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Paper 11
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS, LLC
Petitioner

v.

SUPERNUS PHARMACEUTICALS, INC.
Patent Owner

Case IPR2013-00371
Patent 8,394,405

Before LORA M. GREEN, SCOTT E. KAMHOLZ, and GEORGIANNA W. BRADEN, *Administrative Patent Judges.*

KAMHOLZ, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background

Amneal Pharmaceuticals, LLC ("Amneal") filed a petition (Paper 1, "Pet.") requesting an *inter partes* review of claims 1-13 and 17-20 of U.S. Patent No. 8,394,405 (Ex. 1007, "the '405 patent"). Patent Owner Supernus Pharmaceuticals, Inc. ("Supernus") filed a preliminary response (Paper 7, "Prelim. Resp."). The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a), which provides as follows:

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

Upon consideration of the petition and preliminary response, we conclude that Amneal has established a reasonable likelihood that it would prevail with respect to claims 1-13 and 17-20 of the '405 patent. Accordingly, we grant the petition and institute an *inter partes* review of claims 1-13 and 17-20 of the '405 patent.

B. The '405 patent

The '405 patent relates to once-daily, sub-antimicrobial formulations of doxycycline. Ex. 1007, 2:38-46. Such formulations can be used to inhibit activity of collagen destruction enzymes, which are associated with human diseases, such as rosacea, without provoking undesired side effects attendant to an antibacterial

dose. *Id.* at 3:6:9. A combination of an immediate-release ("IR") portion with 30 mg doxycycline and a delayed-release ("DR") portion with 10 mg doxycycline facilitates once-daily dosing by providing a steady-state blood level of 0.1 to 1.0 µg/ml or 0.3 to 0.8 µg/ml. *Id.* at 3:61-68; 10:14-20. The composition may be a pellet, combination of pellets, tablet, or capsule. *Id.* at 5:50-64. The DR portion may have an enteric polymer, such as hydroxypropyl methylcellulose phthalate. *Id.* at 7:24-30. The IR and/or DR portions may incorporate one or more excipients. *Id.* at 6:16-42. Examples of excipients include binders, such as hydroxypropyl methylcellulose; disintegration agents, such as cross-linked polyvinylpyrrolidone; and filling agents, such as lactose. *Id.* at 6:20-31.

Claim 1 is illustrative of the claimed subject matter and is reproduced below.

> 1. An oral pharmaceutical composition comprising about 40 mg of total doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml, wherein the composition consists of 70 to 80 percent of the doxycycline formulated as an immediate release (IR) formulation and 20 to 30 percent of the doxycycline formulated as a delayed release (DR) formulation.

C. Prior Art Relied Upon in the Petition

Amneal relies upon the following references, as well as the declaration of Glenn A. Van Buskirk, Ph.D. (Ex. 1022):

Ashley '932	WO 02/080932 A1	Oct. 17, 2002	Ex. 1002
Ashley '854	Ser. No. 60/281,854	filed Apr. 5, 2001	Ex. 1003
Ashley '106	WO 02/083106 A1	Oct. 24, 2002	Ex. 1004

Sheth	US 5,348,748	Sep. 20, 1994	Ex. 1005
Webster	"Treatment of Rosacea," *Sem. Cutan. Med. & Surg.*, 20(3):207-208	Sep. 2001	Ex. 1018

D. The Asserted Grounds of Unpatentability

Amneal asserts that the challenged claims are unpatentable based on the following grounds:

Reference(s)	**Basis**	**Claims challenged**
Ashley '932, as it incorporates Ashley '854	§ 103	1-13 and 17-20
Ashley '932, as it incorporates Ashley '854, and Sheth	§ 103	1-13 and 17-20
Ashley '106 and Sheth	§ 103	1-13 and 20
Ashley '106, Sheth, and Webster	§ 103	17-19

II. DISCUSSION

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a

claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "about"

Amneal and Supernus agree that the term "about" should be construed as the '405 patent defines it, viz.:

> "About" means within the pharmaceutically acceptable limits found in the United States Pharmacop[e]ia (USP-NF 21), 2003 Annual Edition, or available at www.usp.org, for amount of active pharmaceutical ingredients. With respect to blood levels, "about" means within FDA acceptable guidelines.

Ex. 1007, 4:8-13; Pet. 6-7; Prelim. Resp. 15. Upon consideration of the record, we adopt the agreed-upon construction, because it is consistent with the ordinary and customary meaning of the claim limitation, when construed in the context of the Specification.

