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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

HOSPIRA, INC.,
Patent Owner.

Case IPR2016-01577
Patent 8,242,158 B1

Before MICHAEL J. FITZPATRICK, SHERIDAN K. SNEDDEN, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

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

INTRODUCTION

Amneal Pharmaceuticals LLC ("Petitioner") filed a Petition for an *inter partes* review of claims 1–4 of U.S. Patent No. 8,242,158 B1 ("the '158 patent," Ex. 1001). Paper 2 ("Pet."). Hospira Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 9 ("Prelim. Resp."). We review the Petition under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–4, we institute an *inter partes* review of the challenged claims.

Related Proceedings

According to the parties, Patent Owner has asserted the '158 patent in *Hospira, Inc. v. Amneal Pharmaceuticals LLC*, No. 1:15-cv-00697 (D. Del.). Pet. 53; Paper 6, 2.

Petitioner has filed IPR2016-01578, IPR2016-01579, and IPR2016-01580, challenging related U.S. Patent Nos. 8,338,470, 8,455,527, and 8,648,106, respectively. Pet. 53; Paper 6, 2.

The '158 Patent

The '158 patent relates to "pharmaceutical compositions comprising dexmedetomidine or a pharmaceutically acceptable salt thereof[,] wherein the composition is formulated as a liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed container as a premixture." Ex. 1001, Abstract; *see also id.* at 1:6–8 ("The present

invention relates to patient-ready, premixed formulations of dexmedetomidine, or a pharmaceutically acceptable salt thereof.").

Dexmedetomidine is an enantiomer of medetomidine. *Id.* at 1:22–23. Before the '158 patent, both medetomidine and dexmedetomidine were known as α_2-adrenoceptor agonists for general sedation/analgesia and the treatment of hypertension or anxiety. *Id.* at 1:14–25. According to the '158 patent, before its invention, "dexmedetomidine ha[d] been provided as a concentrate that must be diluted prior to administration to a patient. The requirement of a dilution step in the preparation of the dexmedetomidine formulation is associated with additional costs and inconvenience, as well as the risk of possible contamination or overdose due to human error." *Id.* at 1:48–53. The '158 patent purportedly provides a dexmedetomidine formulation that avoids the expense, inconvenience, delay, and risk of contamination or overdose. *Id.* at 1:53–55.

Illustrative Claim

Claim 1, the sole independent claim, is illustrative and is reproduced below:

> 1. A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL disposed within a sealed glass container.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds, each of which challenges the patentability of claims 1–4:

Basis	References
§ 103	Precedex Label[1] and Palmgrén[2]
§ 103	The '867 patent,[3] Precedex Label, and Palmgrén
§ 103	Precedex Label, De Giorgi,[4] Eichhorn,[5] Palmgrén, and Lavoisier[6]

In support of their respective positions, Petitioner relies on the Declarations of Dr. James Gordon Cain (Ex. 1002) and Dr. Alpaslan Yaman (Ex. 1003), and Patent Owner relies on the Declarations of Dr. Robert Linhardt (Ex. 2005) and Dr. Michael Ramsay (Ex. 2006).

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[1] Prescribing Information for Precedex (dexmedetomidine hydrochloride) injection (Ex. 1007).
[2] Palmgrén et al., *Drug Adsorption to Plastic Containers and Retention of Drugs in Cultured Cells under In Vitro Conditions*, 64 EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS 369–78 (2006) (Ex. 1017).
[3] Aantaa et al., U.S. Patent No. 6,716,867, issued Apr. 6, 2004 (Ex. 1006).
[4] De Giorgi et al., *Risk and Pharmacoeconomic Analyses of the Injectable Medication Process in the Paediatric and Neonatal Intensive Care Units*, 22 INTERNATIONAL JOURNAL FOR QUALITY IN HEALTH CARE 170–78 (2010) (Ex. 1015).
[5] Eichhorn, John H., *APSF Hosts Medication Safety Conference: Consensus Group Defines Challenges and Opportunities for Improved* Practice, 25 APSF NEWSLETTER 1, 3–8 (2010).
[6] Product sheet for Lavoisier sodium chloride 0.9% injectable solution (2009).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

The parties dispute the construction for the term "ready to use," which appears in all challenged claims. *See* Pet. 12–13; Prelim. Resp. 8–11. According to Petitioner, an ordinary artisan "would understand the term 'ready-to-use' to mean 'requiring no further dilution or reconstitution before transfer to an administration device.'" Pet. 12. Patent Owner urges that we construe the term to mean "formulated such that it is suitable for administration to a patient *upon manufacture* without dilution or reconstitution by a clinician, hospital personnel, caretaker, patient, or any other individual." Prelim. Resp. 8–9 (emphasis added).

