IPR2014-00115 as Wyeth Ex. 2011


Ex. 1022  Declaration of Robert O. Williams III, Ph.D., filed in IPR2014-00115 as Wyeth Ex. 2009

Ex. 1023  Redacted Deposition Transcript of Dr. Robert O. Williams III, Ph.D., dated September 30, 2014, filed in IPR2014-00115 as Wyeth Ex. 2176

Ex. 1024  Declaration of Lester A. Mitscher, Ph.D., filed in IPR2014-00115 as Wyeth Ex. 2008

Ex. 1025  Redacted Deposition Transcript of Dr. Lester Mitscher, dated September 23, 2014, filed in IPR2014-00115 as Wyeth Ex. 2175


Ex. 1027  International Pharmaceutical Excipients Council FAQs, *available at* http://ipecamericas.org/about/faqs#comment-0 (modified on 2010-08-26)
Ex. 1028  Curriculum vitae of Raj Suryanarayanan, Ph.D.

I. INTRODUCTION

Petitioner requests inter partes review of all claims of U.S. Patent No. 7,879,828 ("the ’328 patent", Ex. 1001) assigned to Wyeth LLC ("Patent Owner"). This Petition demonstrates that there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims, and thus a trial for inter partes review must be instituted. Evidence in this petition establishes that Claims 1 to 23 of the ’828 patent are unpatentable under 35 U.S.C. § 103( ). Petitioner respectfully requests that Claims 1 to 23 of the ’828 patent be judged unpatentable and canceled.

II. COMPLIANCE WITH REQUIREMENTS FOR AN INTER PARTES REVIEW PETITION

A. Grounds for standing

Petitioner certifies that the ’828 patent is available for inter partes review and that Petitioner is not barred or estopped from requesting an inter partes review challenging the ’828 patent claims on the ground identified herein.

The ’828 patent is the subject of pending IPR2014-00115 (hereinafter “the ’115 IPR”), filed by Apotex. Even should a written decision issue in the ’115 IPR, Apotex is not estopped from filing or proceeding with the present IPR, because
neither of the present grounds was instituted by the Board in the ’115 IPR, and the final written decision in that case will not address either of the present grounds.

Ground 1 in the present petition was previously presented as Ground 6 in the ’115 IPR petition, but Ground 6 was not considered by the Board in the ’115 IPR. Present Ground 1 is based on a different combination of references than Ground 1 at issue in the ’115 IPR and on additional expert testimony. Ground 1 in the present petition was not raised and could not have been raised during the ’115 IPR, because the Board declined to institute the ’115 IPR on Ground 6, which it deemed “redundant.” Petitioner respectfully disagrees because Ground 6 was based on a different combination of references and different motivations to a person of ordinary skill in the art.

In the ’115 IPR, Patent Owner argued that the combination CN ’550, Naggar, and Pawelczyk did not provide motivation to make the claimed composition, because CN ’550 does not expressly mention a particular degradation pathway of tigecycline in acidic solutions (epimerization). See, e.g., Ex. 1029, 39:17-21. The present petition relies on different combinations of references, including CN ’550, Kirsch, and Herman, which clearly provide motivation to a person skilled in the art to make the claimed composition, in order to reduce degradation caused by water, heat, and oxygen, without reference to any specific degradation mechanism.
Ground 2 is not redundant and is properly raised in the present IPR. Ground 2 combines the references cited in Ground 1, which themselves could not have been raised in the ’115 IPR, as noted above, with additional references in a new combination that was not raised during the ’115 IPR, thereby presenting an additional ground of unpatentability that was not considered by the Board in the ’115 IPR. See Wavemarket Inc. v. Locationet Sys. Ltd., IPR2014-00920, Paper 11, at 9-10 (instituting a second IPR where the specific combination of prior art references was not asserted in an earlier IPR petition); Medtronic, Inc. v. Robert Bosch Heathcare Sys., Inc., IPR2014-00488, Paper 17, at 11-12 (same).

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. See Apotex Inc. v. Wyeth LLC, IPR2014-00115, Paper 10, at 9. However, to the extent that 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. Apotex 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.

Furthermore, Grounds 1 and 2 are supported by both the expert Declaration of Raj Suryanarayanan, Ph.D. and by the sworn testimony of Patent Owner’s own
witnesses from the ’115 IPR supporting these grounds. Patent Owner’s witness testimony could not have been presented in the Petition for the ’115 IPR. This is another reason that the present grounds could not have been raised during the ’115 IPR.

B. Payment of fee for inter partes review

The Director is authorized to charge the fees specified by 37 C.F.R. § 42.15( ) to Deposit Account No. 194880.

C. Mandatory notices (37 C.F.R. §42.8(b))

1. Real party-in-interest (37 C.F.R. §42.8(b)(1))

The real parties-in-interest for this petition are Apotex Inc., Apotex Corp., and Apotex Holdings Inc. (collectively referred to as “Apotex”).

2. Related matters (37 C.F.R. §42.8(b)(2))

On information and belief the ’828 patent has been involved in litigations styled Vyeth Holdings Corp., et al. v. Sandoz Corp., Civil Action No. 09-955-LPS-CJB (D. Del.); Pfizer Inc. et al. v. Fresenius Kabi USA LLC, Case No. 1:13-cv-01893-SLR (D. Del.); Pfizer Inc. et al. v. CFT Pharmaceuticals LLC, Case No. 1:14-cv-00781-S-R (D. Del.); and Pfizer Inc. et al. v. Abbott Laboratories et al., Case No. 1:1-cv-00872-SLR (D. Del.). Apotex is not a party to the above litigations.
The ’828 patent has also been involved in *inter partes* review proceedings in IPR2014-00115, *Apotex, Inc. v. Wyeth LLC*, in which Apotex was a party, and IPR2014-01259, *Initiative for Responsibility in Drug Pricing LLC v. Wyeth LLC*, in which Apotex was not a party.

### 3. Lead and backup counsel (37 C.F.R. §42.8(b)(3))

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### 4. Service information (37 C.F.R. §42.8(b)(4))

Petitioner consents to electronic service by e-mail at the e-mail addresses of counsel provided above.

### 5. Power of Attorney (37 C.F.R. §42.10(b))

A power of attorney accompanies this Petition.
III. STATEMENT OF PRECISE RELIEF REQUESTED

pursuant to 37 C.F.R. §§ 42.22(a)(1) and 42.104(b), claims 1-23 of the ’828 patent are unpatentable for the following reasons.

A. Identification of prior art and challenged claims

Round 1: Claims 1-3, 6-9, 12-13, 18, and 19 are unpatentable under 35 U.S.C. § 103(a) as being obvious over CN ’550 (Ex. 1003) in view of Herman (Ex. 1006), and Kirsch (Ex. 1007).

Round 2: Claims 4, 5, 10, 11, 14-17, and 20-23 are unpatentable under 35 U.S.C. § 103(a) as being obvious over CN ’550 in view of Herman (Ex. 1006), Kirsch (Ex. 1007), Pawelczyk (Ex. 1008), and Remmers (Ex. 1009).

B. Supporting evidence relied upon

pursuant to 37 C.F.R. §§ 42.22(a)(2) and 42.104(b) 4) and (5), a full statement of the reasons why each of claims 1–23 of the ’828 patent should be held unpatentable under 35 U.S.C. § 103(a) is provided in Section X below by reference to the supporting evidence, including the exhibits identified above. Petitioner relies on the expert declaration of Raj Suryanarayanan, Ph.D. (Ex. 1002).

Dr. Suryanarayanan is a Professor in the Department of Pharmaceutics, University of Minnesota, where his research and teaching focuses on pharmaceutical materials science as it relates to pharmaceutical formulations, including the physical characterization of drugs and excipients, phase transitions
that occur during pharmaceutical processing, specifically during freeze-drying (lyophilization), and optimization of freeze-drying of pharmaceuticals. Ex. 1002, ¶ 3. Since 2006, Dr. Suryanarayanan has held the William and Mildred Peters Endowed Chair at the Department of Pharmaceutics. Id. Dr. Suryanarayanan has published extensively in the field of freeze-drying (lyophilization). Id. at ¶ 4. Dr. Suryanarayanan’s curriculum vitae is attached as Ex. 1028.

IV. OVERVIEW OF THE ’828 PATENT


The ’828 patent relates to pharmaceutical compositions containing tigecycline, an antibiotic; lactose, a commonly used pharmaceutical excipient; and hydrochloric or gentisic acid having a specified pH “in a solution.”. Ex. 1002, ¶ 11. The ’828 patent contains the following admissions with respect to prior art pharmaceutical compositions containing tigecycline:

- Tigecycline is a known member of the tetracycline family of antibiotics and is a chemical analog of minocycline. Ex. 1001, 1:23-24.
- Tigecycline has historically been administered intravenously, using intravenous solutions that have been prepared from lyophilized (i.e.,
freeze-dried) powders and is currently manufactured as a lyophilized powder. Ex. 1001, 1:46-56.

