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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA LLC,
Petitioner,

v.

CUBIST PHARMACEUTICALS LLC,
Patent Owner.

Case IPR2015-01572
Patent 8,058,238 B2

Before BRIAN P. MURPHY, JON B. TORNQUIST, and TINA E. HULSE, *Administrative Patent Judges*.

TORNQUIST, *Administrative Patent Judge*.

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

I. INTRODUCTION

Fresenius Kabi USA LLC ("Petitioner") filed a corrected Petition (Paper 7, "Pet.") requesting institution of *inter partes* review of claims 20, 45–47, 49–52, 54–91, 108–111, 147–150, 168–175, 178, 180–183, and 190–192 of U.S. Patent No. 8,058,238 B2 ("the '238 patent"). On September 15, 2015, we granted the parties' joint motion to limit the Petition to claim 91. Paper 15, 3. Cubist Pharmaceuticals LLC (f/k/a Cubist Pharmaceuticals, Inc., "Patent Owner") timely filed a Preliminary Response (Paper 18, "Prelim. Resp.") to the limited Petition.

We have jurisdiction under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." For the reasons given below, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to claim 91. Accordingly, we do not institute an *inter partes* review.

A. Related Proceedings

The parties indicate that the '238 patent is at issue in: *Cubist Pharms., Inc. v. Hospira, Inc.*, 1:12-cv-00367-GMS (D. Del.); *Cubist Pharms., Inc. v. Agila Specialties Inc. and Mylan Laboratories Limited*, 1:13-cv-01679-GMS (D. Del); *Cubist Pharms., Inc. v. Fresenius-Kabi USA LLC*, 1:14-cv-00914-GMS (D. Del.); and *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, 805 F.3d 1112 (Fed. Cir. 2015) (pending request for rehearing). Pet. 3–4; Paper 5, 2–3; Paper 19, 1. The '238 patent is also at issue in *inter partes* review proceedings: IPR2015-01566, IPR2015-01570, and IPR2015-01571. Pet. 4; Paper 5, 3.

B. The '238 Patent

The '238 patent, titled "High Purity Lipopeptides," discloses a highly purified form of daptomycin (also known as LY146032), "a lipopeptide antibiotic with potent bactericidal activity against gram-positive bacteria." Ex. 1001, 1:21–24, 1:58–61. More particularly, the '238 patent is directed to "providing commercially feasible methods to produce high levels of purified lipopeptides," such as daptomycin. *Id.* at 3:50–52.

The '238 patent describes several methods of purifying lipopeptides, and daptomycin in particular, to achieve a highly pure composition. One method involves a size separation technique, where a lipopeptide is converted from a monomer to a micelle (aggregate) and back to a monomer during the purification process, in order to separate the lipopeptide from low molecular weight and high molecular weight impurities. *Id.* at 5:56–6:10. The '238 patent indicates that ultrafiltration is preferred for purifying lipopeptides using this size separation technique. *Id.* at 6:11–13.

C. Illustrative Claims

Claim 91 depends from claim 85, which in turn depends from independent claim 49. Claims 49, 85, and 91 are reproduced below:

> 49. A purified daptomycin composition comprising daptomycin of greater than or about 93% purity relative to impurities 1–14 defined by peaks 1–14 shown in FIG. 12, the daptomycin being obtained by a process comprising the step of forming an aggregate comprising daptomycin.

Ex. 1001, 40:33–37.

> 85. A method for preparing a pharmaceutical composition comprising combining the composition of claim 49 with a pharmaceutically acceptable carrier or excipient.

Id. at 42:54–56.

> 91. The method of claim 85 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

Id. at 43:4–6.

D. Prior Art Relied Upon

Petitioner relies upon the following prior art references, as well as the declaration testimony of Dr. Ralph Tarantino (Ex. 1005):

U.S. Patent No. 4,874,843, issued October 17, 1989 (Ex. 1007, "the '843 patent").

U.S. Patent No. 5,912,226, issued June 15, 1999 (Ex. 1010, "the '226 patent").

Catherine N. Mulligan & Bernard F. Gibbs, *Recovery of Biosurfactants by Ultrafiltration*, 47 J. CHEM. TECH. BIOTECHNOLOGY 23–29 (1990) (Ex. 1013, "Mulligan");

Lin et. al., *General Approach for the Development of High-performance Liquid Chromatography Methods for Biosurfactant Analysis and Purification*, 825 JOURNAL OF CHROMATOGRAPHY A 149–159 (1998) (Exhibit 1015, "Lin II"); and

Jeremy H. Lakey and Marius Ptak, *Fluorescence Indicates a Calcium-Dependent Interaction Between the Lipopeptide Antibiotic LY146032 and Phospholipid Membranes*, BIOCHEMISTRY 27, 4639–4645 (1988) (Exhibit 1033, "Lakey").

