

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS-KABI USA LLC
Petitioner,
v.

CUBIST PHARMACEUTICALS, INC.
Patent Owner.

Case IPR2015-00223
Patent 6,852,689 B2

Before LORA M. GREEN, TINA E. HULSE, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

PAULRAJ, *Administrative Patent Judge*

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

I. BACKGROUND

Fresenius-Kabi USA LLC (“Petitioner”) filed a Petition for *inter partes* review of claims 1–5 and 10–57 of U.S. Patent No. 6,852,689 B2 (Ex. 1001, “the ’689 patent”). Paper 2 (“Pet.”). Cubist Pharmaceuticals, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 10 (“Prelim. Resp.”). Taking into account the Petition and Patent Owner’s Preliminary Response, we determined that there was a reasonable likelihood that challenged claims 1–5 and 10–57 are unpatentable. Pursuant to 35 U.S.C. § 314, we instituted *inter partes* review, on May 14, 2015, as to claims 1–5 and 10–57 of the ’689 patent. Paper 13 (“Dec.”).

After institution, Patent Owner filed a Patent Owner Response. Paper 23, “PO Resp.”. Petitioner filed a reply to the Patent Owner Response Paper 32 (“Pet. Reply”).

On August 20, 2015, the parties filed joint motions to seek to remove from consideration claims 1–5, 10–50, and 53–57, and thereby to limit the Petition to claims 51 and 52 pursuant to a Joint Stipulation and Agreement between the parties. See Paper 25; Ex. 1026 (unredacted version); Ex. 1027 (redacted version). The parties also filed joint motions to treat the Stipulation and Agreement as business confidential information, to be kept separate from the files of the involved patents. See Paper 26. These motions were granted on September 18, 2015. See Paper 28. The scope of *this inter partes* review is therefore limited to claims 51 and 52 of the ’689 patent.

A hearing was held on February 8, 2016, a transcript of which appears in the record. Record of Oral Hearing, Paper 42 (“Tr.”).

We have jurisdiction under 35 U.S.C. § 6(c). This is a Final Written Decision under 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73 as to the patentability of the challenged claims. For the reasons discussed below, we determine that Petitioner has shown by a preponderance of the evidence that claims 51 and 52 are unpatentable.

A. Related Proceedings

In addition to this proceeding, we have instituted an *inter partes* review of a related patent, U.S. Patent No. 6,468,967 B1 (“the ’967 patent”), based on a petition filed by the same Petitioner. See IPR2015-00227, Decision on Institution of *Inter Partes* Review (PTAB May 14, 2015) (Paper 13). A Final Written Decision in that proceeding has issued concurrently with this Decision.

Further, in *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, No. 12-cv-00367 (D. Del.), the U.S. District Court for the District of Delaware held that claims 51 and 52 of the ’689 patent were obvious over the same prior art considered in this proceeding. Ex. 1024. The U.S. Court of Appeals for the Federal Circuit affirmed the holding of obviousness on November 12, 2015. See *Cubist Pharms., Inc. v. Hospira, Inc.*, 805 F.3d 1112 (Fed. Cir. 2015). On January 22, 2016, the court denied Patent Owner’s Petition for Panel Rehearing and Rehearing *En Banc*. Ex. 1036. Although Patent Owner emphasizes that the *Hospira* case “is a separate proceeding based on a different record, [with] different experts testifying” (Tr. 27:2–12), we find that the arguments and evidence presented in this proceeding are largely duplicative of what the district court and Federal Circuit have already

considered in *Hospira*.¹ Moreover, the “preponderance of the evidence” standard for determining unpatentability in an *inter partes* review is lower than the “clear and convincing evidence” standard for proving invalidity in district court litigation. See 35 U.S.C. § 316(e); *Microsoft Corp. v. i4i Ltd. P’ship*, 564 U.S. 91, 95 (2011). Nonetheless, while we have taken the Federal Circuit’s *Hospira* decision into account, we have independently considered the patentability of the challenged claims based on the specific evidence of record before us and the legal standards applicable to an *inter partes* review.²