- The ’828 patent generally discloses that “in solution, tigecycline oxidation is relatively rapid. Under current manufacturing, storage, and administration conditions, the most prevalent form of degradation is via oxidation.” Id. at 2:23-28.

- Tigecycline degrades rapidly in water at pH 7.8, principally by oxidation. Id. at 1:50-51; 2:23-42.

- “At low pH, however, another degradative process occurs, epimerization. At lower pHs, epimerization emerges as the most predominant degradation pathway.” Id. at 2:46-50. Epimerization is a known degradation pathway in tetracyclines. Id. at 3:31-37.

- “In the lyophilized state, tigecycline follows the same degradation pathways as in solution, but the rate of degradation is slower. Thus, when tigecycline is lyophilized in water such that the pH is about 7.8, the resulting lyophilized cake exhibits oxidative degradation, albeit at a slower rate than in solution. Similarly, when tigecycline is lyophilized in an acidic solution, the primary degradation pathway is epimerization and it also occurs at a slower rate than in solution.” Id. at 3:23-31.
• Conventional methods for reducing epimer formation in tetracyclines include “avoiding contact with moisture including water-based solutions.” *Id.* at 3:46-54.

• “Tetracycline epimerization is also known to be temperature dependent, so production and storage of tetracyclines at low temperatures can also reduce the rate of epimer formation.” *Id.* at 3:56-62.

The ’828 patent discloses that when the pH of a solution containing tigecycline is lowered to reduce oxidative degradation, as admittedly known in the prior art, “suitable carbohydrates act to stabilize tigecycline against epimer formation at acidic pHs.” Ex. 1001, 4:56-59. Suitable carbohydrates include conventional pharmaceutical lyophilization excipients, such as lactose, sucrose, glucose, and dextran. *Id.* at 5:14-26; 5:57-59; Ex. 1002, ¶ 13.

V. **THE BROADEST REASONABLE CONSTRUCTION OF CLAIM TERMS**

Pursuant to 37 C.F.R. §§ 42.104(b)(3) and 42.100(b), Petitioner states that the challenged claims should be given their plain and ordinary meaning, in light of the specification. As stated by the Board in the ’115 IPR Institution Decision (Paper No. 10), p. 5, “[t]he terms in the challenged claims need not be construed expressly for purpose of this decision.” Petitioner therefore considers that express constructions are not required for the terms in the challenged claims. This
The proposed interpretation is offered only to comply with § 42.100(b) and does not constitute Petitioner’s interpretation or construction of the claims under the different claim construction standard required in federal court litigation.

VI. A PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art in the field of the ’828 patent would have been a pharmaceutical scientist with at least a M.S. degree, with three years of additional experience in pharmaceutical formulation or a Ph.D. degree in Pharmaceutical Sciences who is familiar with pharmaceutical formulation. Ex. 1002, ¶ 9. The knowledge typically possessed by a person of ordinary skill in the art would have included an understanding of pharmaceutical formulations, their stabilization, and their preparation techniques, which would include lyophilization. Id. at ¶10. A person of ordinary skill in the art relating to pharmaceutical formulation will typically work with chemists and other scientists as a member of a team of skilled workers. Id. at ¶ 9.

VII. TETRACYCLINE ANTIBIOTICS

As stated in the ’828 patent, tigecycline is a widely-used antibiotic that is a member of the tetracycline family and an analog of minocycline. Ex. 1001, 1:23-24; Ex. 1002, ¶ 14. Tigecycline differs from minocycline only in the group that is substituted at the 9-position in the tetracycline nucleus. Ex. 1001, 2:51-3:15; Ex. 1002, ¶ 14.
A. Oxidative degradation of tetracyclines

The ’828 patent states that tigecycline undergoes oxidative degradation in aqueous solution at a pH that is higher than the pKa of the phenolic group on tigecycline. Ex. 1001, 2:23-50; Ex. 1002, ¶ 15. The ’828 patent does not disclose this pKa, or any other pKa of tigecycline. If the pH of the solution is less than the undisclosed pKa of the phenolic group, then oxidation occurs to “a lesser extent,” but epimerization occurs “at lower pHs.” Ex. 1001, 2:46-50; Ex. 1002, ¶ 15. Oxidation is thus the primary degradation pathway at “higher pHs,” and epimerization is the most predominant degradation pathway at “lower pHs.” Id. The ’828 patent does not describe the “lower pHs” at which epimerization

1 Petitioner is unaware of any prior art publication disclosing the pKas of tigecycline. Ex. 1026 in IPR2014-00115, which discloses this information, was not published before it was electronically signed by the FAA on June 15, 2005. See exhibit page 30.
“emerges” as the “most predominant” degradation pathway and does not describe the quantitative relationship between oxidation and epimerization at this pH, or indeed at any other solution pH. Ex. 1002, ¶ 16. There is no more specific information and no experimental data concerning oxidation in the ’828 patent. Id.

Specifically with respect to minocycline, Pawelczyk (Ex. 1008) discloses that minocycline can epimerize and be oxidized and that the compound should be particularly susceptible to oxidation due to presence of a dimethylaminophenol moiety in the molecule. Ex. 1008, p. 409; Ex. 1002, ¶ 17. Pawelczyk investigated the stability of minocycline in aqueous solutions within a broad pH range, both under aerobic and anaerobic conditions. Ex. 1008, p. 409; Ex. 1002, ¶ 17. Pawelczyk discloses that oxidation of minocycline occurs in an aqueous solution having a pH from about 1 to about 10. Ex. 1002, ¶ 17. As shown in Fig. 6, reproduced below, Pawelczyk teaches that the rate of oxidation of minocycline decreases in aqueous solution as the pH is reduced below about 7.5. Ex. 1002, ¶ 18; Ex. 1008, Fig. 6, Table 1. Additionally, from Fig. 6 it is evident that the reaction rate levels off at a pH above about 7.5. Ex. 1002, ¶ 18.
Pawelczyk concluded that “[o]xidation is a predominant process of MC degradation above pH 5.” Ex. 1008, p. 417; Ex. 1002, ¶ 18.

Pawelczyk further teaches that the decomposition of minocycline in solution is temperature dependent, increasing with rising temperature. Ex. 1002, ¶ 19. Fig. 1 and Tables 1 and 2 teach that under anaerobic conditions, increasing temperature increases the decomposition rate of minocycline. *Id.* Pawelczyk’s Table 3 likewise teaches that the decomposition rate of minocycline increases with increasing temperature in air atmosphere. *Id.*

Pawelczyk also discloses that under a nitrogen atmosphere, *i.e.*, in the absence of oxygen, minocycline is degraded by a “water-evoked spontaneous reaction,” and “its rate depends on the charge of the substrate.” *Id.* at ¶ 20; Ex. 1008, pp. 414-415. Accordingly, it was known that the degradation of minocycline occurs in the presence of water and increases with temperature. Ex. 1002, ¶ 20.
It was therefore known from Pawelczyk that oxidation is a predominant
degradation path way of tetracyclines, including minocycline, in “higher” pH
aqueous solutions. A person of ordinary skill in the art would have sought to avoid
degradation of tetracyclines by oxygen, by reducing the pH of an aqueous solution
containing a tetracycline, including minocycline and tigecycline. Ex. 1002, ¶ 107.

**B. Epimerization of tetracyclines**

Since 1963 it has been known that tetracyclines undergo a reversible
epimerization in aqueous solution at a pH between 2.4 and 6.0 and that the
epimerization reaction takes place most rapidly at a pH between 3 and 4. Ex.
1002, ¶ 22; Ex. 1009, p. 126. 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. As shown in Fig. 6, reproduced below, the maximum
epimer content was 55% and occurred at a pH of 3.2. Ex. 1002, ¶ 23. The epimer
concentration decreased to less than 40% at pH 4.0 and 5.0 and to less than 20% at
pH 6.0. Id.
It was thus well known by 1963 that tetracyclines undergo an epimerization reaction in aqueous solutions over the pH range of 2.4 to 6.0 and that the highest epimer content was observed at pH 3.2. *Id.* at ¶ 24. It was known that the extent of epimerization was reduced when the pH of the solution is increased either to 4.0 or to 5.0 and that degradation by epimerization was further reduced at pH 6.0. *Id.* It was also well-known by 1963 that the epimerization reaction was temperature dependent and increased more than 3-fold when the solution temperature was increased from 23º C to 37º C. Ex. 1009, p. 755, Table VI.