E. Asserted Ground of Unpatentability

Petitioner contends that claim 91 would have been obvious under 35 U.S.C. § 103 over '843 patent, the '226 patent, Mulligan, Lin II, and Lakey. Pet. 5; Paper 15, 2.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, "[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *In re Cuozzo Speed*

Tech., LLC, 793 F.3d 1268, 1275 (Fed. Cir. 2015). Under this standard, we may take into account definitions or other explanations provided in the written description of applicant's specification. *See In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). 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).

Upon review of Petitioner's and Patent Owner's arguments, as well as the recited prior art references, we conclude that no claim terms require construction for purposes of this Decision. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only those claim terms that are in dispute and necessary to resolve the controversy need be construed).

B. Obviousness of Claim 91 over the '843 patent, the '226 patent, Mulligan, Lin II, and Lakey

Petitioner asserts that claim 91 would have been obvious over the '843 patent, the '226 patent, Mulligan, Lin II, and Lakey. Pet. 14–31. In support of this argument, Petitioner relies upon the declaration testimony of Dr. Tarantino. Ex. 1005. Patent Owner opposes. Prelim. Resp. 6–11.

1. The '843 Patent

The '843 patent issued October 17, 1989, and is prior art under 35 U.S.C. § 102(b). Pet. 7. The '843 patent is directed to a "new chromatographic process for purifying fermentation products, particularly the antibiotic LY146032 [(daptomycin)], from fermentation broths by use of a non-functional resin in reverse mode." Ex. 1007, 1:5–8. This "reverse method" removes impurities from daptomycin and "improves the final purity

from about 80% to about 93%" and the overall yield "from about 5% to about 35%." *Id.* at 2:40, 43–45; Ex. 1005 ¶ 79.

2. The '226 Patent

The '226 patent discloses, *inter alia*, "an improved antibacterial composition" of daptomycin that is in "substantially pure form."[1] Ex. 1010, 8:53–55. In Example 5 of the '226 patent, high performance liquid chromatography ("HPLC") is used to identify and purify daptomycin. *Id.* at 13:5–52. This example discloses HPLC retention times of 847 seconds for β-isomer daptomycin, 880 seconds for daptomycin, and 1238 seconds for anyhdro-daptomycin. *Id.* at 13:45–52.

The '226 patent also discloses that the purified daptomycin may be formulated for therapeutic treatment of bacterial infections: "For example, a compound of this invention can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers and the like." *Id.* at 9:51–60.

3. Mulligan

Mulligan published in 1990 and is prior art under 35 U.S.C. § 102(b). Pet. 9. Mulligan discloses the use of ultrafiltration to purify micelle-forming biosurfactants, such as surfactant. Ex. 1013, Abstract. Mulligan reports that the "ability of surfactant molecules to form micelles at concentrations above the critical micelle concentration allows these aggregates to be retained by

[1] In the '226 patent, "substantially pure form" refers to daptomycin that "contains less than 2.5 percent of a combined total of anhydro-[daptomycin] and isomer-[daptomycin]." Ex. 1010, 8:58–60. Anhydro-daptomycin and β-daptomycin are the major impurities identified in the '238 patent as impurity numbers 13 and 8, respectively. Ex. 1001, 33:63–34:19, 34:49–52, 62–65.

relatively high molecular weight cut-off membranes." *Id.* Mulligan further reports that the use of certain identified ultrafiltration membranes increased surfactin yields to over 97% and "dramatically reduced" recovery costs. *Id.* at 26, 27 (Table 1); Ex. 1005 ¶ 90. Mulligan also notes that the disclosed method of purification using ultrafiltration may be used for any "molecules that tend to aggregate above certain concentrations." Ex. 1013, 27–28.

4. Lin II

Lin II was published in November 1998 and is prior art under 35 U.S.C. § 102(b). Pet. 11. Lin II discloses the use of a combination of ultrafiltration (size separation) and HPLC to purify biosurfactant molecules "without any prior structural information of the biosurfactants." Ex. 1015, 151, Abstract; Ex. 1005 ¶ 100. The Lin II method first separates biosurfactant micelles from small molecule impurities using ultrafiltration. Ex. 1015, 151. The biosurfactant micelles are then dissociated through the addition of alcohol to form monomers that pass through an ultrafiltration membrane, thereby separating the monomeric biosurfactant molecules from larger macromolecule impurities. *Id.* at 153–154, 156.

Lin II reports that the size-separated biosurfactant molecules may be further purified using HPLC to form "homogeneous biosurfactant samples useful for biophysical and chemical analysis." Pet. 11 (citing Ex. 1005 ¶¶ 98–100). Lin II further reports that the disclosed method "can be applied for the development of an HPLC assay for any biosurfactant as long as the concentration of biosurfactants in the fermentation broth is higher than the critical micelle concentration." *Id.* (citing Ex. 1015, 150–51).

5. Lakey

Lakey was published in 1988 and is prior art under 35 U.S.C. § 102(b). Pet. 12. Lakey discloses that daptomycin (LY146032) may exist in either monomeric or aggregate form, with aggregation of daptomycin occurring at "concentrations higher than 10^{-3} M." Ex. 1033, 4643; Ex. 1005 ¶ 104. Dr. Tarantino testifies that one of ordinary skill in the art would understand the aggregates reported in Lakey "were in fact micelles." Ex. 1005 ¶ 104.