B. The ’689 Patent

The ’689 patent relates to methods for administering a therapeutically effective amount of the antibiotic daptomycin in a manner that minimizes skeletal muscle toxicity. Ex. 1001, 3:16–21. Daptomycin has potent bactericidal activity against Gram-positive bacteria, which can cause serious and life-threatening diseases. *Id.* at 1:26–29. Prior clinical trials and toxicology studies in animals found that skeletal muscle was the primary target tissue of daptomycin toxicity. *Id.* at 2:22–24. Although low doses of daptomycin do not cause muscle toxicity, certain types of Gram-positive bactericidal infections, such as deep-seated infections, or those caused by

¹ In addition to the same prior art, the evidence of record before us includes certain testimony from the *Hospira* litigation. See, e.g., Ex. 1033 (testimony of Drs. Zeckel and Eisenstein); Ex. 1034 (testimony of Dr. Guglielmo, S. Murray, and Dr. Rausser); Ex. 2062 (testimony of Robert Charles Moellering).

² Patent Owner has represented that the only basis for continuing to proceed with this *inter partes* review is that it is seeking Supreme Court review of the Federal Circuit’s *Hospira* decision. Tr. 25:18–26:6; see Ex. 1037 (Petition for a Writ of Certiorari).

antibiotic-resistant bacterial strains, may require higher doses of daptomycin for effective treatment. *Id.* at 2:33–38. Thus, according to the Specification, “there is a great need to develop methods for administration of effective amounts of daptomycin that will also minimize adverse skeletal muscle effects.” *Id.* at 2:42–45.

The Specification discloses the results of several studies that suggest that daptomycin-associated skeletal muscle toxicity is not related to the peak concentration of drug that occurs in the bloodstream after administration. *Id.* at 4:39–41. Nor does toxicity appear to relate to the total concentration of daptomycin in the bloodstream for 24 hours (i.e., the AUC_{24h}). *Id.* at 4:41–44. Instead, the Specification states that “the data suggest that the dosing interval is the key determinant of muscle toxicity, rather than just the magnitude of the dose itself.” *Id.* at 4:48–50. Accordingly, the Specification discloses methods of providing daptomycin at a dosing interval of 24 hours or greater to minimize skeletal muscle toxicity and allow for higher peak concentrations of daptomycin. *Id.* at Abstract.

C. Illustrative Claims

The challenged claims 51 and 52 each depend on claim 48, which in turn depends on independent claim 47. Independent claim 47 of the ’689 patent is reproduced below:

47. A method for administering daptomycin, comprising the step of administering to a human patient in need thereof a therapeutically effective amount of daptomycin in a dose of at least 3 mg/kg of daptomycin at a dosage interval that minimizes skeletal muscle toxicity, wherein the dose is repeatedly administered at a dosage interval of once every 48 hours.

Claims 51 and 52 further limit the dose of daptomycin to 4 mg/kg and 6 mg/kg, respectively.

D. Ground for Unpatentability

In view of our Decision to Institute (Paper 13) and our Order on the Motion to Limit the Petition (Paper 28), the only ground of unpatentability before us in this *inter partes* review is the obviousness of claims 51 and 52 over the '226 patent,³ Rotschafer,⁴ and Woodworth.⁵ Dec. 15.

II. DISCUSSION

A. Claim Construction

We interpret claims using the “broadest reasonable construction in light of the specification of the patent in which [they] appear[.]” 37 C.F.R. § 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015) (“Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA,”⁶ and “the standard was properly adopted by PTO regulation.”), *cert. granted sub nom. Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 890 (mem.) (2016). Under the broadest reasonable construction standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the

³ Baker et al., US 5,912,226, issued June 15, 1999 (Ex. 1011). We refer to this reference as “the '226 patent” because that is how it is identified by both Petitioner and Patent Owner.

⁴ John C. Rotschafer et al., *Therapeutic Update on Glycopeptide and Lipopeptide Antibiotics*, 8 PHARMACOTHERAPY 211–219 (1988) (Ex. 1012).

⁵ J. R. Woodworth et al., *Single-dose Pharmacokinetics and Antibacterial Activity of Daptomycin, a New Lipopeptide Antibiotic, in Healthy Volunteers*, 36 ANTIMICROB. AGENTS & CHEMOTHER. 318–25 (1992) (Ex. 1013).