Based on Pawelczyk and Remmers, a person of ordinary skill in the art would understand that both oxidation and epimerization of tetracyclines, including minocycline and tigecycline, occur in aqueous solutions within a pH range from about 2.4 to about 6. Ex. 1002, ¶ 25. Pawelczyk would have motivated a person of ordinary skill in the art to reduce the pH of an aqueous solution containing minocycline to a pH below about 7.5, and preferably to about 5, to limit the rate of
oxidation of the compound in solution. *Id.* Remmers, on the other hand, would have motivated a person of ordinary skill in the art to increase the pH of a solution containing a tetracycline from 3.2 to about 6, in order to reduce epimerization of the compound in an acidic solution. *Id.* A person of ordinary skill in the art would have sought to preserve the amount of active tetracycline antibiotic, by adjusting the pH to avoid epimerization and oxidation of the compound in aqueous solution. *Id.*

In 1992, Ritter confirmed that tetracycline antibiotics, including minocycline, undergo degradation by epimerization in protic solvents, including aqueous media, and that “the degradation appears to start immediately upon solution and continues rapidly until an equilibrium is reached in the concentration of tetracycline and epimer. This equilibrium point is temperature and pH dependent, with more epimer being formed at higher temperatures and lower pH.” Ex. 1010, 2:6-25; Ex. 1002, ¶ 26. Furthermore, “[e]ven after this equilibrium is reached, degradation continues to take place due to oxidation and other side reactions. This leads to limited life for such tetracycline products in aqueous media.” Ex. 1010, 2:21-25; Ex. 1002, ¶ 26.
VIII. TETRACYCLINE, TIGECYCLINE, AND MINOCYCLINE ARE DEGRADED BY WATER, HEAT, AND OXYGEN

As stated in the ’828 patent, tetracyclines, including tigecycline, degrade in solid formulations, principally by oxidation and epimerization that are promoted by exposure to heat, humidity, and oxygen. Ex. 1002, ¶ 27; Ex. 1001, ’828 patent at 3:23-25 (“In the lyophilized state, tigecycline follows the same degradation pathways as in solution, but the rate of degradation is slower.”); id. at 3:46-54 (conventional methods for reducing epimer formation in tetracyclines include “avoiding contact with moisture including water-based solutions”); id. at 3:56-62 (“Tetracycline epimerization is also known to be temperature dependent, so production and storage of tetracyclines at low temperatures can also reduce the rate of epimer formation.”) (citing Pawelczyk, Ex. 1008). Degradation is also increased by water, including water vapor, and oxygen. Ex. 1002, ¶ 27; Ex. 1001, 3:46-54 (conventional methods for reducing epimer formation in tetracyclines include “avoiding contact with moisture including water-based solutions”).

The problems of degradation of tigecycline by oxidation and by contact with moisture, including water-based solutions, were known problems with tetracycline antibiotics, including minocycline. Ex. 1002, ¶ 28. It was similarly known that minocycline undergoes spontaneous water-evoked degradation as well as oxidation.
in aqueous solutions and that degradation rate of minocycline is temperature dependent. *See* Ex. 1008, Fig. 1, Tables 2 and 3; Ex. 1002, ¶ 28.

Tigecycline and minocycline are both marketed as freeze-dried powders to be reconstituted into solution for intravenous administration because they are known to be unstable in aqueous solutions. Ex. 1002, ¶ 29. The original Tygacil® lyophilized powder, without lactose, was stable in aqueous I.V. solution at room temperature for at most 6 hours. Ex. 1019, p. 16; Ex. 1002, ¶29. As stated in the ’828 patent, tigecycline has a short admixture time, and “the reconstitution time is essentially zero because in solution, tigecycline oxidation is relatively rapid.” Ex. 1001, 2:23-26. It was similarly known that minocycline undergoes discoloration on exposure to strong light and/or moist air, and epimerizes in solution. Ex. 1002, ¶ 29; Ex. 1015, p. 1150. A person of ordinary skill in the art would have sought to extend the stability of minocycline and tigecycline against degradation by water, oxygen, heat, and light, both in solution and in lyophilized formulations. Ex. 1002, ¶ 29.

The discovery that lactose is effective to stabilize tetracycline antibiotics against degradation caused by oxidation, heat, and humidity was made long before the earliest filing date referenced in the ’828 patent. In 1974, Trivedi investigated the degradation of tetracycline, which is “very seriously affected and tremendously destroyed at higher humidities and higher temperatures.” Ex. 1011, p. 184 and
Table II, p. 183. Trivedi evaluated the degradation of tetracycline in compositions containing 9 diluents at 5º C, room temperature, 37º C, and 45º C and at 30% and 45% relative humidity, over a period of 60 days. Id. at 179. Based on these experimental results, Trivedi concluded that “[a]s regards the stability of tetracycline hydrochloride with selected diluents is concerned mannitol is found to be the best maintaining the first grade throughout except at 50º followed by lactose.” Id. at 184. Trivedi thus discloses a composition of tetracycline and lactose that is stable against degradation under high temperature and humidity conditions.

The problems of minocycline degradation caused by heat, water, and oxygen were notoriously well known since 1982 from Pawelczyk (Ex. 1008). Ex. 1002, ¶ 30. These are the same problems of degradation of tigecycline on storage and in aqueous solutions. The stabilization of minocycline against degradation caused by heat, water, and oxygen during transportation and storage are the goals disclosed in CN ’550 for using the disclosed “freeze drying supporting agents” in the claimed lyophilized powder composition. Ex. 1004, Summary and p. 1; Ex. 1002, ¶ 30.
IX. LYOPHILIZATION TECHNIQUES ARE USED TO IMPROVE THE STABILITY OF PHARMACEUTICAL COMPOSITIONS

A. Lyophilization processes are conventionally used for drugs that are unstable in contact with water

freeze-drying, often referred to as lyophilization, is routinely used to solve the problem of aqueous instability. Ex. 1002, ¶ 1. The removal of water by lyophilization yields a product that can be stored in the form of a dry powder for an extended period of time and then reconstituted for parenteral administration immediately prior to use. Id.

As explained by Avis:

Soon after World War II, the pharmaceutical industry began considering the process for the preparation of sterile injectable dosage forms which could not be formulated into stable solutions. … Substances that degrade in solution become candidates for freeze-drying.

Ex. 1016, p. 217.

As shown in Kirsch (Ex. 1007, p. 91), a conventional lyophilization process consists of three stages: freezing, primary drying, and secondary drying.
As described in Avis:

The process of freeze-drying generally involves: (1) dissolving the drug and excipients in a suitable solvent (frequently water); (2) sterilizing the bulk solution by passing it through a bacteria-retentive filter; (3) filling into individual sterile containers; (4) freezing the solution by placing the open containers on cooled shelves in a freeze-drying chamber or prefreezing in another chamber; and (5) applying a vacuum to the chamber and heating the shelves in order to sublime the water from the frozen state.

Ex. 1002, ¶ 34; Ex. 1016, p. 218.
In the freezing step when an aqueous solution containing a drug is cooled, the first event observed usually is ice crystallization. Ex. 1002, ¶ 35. This causes freeze concentration of the solute. Id. Crystallization of the solute may then occur. Id. However, the solute may also remain in an amorphous state. Id.; Ex. 1017, p. 194.

The initial freezing stage is described in Avis, as follows:

The initial freezing process is of critical importance since it will influence the pattern of the sublimation phase. The latter phase must occur from the solid state throughout the cycle. Appropriate cooling cycles must be determined in order to obtain an appropriate structure of the frozen mass, which is a function of the rate of freezing and the final freezing temperature. The rate of freezing also affects the size of ice crystals. The slower the rate of freezing, the larger the ice crystals that form.

Ex. 1016, p. 219.

In the primary drying step of a typical lyophilization process, the ice formed during freezing is removed by sublimation at subambient temperatures under vacuum. Ex. 1002, ¶ 39.

The ’828 patent contains no disclosure relating to the primary drying step of the lyophilization process that was used in the patent examples. Ex. 1002, ¶ 40; Ex. 1023, Williams Dep. Tr., 207:18-208:15.
In the secondary drying step of a typical lyophilization process, the relatively small amount of sorbed water remaining in the matrix is reduced by desorption. Ex. 1002, ¶ 41. During this stage, the shelf temperature is increased to promote desorption and achieve the desired residual water content in the final lyophile. Id.

The ’828 patent contains no disclosure relating to the secondary drying step of the lyophilization process that was used in the patent examples. Ex. 1002, ¶ 42; Ex. 1023, Williams Dep. Tr., 208:16-20.

The CN ’550 patent provides both a general description of lyophilization process parameters and a specific lyophilization process that provides a “powder injection that features stable light, thermal, oxygen, and water properties.” Ex. 1004, p. 3. It is well known to persons skilled in the art that lyophilization process conditions are important in determining the properties of a lyophilized drug formulation. Ex. 1023, Williams Dep. Tr., 118:21-124:21.

In contrast to CN ’550, the ’828 patent provides no information on the lyophilization process that was used in the examples, other than the initial freezing temperature and the use of dry ice with acetone, or a freeze dryer in the freezing step. Ex. 1002, ¶ 43; Ex. 1023, Williams Dep. Tr., 206:14-208:20. During the ’115 IPR, Christian Ofslager testified that the epimer content of a lyophilized formulation of tigecycline and lactose can double, depending on the temperature of
B. Lactose and mannitol are two of the most commonly used lyophilization supporting agents

Lyophilized drug formulations are frequently prepared using excipients that are added prior to freeze-drying. Ex. 1002, ¶ 44. CN ’55 refers to these excipients as “freeze drying supporting agents,” but pharmaceutical formulation scientists generally refer to any ingredient other than an active ingredient as an “excipient.” Id. Excipients such as lactose and mannitol are also referred to as “bulking” agents (Herman, Ex. 1006) or as “diluents” (Kirsch, Ex. 1007) that provide a physical matrix for the pharmaceutical ingredients. Id.

