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Paper 92
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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 IPR2013-00372
Patent 8,394,406 B2

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

KAMHOLZ, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background

Amneal Pharmaceuticals, LLC ("Amneal") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review of claims 1–12 and 16–21 of U.S. Patent No. 8,394,406 B2 (Ex. 1009, "the '406 patent"). The Board instituted trial for the challenged claims on the ground, asserted by Amneal, of obviousness over WO 02/080932 A1 (Ex. 1002, "Ashley '932"), which incorporates by reference provisional patent application serial No. 60/281,854 (Ex. 1003, "Ashley '854") and U.S. Patent No. 5,348,748 (Ex. 1005, "Sheth"). Decision to Institute (Paper 8, "Dec.") 14.

After institution of trial, Patent Owner Supernus Pharmaceuticals, Inc. ("Supernus") filed a Patent Owner Response in redacted (Paper 39, "Resp.") and unredacted (Paper 38) forms. Amneal filed a Reply (Paper 56, "Reply"). Supernus did not file a Motion to Amend.

Amneal filed a Motion to Exclude certain of Supernus's evidence (Paper 69, "Pet. Motion to Exclude"). Supernus filed an Opposition in redacted (Paper 80) and unredacted (Paper 81) forms, and Amneal filed a Reply (Paper 84).

Amneal relies upon declarations from Dr. Glenn A. Van Buskirk in support of its Petition (Ex. 1022) and its Reply (Ex. 1066). Supernus relies upon a declaration from Dr. Edward M. Rudnic in support of its Response (Ex. 2016), as well as deposition testimony from Dr. Van Buskirk

(Exs. 2015, 2193).[1] Amneal relies upon deposition testimony from Dr. Rudnic in its Reply (Ex. 1052). Supernus filed a Motion for Observations on Cross-Examination of Amneal's Reply witnesses (Paper 74, "Obs."), and Amneal filed a Response to the Observations (Paper 76, "Obs. Resp.").

Oral argument was conducted on August 12, 2014. A transcript is entered as Paper 90 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6(c). This final written decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Amneal has not proved that claims 1–12 and 16–21 are unpatentable.

Amneal's Motion to Exclude Evidence is dismissed as moot.

B. The '406 Patent

The '406 patent relates to once-daily, sub-antimicrobial formulations of doxycycline. Ex. 1009, 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, a combination of pellets, a tablet, or a capsule. *Id*. at 5:50–64. The DR portion may have an enteric polymer, such as hydroxypropyl

[1] The parties rely on the testimony of other witnesses, but that evidence is not listed here because it is not cited in this decision.

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 (HPMC); 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, with line breaks added for clarity.

> 1. An oral pharmaceutical composition comprising less than 50 mg of total doxycycline, which at a once-daily dosage will give steady state blood levels of the doxycycline between 0.1 µg/ml and 1.0 µg/ml, and a C_{max} of the doxycycline between 0.4 µg/ml and 0.8 µg/ml, the composition consisting of
>
> (i) an immediate release (IR) formulation of the doxycycline,
>
> (ii) a delayed release (DR) formulation of the doxycycline comprising at least one enteric polymer, and
>
> (iii) one or more pharmaceutically acceptable excipients,
>
> wherein the doxycycline in the IR and DR formulations is in a ratio of 75:25.

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).

The only term requiring construction for purposes of this decision is "delayed release." Neither party proposed a construction of this term in its principal brief. The '406 patent, too, does not provide an express definition of this term. Tr. 42:7–9.

In response to a request during oral argument, Tr. 48:7–21, the parties identified the record evidence they rely on concerning construction of "delayed release." Amneal cited paragraphs 19 and 20 of Dr. Van Buskirk's Second Declaration (Ex. 1066) and paragraph 110 of Dr. Rudnic's Declaration (Ex. 2016). Tr. 70:19–71:20.[2] Supernus cited column 7, lines 47–53 and Figures 2 and 3 of related U.S. Patent No. 8,206,740 (Ex. 1001); paragraph 20 of Dr. Van Buskirk's Second Declaration; paragraph 177 of Dr. Rudnic's Declaration; the definition of "delayed release" on page 7 of Exhibit 2047; the definition of "delayed release" on page 30 of Exhibit 2058; the definition of "enteric coated" on page 32 of Exhibit 2058; and passages from the transcript of Dr. Van Buskirk's second deposition at page 11, line 7, to page 13, line 6 and at page 16, line 14, to page 17, line 2 (Ex. 2193). Tr. 80:11–81:20. Supernus also cited a passage from the transcript of Dr. Van Buskirk's first deposition in argument that indirectly

[2] Citations to the record given during oral argument were made with respect to the record in case IPR2013-00368, which involves U.S. Patent No. 8,206,740, of which the '406 patent is a continuation. *See* Tr. 14:8–9; Resp. 4. The citations here are adjusted as needed to refer to the same material cited during the oral argument.

addresses construction of "delayed release." Resp. 20 (citing Ex. 2015, 170:3–171:2).