The '158 patent describes "ready to use" compositions as "premixed compositions that are suitable for administration to a patient without dilution." Ex. 1001, 3:56–59. The parties appear to agree that "ready to use" is equivalent to a "premixture." *See* Pet. 12 n.2; Prelim. Resp. 9. According to the '158 patent,

> The terms "premix" or "premixture" as used herein refers to a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient. For example, in contrast to non-premixed formulations of dexmedetomidine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual.

Ex. 1001, 3:48–55.

The description in the '158 patent as to the scope of "ready to use" is sufficient for purposes of this decision, and we need not further address the term at this time. That is because, even under Patent Owner's proposed construction (i.e., the ready-to-use formulation must be suitable for administration *upon manufacture*), we determine Petitioner has established a reasonable likelihood that it would prevail in its obviousness challenge. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (instructing that claim terms need only be construed to the extent necessary to resolve the controversy).

Obviousness over the Combination of Precedex Label, De Giorgi, Eichhorn, Palmgrén, and Lavoisier

Petitioner argues that claims 1–4 would have been obvious over Precedex Label, in view of the knowledge of one of skill in the art at the time of filing, as evidenced by De Giorgi, Eichhorn, Palmgrén, and Lavoisier. Pet. 35–45. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

Relevant Prior Art

Precedex Label shows the prescribing information for "Precedex (dexmedetomidine hydrochloride) injection." Ex. 1007, 1. It bears a mark

showing "Revised: 09/2010." *Id.* at l. 80. Relying on that line, Petitioner asserts that Precedex Label "was published September 2010." Pet. 15 (citing Ex. 1007, 1). Patent Owner does not challenge, and based on the current record, we have no reason to doubt, that Precedex Label qualifies as prior art under 35 U.S.C. § 102(b).

Precedex Label states that dexmedetomidine hydrochloride is provided at a concentration of "200 mcg/2 mL (100 mcg/mL) in a glass vial." Ex. 1007, l. 40. The drug is "[f]or intravenous infusion following dilution" (*id.* at l. 8) and "must be diluted in 0.9% sodium chloride solution to achieve required concentration (4 mcg/mL) prior to administration" (*id.* at ll. 175–76). It teaches preparing the infusion solutions at the volume of 50 mL. *Id.* at ll. 180–81.

Palmgrén describes the results of experiments on adsorption of certain drugs, including medetomidine, to various plastic containers. Ex. 1017, Abstract. According to Palmgrén, medetomidine was "known to interact with PVC [polyvinylchloride] and polystyrene plastic." *Id.* at 370. Palmgrén reported that the loss of basic drugs, including medetomidine, to modified polystyrene-plastic was much higher than to glass and polypropylene. *Id.* at 374.

De Giorgi describes the results of a study designed to analyze safety risks in injectable medications. Ex. 1015, Abstract. According to De Giorgi, microbial contamination, dosage errors, and dilution errors are among the top errors observed. *Id.* at 173. De Giorgi suggests that ready-to-use syringes "offer a safe alternative to reduce microbiological contamination and dilution errors and avoid drug wastage." *Id.* at 176.

Eichhorn summarizes the recommendations from a consensus conference to address persistent problems of medication safety in the operating room. Ex. 1016, 1. According to Eichhorn, "[t]he proposed new paradigm to reduce medication errors causing harm to patients in the operating room is based on **Standardization, Technology, Pharmacy/Prefilled/Premixed, and Culture (STPC)**." *Id.* Eichhorn suggests that "providing 'ready-to-use' medications in the operating room whenever possible that are prepared by outsource specialty companies who do that exclusively should decrease medication errors in the operating room." *Id.* at 5.

Lavoisier is a product sheet for a 0.9% sodium chloride solution as an injectable solution. Ex. 1018, 1. The document bears a mark of "DATE OF REVISION June 2009." *Id.* at 2. Petitioner appears to rely on that information to support its assertion that Lavoisier qualifies as prior art under 35 U.S.C. § 102(b). Pet. 18 (citing Ex. 1018, 2). Patent Owner does not challenge, and based on the current record, we have no reason to doubt, the prior-art status of Lavoisier.

Lavoisier describes various forms of packaging for the product, including glass ampoules in a volume of 2 ml, 5, ml, 10 ml, or 20 ml. Ex. 1018, 1.