1. Herman teaches that lactose is superior to mannitol as a bulking agent for water-sensitive drugs

Lactose and mannitol are “two of the most commonly used bulking agents in freeze-dried injectable formulations....” Ex. 1002, ¶ 45; Ex. 1006, p. 1467; see also Ex. 1012, p. 182 (“[C]ommon excipients used for bulking agents in the pharmaceutical industry are mannitol, glycine, lactose, and sucrose.”).

In a lyophilized composition, these compounds can act as bulking agents. Ex. 1012, ¶ 46. Lactose, for example, provides physical support for drugs in the
lyophilized compositions disclosed by Kirsch and Herman and also acts to chemically stabilize the drugs against degradation by hydrolysis, by reducing the amount of water coming in contact with the drug in the lyophilized product. *Id.*; Ex. 1006, p. 1472; Ex. 1007, p. 94. Herman considers that lactose in these formulations can act as an “internal desiccant” that prevents chemical degradation of the water-sensitive drugs, caused by residual water in the lyophilized composition. Ex. 1002, ¶ 46; Ex. 1006, p. 1472. Herman further discloses that lactose is superior to mannitol for stabilizing lyophilized methylprednisolone sodium succinate against hydrolysis resulting from residual moisture in the lyophilized formulation. Ex. 1002, ¶ 47.

Herman investigated the effects of mannitol and lactose on the stability of methylprednisolone sodium succinate as a freeze dried solid. This prodrug is known to be unstable in aqueous solution. Ex. 1006, p. 1467. Herman compared the stability against degradation (hydrolysis) of lyophilized compositions containing: (i) 125 mg drug and 125 mg mannitol or lactose (a 1:1 weight ratio), and (ii) 40 mg drug and 210 mg mannitol or lactose (a 1:5.25 weight ratio). *Id.* at 1467 and 1468, Fig. 1. The residual moisture levels were less than 1% in all samples tested, with no significant difference in residual moisture among different formulations. *Id.* at 1468; Ex. 1002, ¶ 48.
With respect to stability of these lyophilized formulations at 40° C after 6 months’ storage, Herman found that the rate of hydrolysis of the drug with mannitol as the excipient is markedly faster than when lactose is used and that the rate of hydrolysis increases as the ratio of mannitol to drug increases. Ex. 1006, p. 1468. Herman concluded that in formulations containing mannitol as the excipient, the mannitol crystallizes either during the freeze drying process or with time during storage, depending on the ratio of mannitol to drug. Id. at 1472. In either case, there is not a significant amount of water associated with the crystalline mannitol. Id.; Ex. 1002, ¶ 49. Mannitol, however, “adsorbs very little moisture for the relative humidity range examined. This is consistent with crystalline material, where the only surface available for water vapor sorption is the surface of crystals.” Id. Herman further considers that “Crystallization of mannitol with time would result in a redistribution of water in the freeze dried matrix and an increase in the amount of water in the drug microenvironment.” Id.

Herman explained these results as follows:

The data reported here are consistent with the work of Zografi and coworkers which support the idea that the effect of water on critical attributes of amorphous drugs is determined not so much by how much water is present, but by where the water is located. The effect on critical product attributes of concentration of water within amorphous regions becomes more important as the fraction of
amorphous material decreases. In formulations containing mannitol as the excipient, the mannitol crystallizes either during the freeze dry process or with time during storage, depending on the ratio of mannitol to drug. In either case, there is not a significant amount of water associated with crystalline mannitol, as shown by the comparative water vapor sorption isotherms.”

*Id.* at 1472 (internal citations omitted).

Herman further comments on the experimental data presented as follows:

In contrast to the mannitol formulations, those containing lactose are markedly more stable because lactose remains amorphous, resulting in a more uniform distribution of water in the freeze dried matrix. This is supported by the water vapor adsorption isotherm data, showing similar affinity of both drug and lactose for water. The similar water vapor adsorption isotherms support the idea that lactose could act, in part, as an internal desiccant by competing for the available water.

*Id.*

2. **Kirsch teaches that lactose is superior to mannitol as a bulking agent for water-sensitive drugs**

Kirsch conducted stability studies of lyophilized products containing lactose, mannitol, and (R,R)-formoterol, a drug that is unstable in aqueous solution. Ex. 1002, ¶ 52; Ex. 1007, pp. 90-91, 92. Kirsch thermally stressed lyophilized products with different residual moisture contents and evaluated their stability. Ex. 1007, p. 92. These formulations contained either mannitol or lactose as an excipient, and their degradation rates were compared.
Comparing the influence of these excipients on the stability of the active ingredient, Kirsch described their effect as follows:

The effect of mannitol on formoterol degradation was profound. In Figure 4, the degradation of formoterol in mannitol (lot B) was significantly greater than that in lactose formulations (lot A) despite the much lower residual moisture content of mannitol-based formulations. This may be attributed to the intimate contact of drug and moisture on the surface of crystalline mannitol. Thus, although the total residual moisture for these formulations is low, the effective moisture content in the vicinity of the drug is high.

Id. at p. 94.

The profound difference in the stabilizing effects of mannitol and lactose could be explained from the X-ray diffraction studies conducted by Kirsch. Ex. 1002, ¶ 54.

Lactose formulations had residual moistures between 1 to 2% (Table 1). XRD showed the absence of crystallinity. Mannitol formulations dried rapidly (lot B, Table 1). Residual moistures were approximately 1%. XRD showed significant crystal structure in the lyophilized mannitol product.

Ex. 1007, p. 93.

Herman likewise reported similar results. Herman observed mannitol crystallization either during the freeze-drying process or during storage. Ex. 1002, ¶ 55. Since water would not associate with the crystalline mannitol, it would be
available to interact with the drug and bring about drug decomposition. *Id.*

Herma had also observed that in contrast to the mannitol formulations, those containing lactose are markedly more stable because lactose remains amorphous, and could act, in part, as an internal desiccant by competing for the available water.” *Id.*

**C. A Maillard reaction between lactose and tigecycline would not be expected in an acidic solution**

Although a formulation scientist would understand that a Maillard reaction could occur between a lactose and a drug having primary or secondary amine substituents, a person of ordinary skill in the art would also understand that the Maillard reaction would not occur under acidic conditions, which promote epimerization of tigecycline. Ex. 1002, ¶ 59.

Virth discloses that fluoxetine may undergo a Maillard reaction in aqueous solutions under basic conditions at high temperatures, but confirms that the Maillard reaction does not occur to any appreciable extent in acidic solutions, even at high temperatures. Ex. 1002, ¶ 60; Ex. 1013, p. 34. Virth discloses that the Maillard reaction is base-catalyzed and does not proceed to a significant extent in an acidic environment. *Id.* Virth describes a Maillard reaction of lactose and fluoxetine, a secondary amine. However, Table 2 of Virth ( ¶ 34) indicates that the reaction of lactose and fluoxetine HCL in aqueous ethanol at 60° C forms Maillard byproducts.
rapidly at pH 8.0 and 8.4, but much more slowly at pH 7.0 and extremely slowly at pH 5.0. (0.0014 percent per hour). At room temperature, a person of ordinary skill in the art would expect the reaction to proceed at a rate at least an order of magnitude lower than the rate at 60° C. Ex. 1002, ¶ 60; see also Ex. 1025, Mitscher Dep. Tr., 211:22-212:213:9. Wirth concludes that the reaction is “readily catalyzed by base.” Ex. 1013, p. 34.

Martins confirms that the Maillard reaction is base-catalyzed, and does not occur in an acidic environment. Ex. 1002, ¶ 61; Ex. 1014, pp. 369-70. At an acidic pH of 2.0-3.5, such as disclosed in CN ’550, a person of ordinary skill in the art would not expect a Maillard reaction to occur between lactose and a compound such as tigecycline or fluoxetine, having a secondary amine group. Ex. 1002, ¶ 61. Indeed, during the ’115 IPR, Wyeth’s expert Dr. Mitscher testified that a Maillard reaction would not be expected between lactose and tigecycline under acidic conditions that promote epimerization of tigecycline. Ex. 1025, Mitscher Dep. Tr., 238:7-241:8, 209:24-211:23.

As disclosed in Wirth, a Maillard reaction could easily be confirmed or eliminated by determining whether an adduct of lactose and tigecycline is present in a solution, by a simple HPLC measurement. Id. at 196:4-7.
Testa discloses a pharmaceutical composition containing tigecycline, which is preferably administered intravenously. Ex. 1018, ¶ [0076]. Testa also discloses that the pharmaceutical composition may contain conventional pharmaceutical additives including lactose. Id., at ¶ [0084]. A person of ordinary skill in the art would have understood from Testa that tigecycline is compatible with this commonly used pharmaceutical excipient. Ex. 1023, Williams Dep. Tr., 252:16-253:5.