Review of the evidence cited by the parties indicates their agreement, as well as that of their experts, that Exhibit 2058 correctly defines "delayed release" as "release of a drug at a time other than immediately following oral administration." Ex. 2058, 30;[3] *see* Ex. 1066 ¶ 20 (citing Ex. 2058, 30); Ex. 2016 ¶¶ 180 n.41, 182. The parties disagree, however, as to whether the broadest reasonable construction of "delayed release" requires further that there be no substantial release in the stomach.

Supernus argues that the delayed release formulations are described in the '406 patent as allowing "no substantial release of doxycycline in the acidic stomach environment of approximately below pH 4.5." Resp. 20–21 (citing Ex. 1009, 7:56–62); *see also* Obs. ¶ 1 (citing Ex. 2193 , 11:7–13:6, 16:14–17:2) (cross-examination testimony of Dr. Van Buskirk agreeing that the above-quoted passage forms part of the identical disclosure in the related '740 patent that Dr. Van Buskirk regards as defining "delayed release."). The cited passage of the '406 patent is reproduced below:

> With the enteric coated pellets, there is no substantial release of doxycycline in the acidic stomach environment of approximately below pH 4.5. The doxycycline becomes available when the pH-sensitive layer dissolves at the greater pH of the small intestine; after a certain delayed time; or after the unit passes through the stomach. The

[3] Exhibit 2058 is a "Guidance for Industry" document issued by the Food and Drug Administration in 1997 that concerns scale-up and post-approval changes for modified release solid oral dosage forms. Ex. 2058, 1.

> preferred delay time is in the range of two to six hours.

Ex. 1009, 7:56–62.

Amneal argues that "delayed release" should be construed broadly enough to include drug release after only a time lag and without respect to whether release occurs in the stomach. Obs. Resp. ¶ 1; Tr. 11:5–11. In particular, Amneal argues that the term "delayed release" encompasses release that begins in the stomach. *Id*. at 11:7. Amneal cites paragraph 20 of Dr. Van Buskirk's Second Declaration in support of this argument, as well as paragraph 110 of Dr. Rudnic's Declaration. Tr. 70:19–71:20 (citing Ex. 1066 ¶¶ 19–20, Ex. 2016 ¶ 110). In paragraph 20 of his Second Declaration, Dr. Van Buskirk cites the definition in Exhibit 2058 with favor. Ex. 1066 ¶ 20. In paragraph 110 of his Declaration, Dr. Rudnic states that Ashley '854 defines a "delayed release agent" as one which "prevents the active ingredient . . . from being made available to the host until some time after initial administration." Ex. 2016 ¶ 110 (citing Ex. 1003, 11:4–6).

Upon consideration of the parties' arguments and cited evidence, we agree with Amneal that the broadest reasonable construction of "delayed release," in light of the specification of the '406 patent, is not limited to formulations requiring that there be no substantial release in the stomach. The portion of the '406 patent specification upon which Supernus relies to support its narrower construction addresses properties of "enteric coated pellets," not a delayed-release component. Ex. 1009, 7:56. The '406 patent discloses formats other than enteric coated pellets, such as an "uncoated matrix tablet," as being delayed-release components. *Id*. at 5:38–40 ("delayed-release portion can be . . . uncoated matrix tablet.").

Consequently, properties of enteric coated pellets do not address the full scope of "delayed release" as that term is used in the '406 patent. We will not read the limitations of an embodiment, even a preferred embodiment, into the construction of a claim term that is plainly used elsewhere in the specification more broadly. *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

As Supernus concedes, Tr. 42:7–9, the '406 patent does not provide an express definition of "delayed release." We turn, therefore, to other evidence of how the term is understood and used by persons of ordinary skill in the art. We find, upon consideration of this evidence, that the term "delayed release" is used, more-or-less uniformly, to refer to formats that allow for release of a drug only after some delay following oral administration. *See, e.g.*, Ex. 2058, 30 (quoted *supra*); Ex. 2047, 7 (defining "delayed release" as "release of a drug (or drugs) at a time other than promptly after administration");[4] Ex. 2016 ¶ 110 (citing definition of "delayed release" in Ashley '854, quoted *supra*, with approval). Those definitions are consistent with one another, both parties and their experts cite them with favor, and we discern nothing in the use of the term "delayed release" in the '406 patent specification that is inconsistent with those definitions or more limiting than them. For these reasons, we determine that the broadest reasonable construction of "delayed release," consistent with the '406 patent, is "release of a drug at a time other than immediately

[4] Exhibit 2047 is a report, of which Dr. Van Buskirk was a co-author, entitled "Workshop II Report: Scaleup of Oral Extended Release Dosage Forms" and published in the *Journal of Pharmaceutical Science and Technology* in 1994. Ex. 2047, 2–3.

following oral administration." *See* Ex. 2058, 30; Ex. 2047, 7; Ex. 1003, 11:4–6.