⁶ The Leahy-Smith America Invents Act, Pub. L. No. 112–29, 125 Stat. 284 (2011) (“AIA”).

art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

1. “at a dosage interval that minimizes skeletal muscle toxicity”

In our Decision to Institute we interpreted the term “at a dosage interval that minimizes skeletal muscle toxicity,” which is recited in independent claim 47, as not requiring anything beyond administering daptomycin at the express dosage intervals recited in the claim. As we noted, the requirement of “minimiz[ing] skeletal muscle toxicity” would be understood as nothing more than the intended result or consequence of administering daptomycin at the specifically recited dosage interval. Dec. 6. Our interpretation is consistent with the Specification, which repeatedly indicates that lengthening the dosing interval is what minimizes skeletal muscle toxicity. The Specification does not indicate that the minimization of skeletal muscle toxicity is due to any variable other than extending the dosage interval to once every 24 hours or more. *See, e.g.*, Ex. 1001, 5:16–19 (“Without wishing to be being bound by any theory, these results may be explained by the hypothesis that skeletal muscle toxicity is related to time between doses for repair of skeletal muscle damage.”).

Patent Owner has sought reconsideration of our claim construction on the grounds that the Examiner, during prosecution, considered minimizing skeletal muscle toxicity to be an “essential element of the invention.” PO Resp. 6–7 (citing Ex. 2013, 3; Ex. 2014, 2–3, 9, 11–12; Ex. 2016, 2; Ex. 2017, 1; Ex. 2018, 2, 4, 9, 13, 18; Ex. 2019, 2). Patent Owner argues that these statements in the prosecution cannot be ignored, even under the broadest reasonable interpretation standard. *Id.* at 7 (citing *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015)).

We find nothing in the prosecution history, however, to suggest clearly that either the examiner or the applicants considered a “dosage interval that minimizes skeletal toxicity” to require anything beyond administering daptomycin at the expressly recited dosage interval required by claim 47 (i.e., once every 48 hours). Indeed, in amending then pending claim 32 in response to the Examiner’s § 112, ¶ 2 rejection on the grounds that the claims do not recite an “essential element of the invention,” the applicants added the *entirety* of the language “wherein said single dose is formulated for administration to a human patient at a dosage interval of once every 24 hours to once weekly and that does not result in muscle toxicity.” Ex. 2013, 3; Ex. 2014, 3. Thus, Patent Owner plainly equated a dosage interval that does not result in muscle toxicity to once every 24 hours to once weekly. Patent Owner has not pointed to any other intrinsic or extrinsic evidence to indicate what else might be required for a dosage interval that minimizes skeletal muscle toxicity. Accordingly, we maintain our claim construction for purposes of this Final Decision.⁷

2. Remaining Claim Terms

We determine that, for purpose of this Final Written Decision, none of the other terms in the challenged claims requires express construction.

⁷ Our construction is applicable under either the broadest reasonable interpretation standard or the claim construction standard articulated in *Phillips v. AWH Corp.*, 415 F. 3d 1303 (Fed. Cir. 2005) (en banc). Indeed, we note that our construction is consistent with the Federal Circuit’s interpretation and treatment of the claims in *Hospira*. Ex. 1031, 17 (affirming district court’s finding that minimizing skeletal muscle toxicity was a “necessary accompaniment to the other disclosed claim limitations”).

B. Overview of the Prior Art

Petitioner relies upon the following prior art references in its patentability challenges.

1. The '226 Patent (Ex. 1011)

The '226 patent relates to an antibacterial drug, designated as LY146032 in the reference, which is acknowledged to be daptomycin. Ex. 1011, Abstract; Ex. 1007 ¶ 17. The '226 patent discloses methods of treating infections caused by gram-positive bacteria by administering an effective dose of daptomycin. Ex. 1011, 10:46–48. The '226 patent states an effective dose is generally between about 0.1 and about 100 mg/kg of the drug, with the preferred dose from about 1 to about 30 mg/kg. *Id.* at 10:53–57. The '226 patent also states that a typical daily dose for an adult human is from about 100 mg to about 1.0 g. *Id.* at 10:57–58.

In practicing the method, the '226 patent discloses that the antibiotic compound can be administered “as a single daily dose or in multiple doses per day.” *Id.* at 10:59–61. The '226 patent discloses further that the treatment regime may require administration over extended periods of time, such as for several days or two to four weeks. *Id.* at 10:62–64. According to the '226 patent, “[t]he amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms involved in the infection.” *Id.* at 10:64–11:2.