X. OBVIOUSNESS OF CLAIMS 1-23

Claims 1-23 of the ’828 patent would have been obvious to a person of ordinary skill in the art in 2005, in view of the disclosure of the prior art, on the following grounds:

**Ground 1:** Claims 1-3, 6-9, 12-13, 18, and 19 are unpatentable under 35 U.S.C. § 103(a) as being obvious over CN ’550 (Ex. 1003) in view of Herman (Ex. 1006), and Kirsch (Ex. 1007).

**Ground 2:** Claims 4, 5, 10, 11, 14-17, and 20-23 are unpatentable under 35 U.S.C. § 103(a) as being obvious over CN ’550 in view of Herman (Ex. 1006), Kirsch (Ex. 1007), Pawelczyk (Ex. 1008), and Remmers (Ex. 1009).
A. Ground 1: Claims 1-3, 6-9, 12-13, 18, and 19 are obvious in view of CN '550, Kirsch, and Herman

Claims 1-3, 6-9, 12-13, 18, and 19 are unpatentable under 35 U.S.C. § 103 as obvious in view of the combination of CN '550 (Ex. 1003), Herman (Ex. 1006), and Kisch (Ex. 1007). CN '550 was published on January 15, 2003, more than one year before the earliest benefit date claimed in the '828 patent and is prior art under 35 U.S.C. § 102(§). References to CN '550 herein are to the translation, Ex. 1004, which is certified pursuant to 37 C.F.R. §42.63(§). See Ex. 1005.

The claims of the '828 patent recite compositions, not processes, and contain no limitation with respect to stability of the composition, to oxidation or epimerization, or to any other decomposition reaction or product. Ex. 1002, ¶ 63.

The disclosure of CN '550 is compared with Claims 1-23 as follows:

<table>
<thead>
<tr>
<th>Claim Chart 1</th>
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<tbody>
<tr>
<td>Claim 1</td>
</tr>
<tr>
<td>1. A composition comprising tigecycline, lactose, and an acid selected from hydrochloric acid and gentisic acid, and the pH of the composition in a solution</td>
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</table>
is between about 3.0 and about 7.0,

| 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. Id. at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 II. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).
The pH of a solution containing minocycline hydrochloride and mannitol is adjusted to 2.0-3.5 with hydrochloric acid in Example 1. Id. p. 4, ll. 20-29.
The pH of a solution containing minocycline hydrochloride and dextran is adjusted to 2.0-3.5 with hydrochloric acid in Example 2. Id. p. 4, l. 40- p.4, l. 4. |

wherein the molar ratio of tigecycline to lactose is between about 1:0.2 and about 1:5

| In Example 1, the composition contains 108 g of minocycline hydrochloride and 210 g of mannitol.
In Example 2, the composition contains 108 g of minocycline hydrochloride and 210 g of dextran. |

| **Claim 2** |
| A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ll.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process). |

| **Claim 3** |
| 3. The composition of claim 1 wherein the composition is in solid form. |
| A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ll.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process). |

<p>| <strong>Claim 4</strong> |
| The composition of claim 1 wherein the pH of the composition in a solution is between about 4.0 and about 5.0. |
| The lyophilized powder has a pH value between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. Id. at p. 1, summary; p. 2, claims 3, 4 and 7; p. 4, ll. 20-29. |</p>
<table>
<thead>
<tr>
<th>Claim 5</th>
<th>The composition of claim 4 wherein the pH of the composition in a solution is between about 4.2 and about 4.8.</th>
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<td>The lyophilized powder has a pH value between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. <em>Id.</em> at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ll. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).</td>
</tr>
<tr>
<td>Claim 6</td>
<td>The composition of claim 1 wherein the acid is hydrochloric acid.</td>
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<td>The pH adjusting agent includes hydrochloric acid. <em>Id.</em> p. 3, ll. 37-39, and Example 1, p.4, ll.16-24.</td>
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<tr>
<td>Claim 7</td>
<td>The composition of claim 2 wherein the acid is hydrochloric acid.</td>
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<td></td>
<td>The pH adjusting agent includes hydrochloric acid. <em>Id.</em> p. 3, ll. 37-39, and Example 1, p.4, ll.16-24.</td>
</tr>
<tr>
<td>Claim 8</td>
<td>The composition of claim 3 wherein the acid is hydrochloric acid.</td>
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<td>The pH adjusting agent includes hydrochloric acid. <em>Id.</em> p. 3, ll. 37-39, and Example 1, p.4, ll.16-24.</td>
</tr>
<tr>
<td>Claim 9</td>
<td>The composition of claim 1 wherein the molar ratio of tigecycline to lactose is between about 1:1.6 and about 1:3.3.</td>
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<tr>
<td></td>
<td>In Example 1, the composition contains 108 g of minocycline hydrochloride and 210 g of mannitol. In Example 2, the composition contains 108 g of minocycline hydrochloride and 210 g of dextran.</td>
</tr>
<tr>
<td>Claim 10</td>
<td>The composition of claim 1 wherein the pH of the composition in a solution is between</td>
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<td>The lyophilized powder has a pH value between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and</td>
</tr>
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</table>

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### Claim 11

11. The composition of claim 1 wherein the pH of the composition in a solution is between about 4.5 and about 5.5.

| about 4.5 and about 6.0. | adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. *Id.* at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ll. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique). |

### Claim 12

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.

<p>| A lyophilized minocycline hydrochloride powder that has stable light, thermal, oxygen and water properties, containing a lyophilized powder supporting agent and a pH adjusting agent. <em>Ex.</em> 1004, p. 1, Summary, p. 2, claim 5; p. 3, lines 19-27. The lyophilized powder supporting agent includes lactose. <em>Id.</em> p. 2, claim 5. The pH adjusting agent includes hydrochloric acid. <em>Id.</em> p. 2, claim 6; and Example 1, p. 4, ll. 20-25. In Example 1, the composition contains 108 g of minocycline hydrochloride and 210 g of mannitol. In Example 2, the composition contains 108 g of minocycline hydrochloride and 210 g of dextran (a polysaccharide). The lyophilized powder has a pH value in a solution between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and excipient in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. <em>Id.</em> at |</p>
<table>
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<tr>
<th>Claim 13</th>
<th>p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ll. 28-29; and; p. 3, l. 36- p. 4, l. 7. (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. The composition of claim 12 wherein the molar ratio of tigecycline to lactose is between about 1:1.6 and about 1:3.3.</td>
<td>In Example 1, the composition contains 108 g of minocycline hydrochloride and 210 g of mannitol. In Example 2, the composition contains 108 g of minocycline hydrochloride and 210 g of dextran.</td>
</tr>
<tr>
<td>Claim 14</td>
<td></td>
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<tr>
<td>14. The composition of claim 12 wherein the pH of the composition in a solution is between about 4.0 and about 5.0.</td>
<td>The lyophilized powder has a pH value between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. <em>Id.</em> at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ll. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).</td>
</tr>
<tr>
<td>Claim 15</td>
<td></td>
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<tr>
<td>15. The composition of claim 14 wherein the pH of the composition in a solution is between about 4.2 and about 4.8.</td>
<td>The lyophilized powder has a pH value between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. <em>Id.</em> at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ll. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).</td>
</tr>
<tr>
<td>Claim 16</td>
<td></td>
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<tr>
<td>16. The composition of claim 12 wherein the pH of the composition in a solution is between about 4.5 and about 6.0.</td>
<td>The lyophilized powder has a pH value between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. <em>Id.</em> at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ll. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).</td>
</tr>
<tr>
<td>Claim 17</td>
<td>7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. <em>Id.</em> at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ill. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).</td>
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<tr>
<td>--------------------------------------------------------------------------</td>
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<tr>
<td>17. The composition of claim 16 wherein the pH of the composition in a solution is between about 4.5 and about 5.5.</td>
<td>The lyophilized powder has a pH value between 0.1 and 7.5, most preferably between 2 and 3.5, and is prepared by dissolving minocycline hydrochloride and a lyophilized powder supporting agent in water and adjusting the pH value of the solution to a pH of 0.1 to 7.5, and preferably 2.0 to 3.5 with a pH adjusting agent. <em>Id.</em> at p. 1, summary; p. 2, claims 3, 4 and 7; p. 3 ill. 28-29; and p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique).</td>
</tr>
<tr>
<td>Claim 18</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ill.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process).</td>
</tr>
<tr>
<td>18. The composition of claim 12 wherein the composition is in solid form.</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ill.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process).</td>
</tr>
<tr>
<td>Claim 19</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ill.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process).</td>
</tr>
<tr>
<td>19. The composition of claim 13 wherein the composition is in solid form.</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ill.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process).</td>
</tr>
<tr>
<td>Claim 20</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ill.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process).</td>
</tr>
<tr>
<td>20. The composition of claim 14 wherein the composition is in solid form.</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ill.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process).</td>
</tr>
<tr>
<td>Claim 21</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1, summary; p. 2, claims 1-7; p. 3, ill.19-22; p. 3, l. 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (lyophilized powder); claim 3 (lyophilization process).</td>
</tr>
<tr>
<td>Claim 22</td>
<td></td>
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<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
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<tr>
<td>22. The composition of claim 16 wherein the composition is in solid</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1,</td>
</tr>
<tr>
<td>form.</td>
<td>summary; p. 2, claims 1-7; p. 3, ll.19-22; p. 3, l. 36- p. 4, l.</td>
</tr>
<tr>
<td></td>
<td>powder); claim 3 (lyophilization process).</td>
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<tr>
<th>Claim 23</th>
<th></th>
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<tbody>
<tr>
<td>23. The composition of claim 17 wherein the composition is in solid</td>
<td>A lyophilized minocycline hydrochloride powder. Ex. 1004, p. 1,</td>
</tr>
<tr>
<td>form.</td>
<td>summary; p. 2, claims 1-7; p. 3, ll.19-22; p. 3, l. 36- p. 4, l.</td>
</tr>
<tr>
<td></td>
<td>powder); claim 3 (lyophilization process).</td>
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</table>