B. Obviousness of claims 1, 2, 5–15, and 19–22 over Ashley '932 and Sheth

Amneal contends that claims 1–12 and 16–21 are unpatentable for obviousness over Ashley '932, as it incorporates Ashley '854, and Sheth. Pet. 20–30; Ex. 1022 ¶¶ 189–395.

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, 7:24–25. 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.[5]

[5] 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. The parties dispute whether the incorporation-by-reference was effective. Resp. 54–55; Reply 12–13. For purposes of this decision, we assume, without deciding, that the incorporation was effective.

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. A delayed-release agent is defined as one that “prevents the active ingredient . . . from being made available to the host until some time after initial administration.” *Id*. at 11:4–6.

2. 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 an initial loading component of quick-release pellets and a secondary loading component of slow-release pellets. *Id*. at 3:48–52. The quick-release pellets in the initial loading component optionally may be coated with a polymer that does not interfere with immediate release of drug from the initial loading component. *Id*. at 10:2–7. Hydroxypropyl methylcellulose (HPMC), when adapted to dissolve completely in the typical stomach pH of below 3.9, is a suitable coating for the initial loading component. *Id*. at 3:16, 10:13, 10:21–22, 10:43–45.

The pellets of the secondary loading component are coated with a mixture of at least two polymers, one that is pH-sensitive and one that is not pH-sensitive. *Id*. at 4:67–5:5. The pH-insensitive polymer may be HPMC. *Id*. at 14:12–14, 15:34–37. The pH-insensitive polymer dissolves rapidly in water. *Id*. at 5:1–2, 12:58–59. Upon oral administration of the dose form, the pH-insensitive polymer erodes and provides a slow release of minocycline in the stomach, *id*. at 7:17, 10:59–60, 15:48–50, of preferably 5

to 20 or 20 to 50 percent of the minocycline it carries. *Id*. at 8:53–62. Dissolution of the pH-sensitive polymer on the secondary loading portion is inhibited but not precluded in the low pH of the stomach. *Id*. at 10:65–67. The pH-sensitive coating dissolves rapidly once the pellet passes to the duodenum, where the pH is typically in the range of 4.0 to 7.5, thereby causing rapid release of the rest of the minocycline in the secondary loading portion. *Id*. at 10:60–65. The secondary loading portion thus provides partly a release of minocycline in the stomach and partly a delayed release of minocycline in the duodenum. *Id*. at 7:15–21, 7:33–35.

Sheth discloses that the ratio of initial loading component to coated secondary loading component may vary from 51:49 to 80:20, with a preferred range of 55:45 to 70:30. *Id*. at 6:10–13, 6:15–20, 18:24–26.

3. Analysis

Amneal argues that Ashley ’932 discloses all limitations of claim 1, except for the requirement that the doxycycline in the immediate release (IR) and delayed release (DR) formulations be in a ratio of 75:25. Pet. 21-24. Amneal argues that one of ordinary skill would have at once envisaged a 75:25 ratio because it is a common incremental ratio within the range of ratios Sheth discloses. *Id*. at 25-26; Ex. 1022 ¶¶ 203, 205-207. Although Amneal 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. 26 (citing Ex. 1022 ¶ 208). Amneal argues that it would have been obvious to

employ an IR:DR ratio of 75:25 in Ashley '932's formulation in light of Sheth's disclosure. Pet. 26-27.

Supernus argues, among other things, that Sheth does not disclose any IR:DR formulations because Sheth fails to disclose a "delayed release" format. Resp. 17–19. Supernus argues that the release provided by Sheth's secondary loading portion is more of a "modified sustained release" that begins slowly but promptly in the stomach, followed by rapid release in the intestine. *Id*. at 18–20 (citing Ex. 2016 ¶¶ 171–85). Dr. Rudnic opined, at least partly on the basis of the disclosure in Sheth that the pH-insensitive polymer dissolves rapidly in water, that drug release would begin from the secondary loading portion "promptly" after oral administration. Ex. 2016 ¶ 176 (citing, *inter alia*, Ex. 1005, 5:1–2). Supernus argues that Sheth's secondary loading portion thus does not fall within the scope of "delayed release," because part of the release occurs in the stomach promptly after administration. Resp. 20.