Analysis

Petitioner refers to Precedex Label for teaching "a liquid formulation of dexmedetomidine hydrochloride stored in a glass vial at a concentration of 200 μg/2 mL (100 μg/mL), which is intended for parenteral administration via intravenous infusion." Pet. 36 (citing Ex. 1007, ll. 175–

84, 207–08, 457). Petitioner also refers to Precedex Label for teaching the "preparation of a 4 μg/mL solution of Precedex for parenteral administration by diluting 2 mL of Precedex in 48 mL of 0.9% sodium chloride injection to a total of 50 mL." *Id.* (citing Ex. 1007, ll. 175–84). Because of this explicit instruction, Petitioner argues, it would have been obvious for an ordinary artisan "to prepare a ready-to-use solution of dexmedetomidine hydrochloride at a concentration of 4 μg/mL, for parenteral administration to a patient via intravenous infusion." *Id.* at 36.

Petitioner contends that it also would have been obvious for an ordinary artisan to store the diluted dexmedetomidine solution in sealed glass containers. *Id.* at 37. Petitioner refers to Precedex Label for teaching that (1) Precedex has a "potential for absorption" when used with some types of natural rubber (*id.* (citing Ex. 1007, ll. 203–06)); and (2) a glass vial is used to store and handle Precedex (*id.* at 39). In addition, according to Petitioner, Palmgrén teaches that (1) "it was well-known that medetomidine, a racemic mixture containing the enantiomer dexmedetomidine, interacts with plastics found in infusion bags and intravenous tubing, which can lead to drug loss and treatment failure" (*id.* (citing Ex. 1017, 370)); and (2) loss of medetomidine is much higher in polystyrene and polycarbonate than in glass and polypropylene (*id.* (citing Ex. 1017, 374–76)). Thus, Petitioner concludes that one of ordinary skill in the art would have had a reason to use a sealed glass container to handle and store dexmedetomidine solutions. *Id.* at 37.

Furthermore, Petitioner asserts that "one of skill in the art would have been motivated to prepare ready to use or premixed, diluted solutions of

Precedex at the 4 μg/mL concentration" because De Giorgi, Eichhorn, and Lavoisier "establish that, at the time of filing, those of skill in the art recognized the need for and indeed had been advocating for additional standardization of drug preparation methods." *Id.* at 39–40.

Patent Owner contends that an ordinary artisan would not have had a reason to combine teachings of Precedex Label and Palmgrén. Prelim. Resp. 27–31. Patent Owner also argues that (1) the combination of Precedex Label and Palmgrén does not teach or suggest a ready-to-use dexmedetomidine composition at a concentration of about 4 μg/mL disposed within a sealed glass container (*id.* at 15–26); and (2) "[t]he addition of [De] Giorgi, Eichhorn, and Lavoisier to this combination cannot remedy this deficiency" (*id.* at 50). We are not persuaded by Patent Owner's arguments.

Patent Owner asserts that an ordinary artisan would not have combined the teachings of Precedex Label and Palmgrén because Palmgrén "evaluated the drug loss of medetomidine due to adsorption in containers of different materials, and not the adsorption of isolated dexmedetomidine." Prelim. Resp. 27. Dr. Linhardt, a declarant for Patent Owner, testifies that an ordinary artisan would not "have necessarily considered sorption testing on medetomidine to be determinative of what storage material should be used for a dexmedetomidine formulation." Ex. 2005 ¶ 136.

The opinion of Dr. Linhardt on this issue is in direct conflict with that of Dr. Yaman, Petitioner's expert. Indeed, in Dr. Yaman's view:

> Because dexmedetomidine is the S-enantiomer of the racemic medetomidine a [person of ordinary skill in the art] POSA would expect that dexmedetomidine would perform the same as medetomidine in polystyrene and glass. Enantiomeric isomers

> are optical isomers that are mirror images of each other. These compounds only present a difference between them with respect to their physiological or pharmacological affect as the body has enantomeric specific receptors. Otherwise, the physio-chemical properties such as solubility, the ability to adsorb or absorp [sic] and their chemical stability are the same and the optical rotation has no impact on these chemical and physical attributes.

Ex. 1003 ¶ 52. For the purpose of deciding whether to institute an *inter partes* review, we view genuine issues of material fact created by testimonial evidence in the light most favorable to Petitioner. 37 C.F.R. § 42.108(c). Thus, for purposes of this Decision, we accept Petitioner's reasoning for why one of ordinary skill in the art would have combined the teachings of Precedex Label and Palmgrén.