CN ’550 discloses a lyophilized minocycline powder containing lactose and hydrochloric acid that is prepared in a solution having a pH that is from 0.1 to 7.5 and preferably 2.0 to 3.5. Ex. 1004, p. 1 (Summary); p. 2 (claims 3, 4, and 7); Ex. 1002, ¶66. The lyophilized powder is stabilized against degradation by light, heat, oxygen, and water, is easy to transport and store and has “very good therapeutic effect.” Ex. 1004, 3:19-21, 29-31; Ex. 1002, ¶66. The “goal” of CN ’550 is expressly identified as a lyophilized powder composition of minocycline that “has stable light, thermal, oxygen and water properties.” Ex. 1004, p. 1 (Summary); 2:19-22; Ex. 1002, ¶66. These goals are achieved by the disclosed lyophilized minocycline formulation. Ex. 1004, 2:24-27; Ex. 1002, ¶66.
Each of the improvements in stability disclosed in CN ’550 would have provided independent motivation to a person of ordinary skill in the art to use the lyophilization process disclosed in CN ’550 to prepare a lyophilized powder, containing tigecycline and a conventional lyophilization supporting agent including lactose. Ex. 1002, ¶¶ 69-70. The issue is whether a person of 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. See Bristol-Myers Squibb Co. v. Teva Pharms. USA, 752 F.3d 967, 976 (Fed. Cir. 2014); citing In re Dillon, 919 F.2d 688, 693, 697 (Fed. Cir. 1990) (en banc) (“it is not required … that the prior art disclose or suggest the properties newly-discovered by an applicant in order for there to be a prima facie case of obviousness”).

It was known in the art that tetracyclines, including minocycline and tigecycline, oxidize in neutral or basic solutions and epimerize in acidic solutions. Ex. 1002, ¶ 67. Although 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. Ex. 1002, ¶ 67; Ex. 1026, Wyeth Patent Owner Response (POR), p. 11; Ex. 1024, Mitscher Decl., ¶ 60. As Wyeth recognized in IPR2014-00115, “it was well accepted that the goal with regard to stability is to maintain as much of the compound as possible in conditions
and over a time period that are relevant to its expected use, irrespective of the particular pathway by which the compound degrades.” Ex. 1026, Wyeth POR, p. 11; see also Ex. 1024, Mitscher Decl., ¶ 61; Ex. 1002, ¶ 67. Dr. Williams agreed that a person of ordinary skill in pharmaceutical formulation “would be concerned with maintaining the level of the active ingredient, and it wouldn't matter to that person how it's degrading.” Ex. 1022, Williams Dep. Tr., 110:12-112:7. Dr. Williams considered that a person of ordinary skill in the art would “want to avoid degradation by light” (id. at 112:8-19); “would want to avoid degradation, really, by any mechanism, including heat” (id. at 113:13-15); and would want to “minimize the -- the degradation due to -- of the drug substance or the drug product due to moisture or exposure to humidity.” Id. at 113:16-25.

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 and to prepare the lyophilized composition in an aqueous solution having a pH from 0.1 to 7.0, preferably from 2.0 to 3.5. Ex. 1002, ¶ 69. Degradation of tigecycline caused by oxygen, water, and heat were also problems with the original, unstable tigecycline formulation. Ex. 1002, ¶ 70; see Ex. 1001, ’828 patent, 2:23-40 (oxidation); 1:60-2:3 (rapid degradation in solution); 3:23-30 (oxidation and epimerization of lyophilized tigecycline on storage); 3:56-59 (heat increases
epimerization of tetracyclines). It is not necessary that CN ’550 expressly describe the mechanisms of degradation or stabilization, which are not claimed in the ’828 patent. See KSR Int’l Co. v. Teleflex, Inc., 550 U.S. 398, 419-420 (2007) (“In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim.”)

1. A composition containing tigecycline, lactose, and hydrochloric acid would have been obvious

CN ’550 does not disclose tigecycline, but discloses a lyophilized powder for injection containing its chemical analog minocycline, a stabilizer including lactose, and a pH value adjusting agent including hydrochloric acid. Ex. 1004, 1:31-33, 3:23-39. The pH of the solution is adjusted to 0.1 to 7.5, or 2.0 to 3.5. Id. p. 2, Claims 4 and 7. As shown in the chart above, every limitation of Claims 1-3, 6-9, 12-13, 18 and 19 is literally disclosed in CN ’550, except for tigecycline.

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. 1002, ¶ 73; 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 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”. Ex. 1002, ¶ 73; Ex. 1001, 1:23-44.

The claimed composition comprising tigecycline, lactose, and hydrochloric acid, having a pH in a solution from 3.0 to 7.0, involves no more than the simple substitution of tigecycline for its known analog minocycline, in the prior art CH ’550 composition, that is ready for this predictable improvement. Ex. 1002, ¶ 73. See KSR, 550 U.S. at 417. A person of ordinary skill in the art would recognize the that technique for stabilizing minocycline disclosed in CN ’550 by using lactose, would improve a composition containing the similar antibiotic tigecycline, and a person of ordinary skill in the art can implement this predictable variation. Ex. 1002, ¶¶ 73-74. See KSR, 550 U.S. at 417 (“If a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.”).

2. The selection of lactose from CN ’550 is obvious in view of Herman and Kirsch

CN ’550 discloses a lyophilized composition containing minocycline, which is an analog of tigecycline, a freeze-drying supporting agent that can be a
commonly used lyophilization bulking agent (lactose, glucose, dextran or mannitol), sodium chloride, or hydrolyzed gelatin; and hydrochloric acid. Ex. 1004, p. 2 (claims 1, 5, and 7). CN ’550 does not include an example in which minocycline is stabilized with lactose. In Example 1, CN ’550 discloses a composition that is stabilized with mannitol. In Example 2, CN ’550 discloses a composition that is stabilized with dextran.

A person of ordinary skill in the art in 2005, seeking to stabilize a lyophilized tigecycline composition, would be motivated by CN ’550 to select lactose, which is one of the most commonly-used pharmaceutical lyophilization excipients, to stabilize the lyophilized composition against degradation caused by water, including moisture, oxygen, heat or light. Ex. 1002, ¶ 76.

A person of ordinary skill in the art, considering the common lyophilization excipients disclosed in CN ’550, would seek to develop a formulation that is stable, to water, considering that tigecycline was known to degrade in aqueous solutions and in a lyophilized composition. Ex. 1002, ¶ 77; Ex. 1001, 3:23-31. A person of ordinary skill in the art would use a lyophilization supporting agent that stabilizes tigecycline against degradation resulting from moisture in the lyophilized composition. Ex. 1002, ¶ 77. Among the lyophilization supporting agents disclosed in CN ’550, two of the most commonly used lyophilization excipients in injectable formulations are lactose and mannitol. Id.; Ex. 1006, p. 1467. A person
of ordinary skill in the art would understand that lactose, which is described as a
“bulking agent” by Herman, and as a “freeze-drying supporting agent” in CN ’550,
“may serve different functions” and “may serve different roles” in a lyophilized
pharmaceutical formulation. Ex. 1002, ¶ 77; Ex. 1023, Williams Dep. Tr., 155:25-
156:12.

Herman investigated the effects of mannitol and lactose on the stability of
methylprednisolone sodium succinate as a freeze dried solid. Ex. 1006. This
prodrug is known to be unstable in aqueous solution. Id., at 1467. Herman
compared the stability against degradation (hydrolysis) of lyophilized
compositions containing: (i) 125 mg drug and 125 mg mannitol or lactose (a 1:1
weight ratio), and (ii) 40 mg drug and 210 mg mannitol or lactose (a 1:5.25 weight
ratio). Id. at 1467 and 1468, Fig. 1.

With respect to stability of these lyophilized formulations at 40° C after 6
months’ storage, Herman found that the rate of hydrolysis of the drug with
mannitol as the excipient is markedly faster than when lactose is used and that the
rate of hydrolysis increases as the ratio of mannitol to drug increases. Id., at 1468.
Herman concluded that in formulations containing mannitol as the excipient, the
mannitol crystallizes either during the freeze dry process or with time during
storage, depending on the ratio of mannitol to drug. Id. at 1472. In either case,
there is not a significant amount of water associated with the crystalline mannitol.
Mannitol, however, “adsorbs very little moisture for the relative humidity range examined. This is consistent with crystalline material, where the only surface available for water vapor sorption is the surface of crystals.” Ex. 1006, p. 1472. Herman further considers that “Crystallization of mannitol with time would result in a redistribution of water in the freeze dried matrix and an increase in the amount of water in the drug microenvironment.” Id.