2. Rotschafer (Ex. 1012)

Rotschafer describes three known antibiotics, vancomycin, teicoplanin, and daptomycin, and states that “the development of new agents

such as teicoplanin and daptomycin may represent useful alternatives if [vancomycin] resistant organisms are encountered.” Ex. 1012, 214. With regard to teicoplanin, Rotschafer teaches that “[t]he dosing regimen used in present teicoplanin clinical trials is 6 mg/kg every 12 hours for the first three doses (used as a loading dose) followed by 6 mg/kg every 24 hours.” *Id.* at 215. Rotschafer further teaches that “[a]s with vancomycin, the dosage requires adjusting in patients with varying degrees of renal function. Two simplified approaches were suggested for modifying dosages: reduce the dose but keep the interval constant, or give the standard dose with a lengthened interval.” *Id.* at 215–16 (footnote omitted). With regard to daptomycin, Rotschafer also teaches that “dosage adjustment appears necessary in patients with impaired renal function.” *Id.* at 217.

3. *Woodworth (Ex. 1013)*

Woodworth describes three studies to define the disposition and pharmacokinetics of daptomycin in healthy volunteers. Ex. 1013, Abstract. Woodworth generally discloses that “[o]n the basis of the drug’s pharmacokinetics and antibacterial activity, doses of 4 to 6 mg/kg/day, possibly in divided doses, are predicted to be effective.” *Id.* In one study, Woodworth administered successive single doses of 2, 3, 4, and 6 mg/kg intravenously with at least 72 hours separating each dose. *Id.* at 319. Woodworth found that daptomycin exhibits extensive protein binding. *Id.* at 320. Woodworth also found that “[n]o adverse events were reported or observed during the course of these studies. All doses were well tolerated.” *Id.* at 321.

C. Obviousness of Claims 51 and 52 over the '226 patent, Rotschafer, and Woodworth

Petitioner asserts that claims 51 and 52 are obvious over the combination of the '226 patent, Rotschafer, and Woodworth. *See* Pet. 24–55 (as applicable to the remaining challenged claims). Petitioner relies upon the Declaration of Dr. Alexander Shepherd, M.D., Ph.D., FRCP to support its arguments. Ex. 1007. We determine that Petitioner has demonstrated, by a preponderance of the evidence, that claims 51 and 52 would have been obvious over the combination the '226 patent, Woodworth, and Rotschafer. We are unpersuaded by Patent Owner's arguments to the contrary.

1. Prima Facie Obviousness

Claims 51 and 52 are directed to a dosing regimen where daptomycin, an antibiotic drug known in the prior art, is repeatedly administered to a human patient in need thereof at a dose of 4 mg/kg or 6 mg/kg, respectively, and at a dosage interval of once every 48 hours.

Petitioner asserts that administration of daptomycin at the specifically claimed doses of 4 and 6 mg/kg would have been obvious because the '226 patent discloses the use of the daptomycin at a "typical daily dose" in humans of "from about 100 mg to about 1.0 g," and "[a]ssuming an average adult human weighs 70 kg, this range corresponds to 1.4 mg/kg to 14 mg/kg." Pet. 25 (citing Ex. 1011, 10:46–58; Ex. 1007 ¶ 27). Petitioner further points to Woodworth's teaching that administering daptomycin at doses of 4 and 6 mg/kg caused no adverse effects and were "well tolerated," and its conclusion that "doses of 4 to 6 mg/kg/day, possibly in divided doses, are predicted to be effective." *Id.* at 29, 37 (citing Ex. 1013, Abstract, 319, 321). Petitioner further asserts that administration of daptomycin at the claimed dosage interval of once every 48 hours would have been obvious

because the '226 patent and Woodworth both teach administration once every 24 hours, and Rotschafer teaches extending the 24-hour dosing interval for patients with impaired renal function. *Id.* at 29 (citing Ex. 1012, 215–217). In addition to these prior art teachings, Petitioner asserts that the skilled artisan would have been motivated to use the claimed dosing regimen in light of daptomycin's similarity to other antibiotic dosing regimens. *Id.* at 30. In particular, Petitioner asserts that the skilled artisan would have known that aminoglycosides have properties that are similar to daptomycin, namely, concentration-dependent killing and a potential toxicity that is reversible. *Id.* at 31 (citing Ex. 1007 ¶¶34–36).