Amneal argues, in reply, that even Dr. Rudnic agrees that there would be a "lag" in the initial release of drug from the secondary loading portion. Reply 7. Amneal cites the following exchange from the transcript of Dr. Rudnic's deposition:

> Q. Would you agree with me that as a result of the water soluble polymer there would be a delay in the release of the drug?
>
> . . .
>
> A. Again, you're over simplifying the question. I think there would be some lag between when the polymer hydrated and the drug diffused through,

> but you wouldn't consider that a delay. It's not designed to delay.

Id. (citing Ex. 1052, 247:20–248:5).

We credit Dr. Rudnic's declaration testimony that inclusion of a water-soluble polymer in the coating of Sheth's secondary loading portion results in release of drug promptly after administration. *See* Ex. 2016 ¶ 176. Amneal does not cite credible evidence to refute Dr. Rudnic's testimony. Although Dr. Rudnic conceded that there must be some lag while the polymer hydrates, we further credit his testimony that this lag, essentially the time required to wet the material, would not be considered a "delay." *See* Ex. 1052, 248:3–5. We agree with Dr. Rudnic that dissolution, however rapid, necessarily requires some finite amount of time to allow interaction of the solvent and the solute. *See* Ex. 1005, 5:1–2. Amneal does not explain why we should not credit all of Dr. Rudnic's testimony on this point.

Because we credit Dr. Rudnic's testimony, we agree with Supernus that Sheth's secondary loading portion is not a "delayed release" portion. A "delayed release" format, when that term is construed to mean "release of a drug at a time other than immediately following oral administration," specifically excludes formats that result in release of drug starting immediately after oral administration. To conclude otherwise would read the phrase "delayed release" out of the claim. *See In re Wilson,* 424 F.2d 1382, 1385 (CCPA 1970) (all limitations of a claim must be considered when considering patentability over prior art). Amneal has not explained how there is any appreciable delay in the onset of drug release from the

secondary loading portion once water in the patient's saliva or gastric fluid has begun to solubilize the pH-insensitive polymer in the coating.[6]

For this reason, we determine that Amneal has failed to show that Sheth discloses a "delayed release" portion.

Amneal's argument that Sheth discloses the claimed IR:DR ratio (or makes the claimed ratio reachable through routine experimentation) thus becomes untenable. Dr. Van Buskirk's evidence concerning ratios in Sheth is premised on an assumption that Sheth's secondary loading portion is a delayed release portion. *See, e.g.*, Ex. 1022 ¶ 59 ("Additionally, the secondary loading coated pellets (the DR component) described in the '748 patent . . ."). That assumption is unwarranted, for the reasons given above. Consequently, Sheth's disclosure of ratios involving the secondary loading portion does not constitute disclosure of ratios involving a delayed release portion. Put another way, Amneal has failed to persuade us that the prior art it cites for disclosure of IR:DR ratios actually discloses such ratios. Without evidence that the claimed IR:DR ratio was known or could have been reached through routine experimentation, Amneal's challenge fails.

For the reasons discussed above, we conclude that Amneal has not proved the unpatentability of claims 1–12 and 16–21 by a preponderance of the evidence.

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[6] Amneal's argument that Sheth uses the words "delayed release" to describe the secondary loading portion, Reply 7 (citing Ex. 1005, 7:34–36), is unpersuasive for similar reasons. Sheth uses those words to describe the effect of the polymer in the coating blend that favors release in the intestine. It does not account for the effects of the other coating polymer, which favors release immediately after oral administration. *See* Ex. 1005, 7:14–41; Resp. 18–19.

III. MOTION TO EXCLUDE EVIDENCE

Amneal moves to exclude Supernus Exhibits 2028, 2029, 2032–2034, 2039, 2049, 2050, 2147, 2149–2154, and 2156. Pet. Motion to Exclude 1.

We dismiss Amneal's motion as moot, because we do not rely on any of the objected-to evidence in our final decision.

IV. CONCLUSION

Amneal has not proved, by a preponderance of the evidence, that claims 1–12 and 16–21 of the '406 patent are unpatentable for obviousness over Ashley '932 and Sheth.

V. ORDER

For the reasons given, it is

ORDERED that claims 1–12 and 16–21 of U.S. Patent No. 8,394,406 B2 are not determined to be unpatentable;

FURTHER ORDERED that Amneal's Motion to Exclude Evidence is *dismissed as moot*; and

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

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