6. Analysis

Claim 91 requires, *inter alia*, a daptomycin composition that is essentially free of each of impurities 1 to 14 defined by peaks 1–14 shown in Figure 12 of the '238 patent. Ex. 1001, 40:33–37, 42:54–56, 43:4–6. The '238 patent indicates that daptomycin is "essentially free" of another compound "when the other compound is present in an amount that is no more than 0.5% of the amount of the daptomycin" lipopeptide preparation. *Id.* at 7:52–56; Pet. 6; Prelim. Resp. 8.

Petitioner contends it would have been obvious to obtain a daptomycin composition that is "essentially free" of impurities 1 to 14 in view of the disclosures of the '843 patent, the '226 patent, Mulligan, Lin II, and Lakey. Pet. 15–31. In support of this argument, Petitioner notes that daptomycin, or LY146032, is an antibiotic intended for therapeutic use. Pet. 19; Ex. 1007, 1:5–8, 1:36–38; Ex. 1005 ¶ 137. Given this therapeutic application, Petitioner contends a person of ordinary skill in the art would have been motivated to increase the purity of daptomycin compositions "as high as possible." Pet. 24; Ex. 1005 ¶¶ 75 (asserting that high levels of

purity for pharmaceutical preparations of antimicrobial agents would have been a target goal for one of ordinary skill in the art), 137.

To achieve this goal, Petitioner contends a person of ordinary skill in the art would have accessed the "extensive tool-box" known in the art for purifying lipopeptide biosurfactants. Pet. 16–17, 23. In particular, Petitioner contends that one of ordinary skill in the art would have understood that the methods disclosed in the '843 patent, the '226 patent, Lakey, Mulligan, and Lin II could be used to obtain a daptomycin composition with a purity level exceeding 99%. Pet. 17–18, 20.

Patent Owner contends Petitioner does not explain why the proposed combination of references would result in a daptomycin composition that is "essentially free" of impurities 1-14. Prelim. Resp. 8–9. According to Patent Owner, Petitioner provides only general statements regarding the disclosures of the prior art references, and the claim chart for claim 91 "includes no citation or support" for obtaining daptomycin that is "essentially free" of impurities 1–14. *Id.* at 8.

We agree with Patent Owner that Petitioner does not provide sufficient argument or evidence to demonstrate that the purification methods set forth in the '843 patent, the '226 patent, Mulligan, and Lin II would result in a daptomycin composition having no more than 0.5% of each of impurities 1–14. As noted by Patent Owner, the Petition does not address directly the limitations of claim 91. *See, e.g.*, Pet. 26–27, 31. For example, the claim chart for claim 91 merely states "*See* claim 85," and the claim charts for claims 49 and 85 do not indicate that the methods set forth in the '843 patent, Mulligan, and Lin II would result in a daptomycin composition that is "essentially free" of impurities 1–14. *Id.* at 26–27, 30.

The Petition does state that compositions purified using the disclosed methods "would have at least approached and likely exceeded 99% purity levels with respect to all impurities present." *Id.* at 20 (citing Ex. 1005 ¶ 148). A 99% purity level, however, would still allow for at least one of the fourteen impurities to be present in the daptomycin composition at a level greater than 0.5%. Thus, we are not persuaded that this evidence demonstrates that the purification methods of the '843 patent, the '226 patent, Mulligan, and Lin II would result in a daptomycin composition that is "essentially free of each of impurities 1 to 14," as recited in claim 91.

In the claim chart for claim 49, the Petition cites to the declaration testimony of Dr. Tarantino, who testifies that the purification methods disclosed in the '843 patent, the '226 patent, Mulligan, and Lin II would have achieved daptomycin compositions approaching "homogeneity" that satisfy the purity limitations of claims 91. Pet. 26-27; Ex. 1005 ¶¶ 146, 161. Dr. Tarantino does not define the term "homogenous," however, and the Petition indicates "homogeneous" compositions have a purity level "approaching at least 99%," which would not necessarily satisfy the requirements of claim 91. *See* Pet. 17–18 (noting that the purification process of Lin II could be used to "obtain homogeneous biosurfactant preparations, *i.e.*, preparations *approaching* at least 99% purity") (emphasis added); Ex. 1005 ¶ 146 (asserting that "additional chromatographic purification" methods applied to the daptomycin produced in the '843 patent "would have at least approached and *likely* exceeded 99% purity levels with respect to all impurities present") (emphasis added). As such, we are not persuaded that Petitioner and Dr. Tarantino provide sufficient argument or evidence to demonstrate a reasonable likelihood that the purification

methods disclosed in the ’843 patent, the ’226 patent, Mulligan, and Lin II would achieve a daptomycin composition within the purity limitations set forth in claim 91.

III. ORDER

In consideration of the foregoing, it is ORDERED that no *inter partes* review is instituted.

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