Patent Owner argues that “[t]he teachings of the '226 patent and Woodworth are broad and generic, and merely an invitation to investigate what dosing regimens might be therapeutically effective.” PO Resp. 13. Relying upon the Declaration of its expert, Dr. Hartmut Derendorf, Ph.D., as well as alleged admissions by Petitioner's expert Dr. Shepherd, Patent Owner contends that a skilled artisan would not limit the dosing range disclosed in the '226 patent to only integer values. *Id.* at 15–16 (citing Ex. 2028 (Derendorf Decl.) ¶¶ 70; Ex. 2027 (Shepherd Depo.), 61:9–16, 83:5–19). Similarly, Patent Owner contends that Woodworth “describes an ‘infinite’ number of dosing regimens, ‘[e]ither in terms of frequency or duration,’” and “a skilled artisan could not predict based on the disclosures in Woodworth what dosage regimens would be safe and effective for patients.” *Id.* at 29 (citing Ex 2027, 60:3–6, 71:10–72:3; Ex. 2028 ¶¶ 72, 77–82, 85, 88).

We find that the teachings of the '226 patent and Woodworth, when considered together and in their entirety, would have guided the skilled

artisan to once-daily administration of daptomycin at doses of 4 mg/kg and 6 mg/kg. Contrary to Patent Owner's arguments, the fact that an infinite number of values can fall within the prior art's non-integer range does not necessarily render its disclosure boundless or otherwise meaningless. We recognize that the '226 patent discloses a broader dosing range than what it claimed, calculated as between 1.4 and 14 mg/kg, which is not limited to only integer values falling within that range. Nonetheless, we find that the '226 patent would sufficiently suggest to the skilled artisan that daptomycin can be administered at dosage amounts falling within the disclosed range as a "single daily dose" (i.e., a dosing interval of once every 24 hours) over extended time periods. Ex. 1011, 10:59–63. Moreover, as noted by the Federal Circuit in the *Hospira* decision, Woodworth more specifically discloses once-daily administration of daptomycin at doses falling within the narrower range of 4 to 6 mg/kg. Ex. 1031, 20. We reach the same conclusion based on our own review of Woodworth. In particular, the endpoints of the range disclosed in the abstract and conclusion of Woodworth, as well as the specific dosages of 4 mg/kg and 6 mg/kg used in the single-dose studies described therein, would have led a skilled artisan to try the claimed dosage amounts for a daptomycin dosing regimen. See Ex. 1013, Abstract ("doses of 4 to 6 mg/kg/day, possibly in divided doses, are predicted to be effective"), 319 ("volunteers were administered daptomycin in successive single doses of 2, 3, 4, and 6 mg/kg"), 324 ("our data suggest that good antibacterial activity would be produced from single doses of 4 to 6 mg/kg").

With respect to Woodworth, Patent Owner argues that the reference discloses only "single dose studies in healthy volunteers," which "did not

involve administering daptomycin repeatedly,” but rather a 72-hour “wash out” period that separated each dose. PO Resp. 21–22. As such, Patent Owner asserts that Woodworth’s single dose studies do “not teach a skilled artisan what efficacy—and particularly what toxicity—can be expected with repeated dosing.” *Id.* at 22–23. Patent Owner further asserts that Woodworth teaches away from the claimed once-daily or extended dosing regimen by “concluding that due to daptomycin’s high protein binding, the dose required for an effective once a day regimen would ‘correspond to a dose of 20–25 mg/kg, which is presently an *unrealistic dose*.’” *Id.* at 24–25.