Herman concluded that “[i]n contrast to the mannitol formulations, those containing lactose are markedly more stable because lactose remains amorphous, resulting in a more uniform distribution of water in the freeze dried matrix. . . . The similar water vapor adsorption isotherms support the idea that lactose could act, in part, as an internal desiccant by competing for the available water.” Id.

Kirsch investigated the effects of diluents and residual moisture on the stability of (R,R)-formoterol in a lyophilized dosage form, suggested by the aqueous instability of the compound. Ex. 1007, p. 89, Abstract. The drug and various excipients, including lactose and mannitol, were lyophilized and placed in humidity chambers (0 to 90% relative humidity) at 25° to 50 °C. Id. Stability was characterized by time-dependent changes using HPLC, pH, and XRD. Id. Kirsch determined that the residual moisture content of the mannitol formulation was ≤1% at all humidity levels (Fig. 3, lot B), which was lower than the residual moisture content of the lactose formulation (Fig. 3, lot A). Id. at 93.
Kirsch found that “the degradation of formoterol in mannitol (lot B) was significantly greater than that in lactose formulations (lot A) despite the much lower residual moisture content of mannitol based formulations. This may be attributed to the intimate contact of drug and moisture on the surface of crystalline mannitol. Thus, although the total residual moisture for these formulations is low, the effective moisture content in the vicinity of the drug is high.” *Id.* at 94.

Herman likewise observed mannitol crystallization either during the freeze-drying process or during storage. Ex. 1002, ¶ 81. Since water would not associate with the crystalline mannitol, it would be available to interact with the drug and bring about drug decomposition. *Id.* Herman had also observed that in contrast to the mannitol formulations, those containing lactose are markedly more stable because lactose remains amorphous, and could act, in part, as an internal desiccant by competing for the available water. *Id.*

Herman and Kirsch concluded that lactose improved the stability of two water-sensitive drugs against degradation by hydrolysis. A person of ordinary skill in the art would understand from Herman and Kirsch that lactose could similarly improve the stability of a lyophilized powder containing other water-sensitive drugs. *Id.* at ¶ 84.

A person of ordinary skill in the art would appreciate that residual water in a lyophilized formulation can cause degradation in a water-sensitive drug, by
hydrolysis in the case of R,R-formoterol or methylprednisolone sodium succinate, and by oxidation or epimerization in the case of tetracycline, minocycline or tigecycline. Ex. 1002, ¶ 85; see, e.g., Ex. 1008, pp. 409, 414-415, 418, Fig. 6, Table 1; Ex. 1015, p. 1150. Wyeth’s formulation expert Dr. Williams agreed in his testimony concerning the degradation of tigecycline in a solid lyophilized cake:

Q. In your opinion, why is there degradation of, say, tigecycline in a solid lyophilized composition?
A. So why is there oxidation or epimerization when it's in a solid cake?
Q. Yes. How does that occur, in your opinion?
A. Oh. Well, the mechanism, I would rely on Dr. Mitcher. I mean, from my experience, there could be -- from lyophilization there could be residual moisture that remains on the surface of the powder. And if the drug is -- has solubility, which tigecycline does, it could dissolve in that water. And if the -- when the drug dissolved in that surface water, whatever pH it's at, if it's susceptible to a degradation process at that pH, then there could be some degradation, from my experience.


A person of ordinary skill in the art, seeking to develop a stable lyophilized formulation of minocycline or tigecycline, considering the lyophilization excipients disclosed in CN ’550, would be encouraged by Kirsch and Herman to
use lactose in the formulation to reduce degradation of the drug associated with residual water in the lyophilized composition, rather than mannitol disclosed in the CN ’550 Example. Ex. 1002, ¶ 86. Dr. Williams testified that under the lyophilization conditions disclosed in Claim 3 of CN ’550, a person of ordinary skill in the art would expect mannitol to crystallize in the lyophilization product. Ex. 1023, Williams Dep. Tr., 192:20-193:1. Dr. Williams considered that what Herman found “is that when mannitol crystallizes, that that – over time that causes a redistribution of water, and then it exacerbates the hydrolysis of the [drug].” Id. at 202:5-9; see also Ex. 1002, ¶ 87.

A person of ordinary skill in the art would be encouraged by Herman and Kirsch to select lactose rather than mannitol as a lyophilization excipient for minocycline or tigecycline in order to reduce the amount of residual water in the solid cake that comes into contact with the active pharmaceutical ingredient. Ex. 1002, ¶ 88.

3. The lactose : tigecycline ratios are obvious for freeze-drying supporting agents

Claims 1 and 12 recite a molar ratio of tigecycline to lactose that is between about 1:0.2 and about 1:5. Claims 9 and 13 recite that the molar ratio of tigecycline to lactose is between about 1:1.6 and about 1:3.3. These claims each refer to a molar ratio of tigecycline to lactose. A person of ordinary skill in the art
would understand that these molar amounts of lactose recited in the claims correspond to specific weights of lactose. Ex. 1002, ¶ 90. As shown in Tables 6a and 6b, the molar ratio (tigecycline to lactose) of 1:1.62 corresponds to a 1:1 weight ratio, and the molar ratio of 1:3.25 corresponds to a weight ratio of 1:2. *Id.* The molar ratio of 1:0.24 corresponds to a weight ratio of 1:0.15, and the molar ratio of 1:4.87 corresponds to a 1:3 weight ratio. *Id.; see* Ex. 1001, 14:1-32 and Tables 6a and 6b. Claims 1 and 12 thus literally encompass a weight ratio of tigecycline:lactose of from about 1:0.15 to about 1:3. Ex. 1002, ¶ 90. Claims 9 and 13 encompass a weight ratio of tigecycline:lactose of from about 1:1 to about 1:2. *Id.*

Example 1 of CN ’550 discloses a composition containing 108 g of minocycline hydrochloride and 210 g of mannitol, as a “freeze drying supporting agent.” Example 2 of CN ’550 discloses a composition containing 108 g of minocycline hydrochloride and 210 g of dextran. CN ’550 discloses that lactose and the other disclosed lyophilization “supporting agents” are effective to stabilize minocycline against light, oxidation, heat, and water.

A person of ordinary skill in the art considering the weight ratio of minocycline hydrochloride to mannitol in Example 1 of CN ’550, and the same weight ratio of minocycline hydrochloride to dextran in Example 2, would consider it obvious to use the same weight ratio of minocycline hydrochloride to
lactose as a “freeze drying supporting agent.” Ex. 1002, ¶ 91. Based on the disclosure of CN ’550, a person of ordinary skill in the art would use the same weight ratios of each disclosed “supporting agent” to stabilize the lyophilized composition containing against degradation caused by light, heat, oxygen and water. Id.

A person of ordinary skill in the art would find it obvious to use conventional lyophilization bulking agents such as lactose in amounts that correspond to the weight ratios of mannitol or dextrose to minocycline in the CN ’550 examples. Ex. 1002, ¶ 92. For this reason, a person of ordinary skill in the art would find it obvious to stabilize a composition containing tigecycline and the lactose in a weight ratio of approximately 108:210. Id. The molar ratio of tigecycline:lactose corresponding to a weight ratio of 108:210 is about 1:3.3, within the scope of Claims 9 and 13, which encompass ratios of “about” 1:3.3. Id. The molar ratios of tigecycline:lactose recited in Claims 1, 9, 12, and 13 are thus obvious in view of the weight ratios of minocycline hydrochloride to stabilizers including mannitol and dextran, disclosed in CN ’550. Id.

4. Obviousness of pH ranges

The “acidic pHs” recited in independent Claims 1 and 12 are a broad range, from between “about 3.0” and “about 7.0.” CN ’550 discloses compositions
having a pH from 0.1 to 7.5 and a preferred pH of 2.0-3.5. Ex. 1004, at p. 1, summary; p. 2, claims 3, 4, and 7; p. 3 ll. 28-29; and p. 3, 36- p. 4, l. 7 (lyophilization process); p. 4, Examples 1 and 2 (preparation technique). The claimed range overlaps the disclosed preferred range of 2.0-3.5 and is within the broader disclosed range of 0.1 to 7.5. The claimed range would therefore have been obvious to a person of ordinary skill in the art. Ex. 1002, ¶ 94; see Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006) (where a claimed range overlaps with a prior art range, there is a presumption that the claimed range is obvious).