We also determine, for purposes of instituting an *inter partes* review, Petitioner has presented sufficient evidence to show that the combination of Precedex Label, De Giorgi, Eichhorn, Palmgrén, and Lavoisier teaches or suggests all limitations of claim 1. Here, we are not persuaded by Patent Owner's arguments because they run afoul of the established principle that "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *See In re Merck & Co*., 800 F.2d 1091, 1097 (Fed. Cir. 1986). For example, Patent Owner emphasizes that "Petitioner does not allege that [De] Giorgi, Eichhorn, or Lavoisier disclose a ready to use composition comprising dexmedetomidine at 4 μg/mL." Prelim. Resp. 49. Patent Owner also alleges that none of De Giorgi, Eichhorn, and Lavoisier teaches dexmedetomidine specifically, and neither De Giorgi nor Eichhorn teaches the use of a sealed glass container. *Id.* at 50–57.

A reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *Merck*, 800 F.2d at 1097. *Id.* Patent Owner is correct that De Giorgi, Eichhorn, and Lavoisier do not specifically mention dexmedetomidine or its concentration. We, nevertheless, agree with Petitioner that the explicit instruction in Precedex Label to prepare a 4 μg/mL solution of Precedex for parenteral administration (Ex. 1007, ll. 175–84) suggests a dexmedetomidine solution for parenteral administration at a concentration of 4 μg/mL, as recited in claim 1. *See* Pet. 36–37.

In addition, although De Giorgi and Eichhorn may not explicitly teach the use of a sealed glass container, Petitioner relies on Precedex Label, Palmgrén, and Lavoisier for this limitation. We find persuasive Petitioner's position that "a POSA would have a reasoned basis for using a sealed glass container when formulating dexmedetomidine solutions because both Palmgren and the Precedex 2010 Label disclosed the use and suitability of glass containers to do so, and also because doing so would avoid potentially adverse interactions with other materials." *See* Pet. 37, 39–42; Ex. 1007, ll. 203–08; Ex. 1017, 370, 374–76; Ex. 1018, 1–2.

Moreover, Petitioner contends that De Giorgi teaches ready-to-use syringes as a safe alternative to reduce microbiological contamination and dilution errors, two of the most critical reasons for treatment failure associated with injectable medications. *Id.* at 40 (citing Ex. 1015, 176). Similarly, Petitioner directs our attention to the strategies to improve medication safety as taught in Eichhorn and the recommendations therein that "[r]outine provider-prepared medications should be discontinued

whenever possible," and "[s]tandardized pre-prepared medication kits by case type should be used whenever possible." *Id.* at 40–41 (citing Ex. 1016, 1). Petitioner also emphasizes Eichhorn's teaching on the safety of intravenous drug delivery systems that "there was a clear preference for manufacturer-prepared completely ready-to-use IV medication in all settings." *Id.* at 41 (citing Ex. 1016, 5). "[M]anufacturer-prepared completely ready-to-use IV medication" is within the scope of "ready to use" under the claim construction proposed by either party. Thus, we are satisfied that there is a reasonable likelihood Petitioner would prevail in showing the combination of the asserted prior art suggests each and every limitation of claim 1, including a "ready to use liquid pharmaceutical composition."

Patent Owner alleges that the invention of the '158 patent provides surprising and unexpected results because "the claimed compositions are surprisingly more stable in sealed glass containers and are able to be stored over prolonged periods of time without significant losses in potency." Prelim. Resp. 32. Stability over prolonged periods of time, however, is not a limitation in any of the challenged claims. Thus, at this preliminary stage, without more evidence and/or explanation, we are not persuaded that Patent Owner has established a nexus between the alleged unexpected results and the merits of the claimed invention. *See In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

In sum, at this stage of the proceeding, we find that Petitioner has offered sufficient evidence to institute an *inter partes* review, and Patent Owner's arguments do not persuade us that we should decline to go forward

with a trial. Based on the current record, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that claim 1 is unpatentable as obvious over Precedex Label, Giorgi, Eichhorn, Palmgrén, and Lavoisier. After considering Petitioner's arguments and evidence with respect to the remaining claims (Pet. 42–45), which Patent Owner does not address separately, and we determine that Petitioner has made a sufficient showing as to those claims, as well.

Other Grounds

Petitioner asserts that claims 1–4 also would have been obvious over the combination of Precedex Label and Palmgrén, or the combination of the '867 patent, Precedex Label, and Palmgrén. Pet. 18–35. In view of our institution of an *inter partes* review of all challenged claims on another ground, as set forth above, we deny institution on these additional grounds. *See* 37 C.F.R. § 42.108(a)–(b).

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1–4 of the '158 patent.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim.

ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted to determine whether claims 1–4 would have been obvious over Precedex Label, in view of the knowledge of one of skill in the art at the time of filing, as evidenced by De Giorgi, Eichhorn, Palmgrén, and Lavoisier;

FURTHER ORDERED that no other ground of unpatentability is authorized in this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '158 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.

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