We are unpersuaded by these arguments, as Woodworth plainly concludes, based on the single dose studies described therein, that daptomycin “doses of 4 to 6 mg/kg/day, possibly in divided doses, are predicted to be effective.” Ex. 1013, Abstract. We agree with the Federal Circuit that, “[w]hile it is true that the Woodworth reference is predictive in nature, it is based on extensive laboratory research, and its predictions of the efficacy of a dosage regimen of 4 mg/kg to 6 mg/kg at daily intervals give rise to a reasonable expectation that dosages in that amount would be effective in patients.” Ex. 1031, 21. We do not consider Woodworth’s description of a simulation that required an “unrealistic dose” of 20 to 25 mg/kg based on certain assumptions to teach away from the claimed doses of 4 mg/kg and 6 mg/kg because it does “not criticize, discredit, or otherwise discourage investigation into the invention claimed.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Indeed, Patent Owner fails to mention in its briefing that Woodworth also describes “[a]nother simulation [that] used concentrations closer to those anticipated from multiple dosing of 6 mg/kg.” Reply 12; Ex. 1013, 324.

Moreover, we are unpersuaded by Patent Owner's arguments that the prior art did not recognize daptomycin's toxicity problem, and thus would not have provided a reasonable expectation of success in achieving a safe and therapeutically effective dosing regimen of the drug. *See, e.g.*, PO Resp. 16–17. As discussed above, we have construed the claim term “at a dosage interval that minimizes skeletal muscle toxicity” to be non-limiting, as the condition is necessarily satisfied by administration of daptomycin at the specifically recited dosage interval of once every 48 hours. Accordingly, the prior art need not have recognized daptomycin's toxicity problem in order to render the claimed methods obvious. Here, Woodworth suggests administration of daptomycin once a day (but only “possibly” in divided doses), “noting possibly safer use in renally impaired patients,” and Rotschafer teaches that dosages may be adjusted in patients with varying degrees of renal function. Ex. 1012, 215–16; Ex. 1013, 324. We find these teachings, in combination with the '226 patent's teaching that daptomycin can be administered as a “single daily dose” (Ex. 1011, 10:59–60), provide sufficient motivation to extend that dosage interval to once every 48 hours for renally impaired patients with a reasonable expectation of success. The skilled artisan need not have predicted the efficacy or safety of such a dosing regimen with absolute certainty in order to render the claimed invention obvious. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (“Obviousness does not require absolute predictability of success.”).

Patent Owner also argues that the pharmacokinetic and pharmacodynamics properties of daptomycin cited by Petitioner do not render the claimed invention obvious. PO Resp. 37–45. We disagree. The evidence of record supports Petitioner's contention that daptomycin exhibits

concentration-dependent killing and the potential to induce a reversible toxicity, similar to aminoglycosides that were administered once daily. *See, e.g.*, Ex. 1007 ¶¶ 34–36 (comparing properties of daptomycin to aminoglycosides), 45–47 (concluding, based on Woodworth’s concentration studies, that the skilled artisan “would have increased the dose of daptomycin—if treating a more severe infection—with a reasonable expectation of success given the [minimum inhibitory concentration (MIC)] and pharmacokinetic profile of daptomycin”). As did the the Federal Circuit in the *Hospira* decision, we find that these “characteristics . . . would have led one of skill in the art to believe that increasing the dosage intervals for daptomycin would give rise to a reasonable expectation of increased efficacy while minimizing the toxic side effects of the drug.” Ex. 1031, 22.

2. Secondary Considerations

In an obviousness analysis, we must consider any objective evidence of nonobviousness (“secondary considerations”) that is presented. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The totality of the evidence submitted may show that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). To be relevant, evidence of nonobviousness must be reasonably commensurate in scope with the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Furthermore, there must be a nexus between the merits of the claimed invention and the evidence of secondary considerations. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

Patent Owner asserts that evidence of long-felt need, failure of others, initial skepticism, unexpected results, and commercial success support the

non-obviousness of the claimed invention. PO Resp. 48–60. We have considered the secondary considerations evidence presented by Patent Owner, but do not find them sufficient, individually or in combination, to “overcome the strong prima facie case of obviousness” made of record. *See Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

The underlying facts that Patent Owner relies upon to support its secondary considerations arguments are set forth primarily in the Declaration of Michael Zeckel, M.D., a Senior Medical Fellow in global patient safety at Eli Lilly and Company (“Lilly”) who was responsible for daptomycin’s clinical development. Ex. 2030. In his Declaration, Dr. Zeckel recounts Lilly’s attempts to develop a therapeutically effective regimen for daptomycin, which began around 1983. *Id.* ¶ 11. As part of early human clinical trials, Lilly administered daptomycin to healthy volunteers at dosages of 2 mg/kg every 24 hours, “which appeared to be safe and achieved plasma daptomycin concentrations believed at that time to be sufficient to inhibit Gram-positive organisms.” *Id.* ¶ 14. After completing these initial studies, however, Lilly conducted a Phase II clinical study of daptomycin at 2 mg/kg/24h, which was voluntarily terminated in June of 1988 due to a lack of proven efficacy in treating more serious infections. *Id.* ¶ 15.