B. Ground 2: Claims 4, 5, 10, 11, 14-17, and 20-23 are obvious over CN ’550 in view of Kirsch, Herman, Remmers, and Pawelczyk

Dependent claims 4, 5, 10, 11, 14-17, and 20-23 are unpatentable under 35 U.S.C. § 103 as being rendered obvious by CN ’550 (Ex. 003), in combination with Herman (Ex. 1006), Kirsch (1007), Pawelczyk (Ex. 1008), and Remmers (Ex. 1009), for the reasons set forth above. The dependent claims recite overlapping pH ranges between about 4.0 and about 6.0, i.e., “between about 4.0 and about 5.0 (claims 4, 14 and 20); “between about 4.2 and about 4.8” (claims 5, 15, and 21); “between about 4.5 and about 6.0” (claims 10, 16, and 22); and “between about 4.5 and about 5.5” (claims 11, 17, and 23). CN ’550 does not expressly disclose a
composition having a pH in a solution between 4.0 and 6.0, although this range is within the broader pH range of 0.1 to 7.5 disclosed in the Chinese reference.

A person of ordinary skill in the art could readily determine pH ranges of an acid solution within the broader range of 0.1 to 7.5 that would be effective to stabilize lyophilized compositions containing tigecycline against degradation in aqueous solutions. Ex. 1002, ¶ 97. It would have been obvious to a person of ordinary skill in the art to use lactose to stabilize a composition containing tigecycline and hydrochloric acid against degradation caused by water, oxygen, heat, and light, by preparing the composition in a solution within any of the mildly acidic pH ranges recited in dependent Claims 4, 5, 10, 11, and 14-17. Ex. 1002, ¶ 97; see Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1376-77 (Fed. Cir. 2005) (prior art range of concentration from 0.01 to 20% by weight anticipates where it encompasses the claimed ranges of up to 10%, 0.025 to 5%, and 0.025 to 10%); Medicem S.A. v. Rolabo S.L., 437 F.3d 1157, 1168 (Fed. Cir. 2006) (the normal desire to improve on prior art provides motivation “to determine where in a disclosed set of percentage ranges is the optimum combination of percentages”) (quotation omitted).

There can be no non-obvious distinction based on the pH ranges recited in the dependent claims, because the ’828 patent admits that there is no significant difference in degradation between tigecycline formulations prepared in solutions
having a pH from 4.5 to 6.0. Ex. 1002, ¶ 98. Table 1 of the ’828 patent shows that there is essentially no difference in epimerization at pH 4.5 (2.53% epimer), pH 5.0 (2.43% epimer), pH 5.5 (2.54%) and pH 6.0 (2.56%). Id. Table 2a further discloses that there is no significant difference between epimer content, or remaining tigecycline content, when the lyophilized powder containing tigecycline and lactose is prepared at pH 4.5 with lactose (1.37% epimer, 98.42% tigecycline) and at pH 3.0 with lactose (1.34% epimer, 98.49% tigecycline).

2 The margin of error in the experimental data disclosed in the ’828 patent is not stated, and it is not possible to determine the accuracy of the experimental results without information on the specific HPLC method and conditions that were used to determine the values, which are not disclosed. Ex. 1023, Williams Dep. Tr., 209:4-210:4; 13:9-17; 15:7-20. Christian Ofslager, who was responsible for developing the process used to manufacture reformulated Tygacil, was unable to describe the margin of experimental error in the ’828 patent data, or in Wyeth’s standard HPCL analytical method. Ex. 1021, Ofslager Dep. Tr., 323:10-324:19; 325:5-326:10. U.S. Patent Pub. No. 2010/0035845 (Ofslager et al.) states that the tigecycline content remaining after time at various pH values is accurate to within ±2%. Mr. Ofslager testified that this indicates that the tigecycline content could
A composition containing tigecycline, lactose and hydrochloric acid having a pH in a solution within each of the ranges recited in Claims 4, 5, 10, 11, and 14-17 (and dependent claims 20-23) would further have been obvious in view of Remmers (Ex. 1009) and Pawelczyk (Ex. 1008), which disclose tetracycline and minocycline compositions that are stable against oxidative degradation and epimerization in solutions having a pH between about 4 and 5. Ex. 1002, ¶ 100.

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. Ex. 1002, ¶ 101. As shown in Fig. 6, the maximum epimer content was 55% and occurred at a pH of 3.2. The epimer concentration decreased to less than 40% at pH 4.0 and 5.0, and to less than 20% at pH 6.0.

![Graph of C4 epimer at equilibrium as a function of pH.](image)

Fig. 6—Equilibrium concentrations of C4 epimer as a function of pH.

have a variation of ±2% due to error in the HPLC analytical method. Id. at 321:21-322:19.
It was thus well known by 1963 that tetracycline undergoes an epimerization reaction in aqueous solutions at pH 2.4 to 6 and that the maximum epimer content occurs at pH 3.2. Ex. 1002, ¶ 102. It was known that the epimerization is significantly reduced when the pH of the solution is increased to 4.0 and 5.0 and that degradation by epimerization is further reduced in an aqueous solution at pH 6.0. *Id.* A person of ordinary skill in the art would have been motivated by Remmers to increase the pH of a solution containing minocycline or tigecycline and lactose to a pH higher than the preferred range of 2.0-3.5 and within the broader range of 0.1 to 7.5 disclosed in CN ’550, in order to reduce epimerization of the tetracycline antibiotic in the acidic solution. Ex. 1002, ¶ 103.

Pawelczyk teaches that oxidation of minocycline occurs in an aqueous solution having a pH from about 1 to about 10. Pawelczyk discloses that the rate of oxidation minocycline is reduced if the pH of the solution is reduced below about 7.5. *Id.* at ¶ 104. Additionally, from Fig. 6, it is evident that the reaction rate levels off at a pH above about 7.5. *Id.*; Ex. 1008, Fig. 6.
Pawelczyk concluded that “[o]xidation is a predominant process of MC degradation above pH 5.” Ex. 1008, p. 417.

It was thus known from Pawelczyk that oxidative degradation of minocycline occurs in aqueous solution at a pH from about 1 to about 10 and that the rate of oxidation decreases when the pH of a solution is reduced below about 7.5, preferably to about 5. Ex. 1002, ¶ 105.

Based on the teachings of Remmers, a person of ordinary skill in the art would adjust the pH of a solution of tetracycline, minocycline or tigecycline to a mildly acidic range of about 4-6, to limit degradation by epimerization. Ex. 1002, ¶ 106. Based on the teachings of Pawelczyk, a person of ordinary skill in the art would reduce the pH of an aqueous solution of minocycline to less than about 7.5, and preferably to about 5 to avoid oxidative degradation. Id. Clearly, a person of ordinary skill in the art would have sought to reduce overall degradation of
tigecycline by seeking a solution pH sufficiently high to reduce epimerization as taught by Remmers, yet sufficiently low to reduce oxidation as taught by Pawelczyk. *Id.*

The pH ranges recited in Claims 1, 4, 5, 10-12, and 14-17 all encompass values within the overlapping range of about 4 to about 5 taught by Pawelczyk and Remmers to reduce degradation of tetracyclines by oxidation and epimerization, and the pH ranges recited in each of these claims would have been obvious in view of CN ’550, in combination with Remmers and Pawelczyk. *Id.* at ¶ 107. *See Perricone, supra,* 432 F.3d at 1376-77; *Medichem, supra,* 437 F.3d at 1168; and *Ormco, supra,* 463 F.3d at 1311 (Fed. Cir. 2006).

Pawelczyk also discloses that under a nitrogen atmosphere, *i.e.*, in the absence of oxygen, minocycline is degraded by a “water-evoked spontaneous reaction,” and “its rate depends on the charge of the substrate.” Ex. 1002, ¶ 108; Ex. 1008, pp. 414-415. A person of ordinary skill in the art would understand that this “water-evoked” decomposition reaction is catalyzed by water and would seek to use a lyophilization matrix that has a high affinity for water, such as lactose. Ex. 1002, ¶ 108. A person skilled in the art would appreciate that in a lyophilized composition with lactose, water would not be available to interact with a drug such as minocycline or tigecycline and that the drug could be stabilized against “water-
evoked” degradation in a lyophilized formulation containing lactose, as taught by Herman (Ex. 1006) and Kirsch (Ex. 1007).  *Id.*

**XI. CONCLUSION**

Petitioner has established a reasonable likelihood that it will prevail in its challenge that claims 1-23 of the ’828 patent are unpatentable under 35 U.S.C. § 103(a), on the grounds set forth above. It is respectfully requested that a trial for *inter partes* review of the ’828 patent claims 1-23 be instituted and that claims 1-23 of the ’828 patent be judged unpatentable and canceled.

Respectfully submitted,

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CERTIFICATE OF SERVICE
(37 C.F.R. §§ 42.6(e) and 42.105(a))

The undersigned hereby certifies that the above-captioned “Apotex Inc.’s Petition for Inter Partes Review of U.S. Patent No. 7,879,828” and true copies of Exhibit Nos. 1001 to 1029 and Apotex Inc.’s Power of Attorney (Inter Partes Review of U.S. Patent No. 7,879,828) were served on March 12, 2015, at the official correspondence address for the attorney of record for the ’828 patent as shown in USPTO PAIR via FedEx®:

Wyeth LLC
Pfizer Intellectual Property
235 East 42nd Street
NYO-235/09/S-20
New York, NY 10017

DATE: March 12, 2015

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