2. "immediate release"

Amneal and Supernus agree that the term "immediate release" should be construed as the '405 patent defines it, as follows:

> By "immediate release" formulation is meant a dosage form that is intended to release substantially all of the active ingredient on administration with no enhanced, delayed or extended release effect. Such a composition of doxycycline can be in the form of a liquid suspension or solution, or as a solid such as a tablet, pellet (used interchangeably with bead or beadlet herein), particle, capsule or gel.

Ex. 1007, 4:14-21; Pet. 6-7; Prelim. Resp. 15. Upon consideration of the record, we adopt the agreed-upon construction, because it is consistent with the ordinary

and customary meaning of the claim limitation, when construed in the context of the Specification.

3. "steady state blood levels"

Amneal and Supernus agree that the term "steady state blood level(s)" should be construed to mean "steady state plasma concentration(s) of doxycycline." Pet. 7; Prelim. Resp. 15. Upon consideration of the record, we adopt the agreed-upon construction, because it is consistent with the ordinary and customary meaning of the claim limitation, when construed in the context of the Specification.

4. "pellet"

Amneal contends that "pellet" should be construed to mean "bead or beadlet, but excluding a granule, tablet, powder, sachet, capsule, gel, dispersion or suspension," and that "pellets" should be construed to mean a plurality of such beads or beadlets. Pet. 7. Amneal cites no evidence or legal authority to justify this construction.

Supernus argues instead that "pellets" should be construed to mean "one or more of a small solid dosage form of reasonable size and robustness suitable for incorporation into, e.g., a capsule or tablet" and cites several passages from the '405 patent as evidence supporting this construction. Prelim. Resp. 16-17.

Neither proposed construction encompasses the broadest reasonable interpretation of this term. Amneal does not explain its many proposed exclusions from the meaning, and Supernus limits the meaning with non-definitional passages from the Specification. For purposes of this decision, we construe "pellet" to have its ordinary and customary meaning, when construed in the context of the

Specification, of "a small solid dosage form," and "pellets" to mean "a plurality of small solid dosage forms."

B. Obviousness of claims 1-13 and 17-20 over Ashley '932

Amneal contends that claims 1-13 and 17-20 are unpatentable for obviousness over Ashley '932, as it incorporates Ashley '854. Pet. 10-19; Ex. 1022 ¶¶ 36-47; 68-163. Supernus opposes. Prelim. Resp. 20-35.

1. Overview of Ashley '932

Ashley '932 discloses administering a tetracycline compound, e.g., doxycycline or minocycline, in sub-antibacterial doses to treat acne, including acne rosacea. Ex. 1002, 5:17-20; 7:3, 24-25. Doxycycline is administered in a sub-antibacterial total daily dose of about 30 to 60 milligrams, to give steady-state blood levels of about 0.1-0.8 μg/ml, preferably 0.4-0.7 μg/ml. *Id.* at 9:17-20; 10:25-11:2. The composition may take, e.g., tablet, capsule, or pill form, *id.* at 14:14-17, and may include excipients, such as lactose. *Id.* at 14:30-31. Ashley '932 discloses that doxycycline may be administered by sustained release, such as 40 mg by sustained release, over a 24-hour period, and cites Ashley '854 for further description of the sustained release formulation. *Id.* at 15:23-16:2. Ashley '932 incorporates by reference Ashley '854 in its entirety. *Id.* at 15:30.[1]

[1] Ashley '932 does not identify Ashley '854 by serial number. Rather, it identifies Ashley '854 by title, filing date, and assignee. Ex. 1002, 15:28-29. For purposes of this decision, we determine that the incorporation-by-reference was effective, because there is no evidence of record to suggest that the identification was ambiguous.

Ashley '854 discloses administering controlled-release compositions of doxycycline to achieve a sub-antibacterial serum level of 0.4 to 0.8 μg/ml. Ex. 1003, 5:15-22. The composition includes a controlled-release agent, which is an instantaneous-release agent, a sustained-release agent, a delayed-release agent, or combinations of these. *Id.* at 5:24-26. The controlled-release agent is of "a larger particle size," to entrap it in the upper gastrointestinal tract, such that at least 50%, preferably greater than 80%, is released in the upper gastrointestinal tract. *Id.* at 16:9-14. A delayed-release agent may be, e.g., a cellulose polymer. *Id.* at 11:7-8. A sustained controlled-release agent may include a cellulose polymer, such as hydroxypropyl methylcellulose (HPMC). *Id.* 11:20-25.

2. Analysis

Amneal argues that Ashley '932 discloses all limitations of claim 1, except for the requirement that 70 to 80 percent of the doxycycline be formulated as an immediate release (IR) formulation and 20 to 30 percent of the doxycycline be formulated as a delayed release (DR) formulation. Pet. 11-14. Amneal argues further that one of ordinary skill in the art would have at once envisaged the claimed percentage ranges from the disclosure in Ashley '854 that at least half of the doxycycline dose be released in the upper GI tract. Pet. 14-15; Ex. 1022 ¶¶ 43, 74.