Lilly hypothesized that the concentrations of unbound daptomycin were not exceeding the MIC (minimum inhibitory concentration required to prevent bacterial growth) throughout the 24-hour dosing interval, resulting in a failure to effectively treat more serious Gram-positive infections. *Id.* ¶ 16; *see also* Ex. 2045 (“Lee 1991a”) (describing clinical failures with 2 mg/kg/24h dosage regimen). Based on the theory that sufficiently high

trough concentrations could be maintained by administering larger doses of daptomycin more frequently, Lilly conducted a Phase II clinical trial with a dosing regimen of 3 mg/kg/12h in patients with Gram-positive bacteremia and endocarditis (i.e., bacterial infection in the heart). Ex. 2030 ¶ 17; Ex. 1015 (“Lee 1991”). Dr. Zeckel states that “Lilly considered this study a failure, because even though daptomycin at 3 mg/kg/12h worked to treat bacteremia, it did not work for endocarditis.” Ex. 2030 ¶ 19. After this study, Lilly conducted a Phase I dose escalation study in healthy volunteers, with a plan to escalate the dose to 4 mg/kg/12h and then 5 mg/kg/12h. *Id.* ¶ 22. However, the results at 4 mg/kg/12h showed “significant skeletal muscle toxicity” based on elevated creatine phosphokinase (CPK) levels. *Id.* Lilly subsequently notified the FDA of these CPK elevations, and the FDA responded by placing all daptomycin studies on clinical hold. *Id.* ¶ 24; *see also* Ex. 2041; Ex. 2042.

Dr. Zeckel states that “Lilly did not continue developing daptomycin after this, because we did not have a theory for what property of daptomycin had caused the CPK elevations, or how to dose daptomycin safely and effectively to treat a full range of infections.” Ex. 2030 ¶ 25. According to Dr. Zeckel, a once-daily administration was not considered as a potential solution to the dosing problem because, after observing failures at 2 mg/kg/24h, it was thought that 12-hour dosing was “needed to maintain free (not protein bound) plasma concentrations throughout the dosing interval and provide an effective dose.” *Id.* ¶ 26.

a. Long-Felt Need/Failure of Others/Skepticism

Patent Owner asserts that, at the time of the invention, there was a long-felt but unsolved need for new antibiotics to treat *S. aureus* and

methicillin-resistant *S. aureus* (“MRSA”) infections due to concerns that vancomycin did not work for all patients, and antibiotic resistance to vancomycin was likely to develop. PO Resp. 49–51. Patent Owner asserts that the non-obviousness of the ’689 patent is also confirmed by the attempt and failure of others to develop the same invention. *Id.* at 52–57.

Specifically, Patent Owner points to Lilly’s attempts and failure to find a daptomycin dosing regimen that would be safe and effective in the treatment of a full range of infections, as summarized above and set forth in the Zeckel Declaration (Ex. 2030). Additionally, Patent Owner asserts that skilled artisans at the time of the invention believed that daptomycin would never be a viable treatment for a full range of MRSA and *S. aureus* infections, and instead recommended developing daptomycin analogs. PO Resp. 57–58 (citing Ex. 2027, ¶ 162; Ex. 2044; Ex. 2043; Ex. 2010).