Supernus argues that the portion of Ashley '854 that Amneal cites for the percentage ranges relates not to putting at least half of the drug in the immediate-release portion of a composition, but rather to using a particle size of the composition that results in at least half of the drug being entrapped and, therefore, released in the upper GI tract. Prelim. Resp. 27-28.

We agree with Supernus. Dr. Van Buskirk, in explaining the relevance of this passage from Ashley '854, states:

> In other words, the proportion of tetracycline that is *immediately released (released in the upper GI tract)* is at least 50%, more preferably greater than 80% when compared to the delayed release or sustained release portions.

Ex. 1022 ¶ 43 (emphasis added). Dr. Van Buskirk interprets Ashley '854's disclosure of release in the upper GI tract as indicating immediate release, but he does not offer sufficient underlying facts or data to support his conclusion. The fact that Ashley '854 favors release of at least half of the drug in the upper GI tract does not amount to a disclosure that at least half of the drug is composed for immediate release. Ashley '854 explains that the composition is "entrapped" in the upper GI tract by making the composition with a larger particle size, which suggests that particle size is at least partly responsible for the release location. *See* Ex. 1003, 16:9-14. Dr. Van Buskirk does not account for the effect of particle size on the release location. It is entirely consistent with Ashley '854—and Amneal offers no credible evidence to the contrary—that more than half of the drug dose is composed for delayed release, yet its particle size traps it in the upper GI tract and causes its release there. Even giving Dr. Van Buskirk's declaration in this regard some weight, we are unpersuaded that Ashley '854 can reasonably be read to disclose that the proportion of doxycycline composed for immediate release is at least 50%.

For these reasons, we determine that Amneal has not demonstrated a reasonable likelihood that claim 1 is unpatentable for obviousness over Ashley

'932. The challenges on this ground to independent claim 17, and to claims 2-13 and 18-20, fail for similar reasons.

C. Obviousness of claims 1-13 and 17-20 over Ashley '932 and Sheth

Amneal contends that claims 1-13 and 17-20 are unpatentable for obviousness over Ashley '932 and Sheth. Pet. 20-29; Ex. 1022 ¶¶ 164-344. Supernus opposes. Prelim. Resp. 20-41.

1. Overview of Sheth

Sheth discloses a once-daily formulation of minocycline that provides an antibacterial total daily dose. Ex. 1005, 6:27-32. The formulation includes both quick-release and delayed-release pellets, with more quick-release than delayed-release pellets. *Id.* at 7:21-23; 18:24-26. In particular, the proportion may vary from 51:49 to 80:20 of quick-release to delayed-release, with a preferred range of 55:45 to 70:30. *Id.* at 6:10-13, 15-20; 18:24-26. The formulation may be provided in the form of a capsule. *Id.* at 11:66-68. The delayed-release pellets may have a coating of hydroxypropyl methylcellulose phthalate. *Id.* at 11:6-10. The quick-release and/or delayed-release portions may include excipients, *id.* at 9:4-6, such as hydroxypropyl methylcellulose, *id.* at 9:12, cross-linked polyvinylpyrrolidone, *id.* 9:11-12, and lactose, *id.* at 9:7.

2. Analysis

Amneal argues that Ashley '932 discloses all limitations of claim 1, except for the requirement that 70 to 80 percent of the doxycycline be formulated as an immediate release (IR) formulation and 20 to 30 percent of the doxycycline be formulated as a delayed release (DR) formulation. Pet. 20-24. Amneal argues that Sheth discloses formulations of minocycline having a range of IR:DR ratios that

encompasses 70:30 to 80:20. *Id.* 24-25; Ex. 1022 ¶¶ 176-179. Although it acknowledges that Sheth concerns antibacterial-strength minocycline formulations, Amneal argues that one of ordinary skill, developing sub-antibacterial doxycycline formulations, would have looked to Sheth's teachings, because the two drugs are members of the tetracycline family, and have comparable structure, function, and utility, and because minocycline was recognized as suitable for sub-antibacterial dosing. Pet. 25 (citing Ex. 1022 ¶ 180). Amneal argues that it would have been obvious to employ an IR:DR ratio range of 70:30 to 80:20 in Ashley '932's formulation in light of Sheth's disclosure. Pet. 25-27.