We have considered the evidence of record, but find that Patent Owner has not demonstrated that any long-felt need, failure of others, or skepticism associated with the development of daptomycin is reasonably commensurate in scope with or has a sufficient nexus to the claimed invention. Patent Owner asserts that there was a long-felt need to replace vancomycin for certain bacterial infections (*S. aureus* and MRSA), and skepticism that daptomycin could satisfy that need. But even assuming that daptomycin administered according to the claimed method satisfied any such need, the claims are not limited to the treatment of only those particular infections. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010) (finding no long-felt need because the claims were broad enough to cover devices that did not solve the problem). Likewise, Patent Owner has not shown how Lilly’s alleged failure to develop a

successful daptomycin dosing regimen for more serious Gram-positive bacterial infections is commensurate in scope with the claimed invention insofar as the claimed invention is not limited to the treatment of more serious infections. Moreover, the evidence of record in this proceeding, which was also considered in the *Hospira* litigation, supports the same conclusion reached by the Federal Circuit. That is, Lilly's decision to discontinue its daptomycin trials was due, at least in part, to economic considerations, *i.e.*, the desire to avoid cannabilizing sales of its own market-leading drug, vancomycin. *See* Ex. 1031, 24; *see also* Ex. 1033, 569:19–22 (Zeckel testimony in *Hospira* litigation), 667:19–668:6 (Eisenstein testimony in *Hospira* litigation).

b. Commercial Success

Patent Owner further asserts that the commercial success of its daptomycin formulation CUBICIN[®], with net revenues totaling over \$5 billion, further supports the non-obviousness of the claims. PO Resp. 59–60. Patent Owner asserts that the dosing regimen claimed in the '689 patent, along with the related '967 patent, reflect the only FDA-approved dosing regimen for CUBICIN[®]. *Id.* at 60 (citing Ex. 2032 (Hall Decl.) ¶¶ 2–3; Ex. 2001, 1 (CUBICIN[®] label).

“Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art.” *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). “Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or ‘nexus’ between an invention and commercial

success of a product embodying that invention, probative of whether an invention was non-obvious.” *Id.*

We have considered the evidence presented, but determine that Patent Owner has not established that the commercial sales of CUBICIN[®] have a sufficient nexus to the claims of the ’689 patent. That the FDA approved a dosing regimen covered by the claims of the ’689 patent does not necessarily mean that CUBICIN[®]’s sales are due to the claimed invention as opposed to other factors. Other than summarily relying upon its sales numbers, Patent Owner has not shown how the specifically claimed dosing regimen, as opposed to other features of daptomycin, have driven the commercial sales of the drug. *See* Ex. 1034, Tr. 1106:14–1109:3 (Patent Owner’s witness, Mr. Stuart Murray, testifying in *Hospira* litigation that Cubist does not have any way to assess how any sales could be attributed to once-daily dosing as opposed to any of the other marketed attributes of CUBICIN[®]).

c. Unexpected Results

Patent Owner asserts that, at the time of the invention, a skilled artisan would not have expected that giving large doses of daptomycin less often would decrease daptomycin’s skeletal muscle toxicity while maintaining its efficacy. PO Resp. 58–59. As such, Patent Owner argues that unexpected results support the non-obviousness of the claims.

We are not persuaded by this contention. As discussed above, even though the prior art did not discuss skeletal muscle toxicity, Woodworth and the ’226 patent specifically suggested a once-daily dosing regimen, and Rotschafer provided an independent reason to extend the dosing interval for renally impaired patients. The fact that the inventors recognized another benefit of the dosing regimen otherwise rendered obvious by this prior art is

not sufficient to impart patentability. *See In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (“It is a general rule that merely discovering and claiming a new benefit of an *old* process cannot render the process again patentable. . . . While the processes encompassed by the claims are not entirely *old*, the rule is applicable here to the extent that the claims and the prior art overlap.”) (citations omitted).

Moreover, in view of the background knowledge of the skilled artisan that daptomycin exhibits similar properties to aminoglycosides (Ex. 1007 ¶¶ 34–36, 79), we do not find that any reduction in skeletal muscle toxicity (while maintaining efficacy) associated with the claimed dosing regimen was necessarily “unexpected.”

We, therefore, find that Patent Owner’s evidence of alleged unexpected results is not sufficient to overcome the showing of obviousness.

III. CONCLUSION

We conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 51 and 52 are rendered obvious under 35 U.S.C. § 103 by the combination of Woodworth, the ’226 patent, and Rotschafer.

This is a Final Written Decision of the Board under 35 U.S.C. 318(a). Parties to the proceeding seeking judicial review of this Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IV. ORDER

Accordingly, it is

ORDERED that claims 51 and 52 of U.S. Patent 6,852,689 are held to be unpatentable;

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

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