Supernus argues that (a) the disclosure in Ashley '854 concerning a "controlled-release" agent refers to a sustained-release profile, not the type of release accomplished by the claimed IR/DR composition; (b) the "absorption window" for doxycycline was information critical to making a once-daily formulation but was not publicly known at the time of invention; (c) one of ordinary skill would not have pursued an IR/DR formulation; (d) minocycline is structurally and physiochemically different from doxycycline; (e) Sheth teaches away from a sub-antibacterial steady-state blood level; and (f) evidence of secondary considerations, including failure by others, long-felt need, unexpected results, and commercial success of ORACEA® brand oral doxycycline capsules, establishes nonobviousness of the '405 patent claims. Prelim. Resp. 20-41, 45-57. As detailed below, none of these arguments persuades us that Amneal has failed to demonstrate a reasonable likelihood that the challenged claims are unpatentable.

As to argument (a), we are satisfied, on the present record, that Ashley '854 discloses an IR/DR-only formulation as one of seven possible combinations of immediate-release, sustained-release, and/or delayed-release agents. *See* Ex. 1003,

5:24-26. That Ashley '854 devotes more attention to formulations including sustained-release agents than to others is irrelevant. As to argument (b), the evidence presently of record does not support Supernus's contention that knowledge of the absorption window was critical to developing a once-daily formation. Although the art of record may not define a doxycycline absorption window expressly, Ashley '854 nevertheless recognizes that tetracycline compound uptake would be enhanced by retention in the upper GI tract, an observation Sheth made, as well, with reference to minocycline. *See* Ex. 1003, 7:4-7; Ex. 1005, 2:19-27. Argument (c) is unpersuasive, because we accept, for purposes of this decision, that Ashley '854 discloses an IR/DR doxycycline formulation. As to argument (d), although we agree with Supernus that doxycycline and minocycline differ from one another at several substituents, and that some evidence of record identifies differences in the drugs' pharmacokinetics, we nevertheless accept Amneal's argument, for purposes of this decision, that the otherwise close relatedness of these two drugs in structure and function makes information about formulation of one relevant to formulation of the other. Argument (e) is unpersuasive, because Amneal relies on Sheth merely for its disclosure concerning the ratio of immediate-release pellets to delayed-release pellets in creating a once-daily dosage form. That Sheth happens to have made this disclosure in the context of an antibacterial dose instead of a sub-antibacterial dose is of no moment, on the present record. As to argument (f), detailed consideration of Supernus's secondary consideration evidence may not be undertaken until Amneal has had an opportunity to test it.

For these reasons, we determine that Amneal has demonstrated a reasonable likelihood that claim 1 is unpatentable for obviousness over Ashley '932 and

Sheth. Amneal has demonstrated a reasonable likelihood that claim 17 is unpatentable for obviousness over Ashley '932 and Sheth for similar reasons. Amneal has demonstrated also a reasonable likelihood that the challenged dependent claims are unpatentable for obviousness over Ashley '932 and Sheth. As summarized in the overviews of Ashley '932 and Sheth, above, one or both of these references disclose all limitations of the challenged dependent claims.

Supernus invites the Board to exercise discretion under 35 U.S.C. § 325(d) and/or 37 C.F.R. § 42.108 to deny the petition. Prelim. Resp. 57-60. We decline the invitation, because we determine that Amneal has demonstrated a reasonable likelihood that the challenged claims are unpatentable.

Accordingly, we institute *inter partes* review of claims 1-13 and 17-20 for obviousness over Ashley '932 and Sheth.

D. Other Challenges

Upon review of the other challenges asserted by Amneal against claims 1-13 and 17-20, we conclude that they are redundant in light of the ground on the basis of which we institute review.

III. CONCLUSION

For the foregoing reasons, we determine that Amneal has demonstrated that there is a reasonable likelihood of its proving unpatentability of claims 1-13 and 17-20 of the '405 patent by a preponderance of the evidence.

The Board has not made a final determination on the patentability of the challenged claims.

IV. ORDER

For the reasons given, it is

ORDERED that the Petition is *granted* with respect to unpatentability of claims 1-13 and 17-20 under 35 U.S.C. § 103(a) for obviousness over Ashley '932 and Sheth;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '405 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial;

FURTHER ORDERED that all other grounds presented in Amneal's petition are *denied*, and no ground other than that specifically granted above is authorized for the *inter partes* review as to claims 1-13 and 17-20; and

FURTHER ORDERED that an initial conference call with the Board is scheduled for 2 PM Eastern Time on January 10, 2014. The parties are directed to the Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,765-66 (Aug. 14, 2012) for guidance in preparing for the initial conference call, and should be prepared to discuss any proposed changes to the Scheduling Order entered herewith and any motions the parties anticipate filing during the trial.

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