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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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AQUESTIVE THERAPEUTICS, INC.,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

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IPR2019-00451
Patent 9,763,876 B2

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Before ZHENYU YANG, JON B. TORNQUIST, and JAMIE T. WISZ, *Administrative Patent Judges.*

WISZ, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Claims Unpatentable
Denying Petitioner's Motion to Exclude
Denying Patent Owner's Motion to Exclude
*35 U.S.C. § 318(a); 37 C.F.R. § 42.64*

# I. INTRODUCTION

## *A. Background*

Aquestive Therapeutics, Inc. ("Petitioner") filed a Petition (Paper 3, "Pet.") requesting an *inter partes* review of claims 1–36 ("the challenged claims") of U.S. Patent No. 9,763,876 B2 (Ex. 1001, "the '876 patent"). Petitioner supported its Petition with the Declaration of Nicholas A. Peppas, Sc.D. (Ex. 1041). Neurelis, Inc.[1] ("Patent Owner") filed a Preliminary Response (Paper 7, "Prelim. Resp."). Upon consideration of the Petition, the Preliminary Response, and the preliminary evidence of record, we determined that Petitioner had demonstrated a reasonable likelihood that it would prevail with respect to at least one of the challenged claims of the '876 patent (Paper 8, "Institution Decision" or "Inst. Dec."). Thus, we instituted review with respect to all of the challenged claims.

Following institution of trial, Patent Owner filed a Request for Rehearing (Paper 10, "Request for Rehearing" or "Req. Reh'g"), which was denied (Paper 14, "Decision on Request for Rehearing" or "Dec. on Req. Reh'g"), and a request for Precedential Opinion Panel (POP) review (Ex. 3001, "POP Request"), which was also denied (Paper 17).

Patent Owner filed a Patent Owner Response (Paper 16, "PO Response" or "PO Resp.") and supported its Response with the Declaration of Sveinbjörn Gizurarson, Ph.D. (Ex. 2012). Petitioner filed a Reply (Paper

[1] Patent Owner informs us that, subsequent to the filing of the Petition, Hale Biopharma Ventures, LLC, the originally named Patent Owner in this case, assigned its rights in the '876 patent to Neurelis, Inc. Paper 6, 2 (citing Reel 048271; Frame 0304).

21, "Reply") with a Declaration of Daniel P. Wermeling, Pharm.D. (Ex. 1150). Patent Owner filed a Sur-Reply (Paper 28, "PO Sur-Reply").

Petitioner and Patent Owner each separately filed Motions to Exclude regarding certain evidence of record (Paper 34, "Pet. MTE"; Paper 35, "PO MTE"). We address each of these Motions in this Decision.

An oral hearing was held on May 14, 2020, and a transcript of the hearing is included in the record (Paper 43, "Tr.").

We have jurisdiction under 35 U.S.C. § 6. After considering the parties' arguments and supporting evidence, we conclude that Petitioner has proven by a preponderance of the evidence that claims 1–36 of the '876 patent are unpatentable. 35 U.S.C. § 316(e).

*B. Real Parties-in-Interest*

Petitioner identifies Aquestive Therapeutics, Inc. (formerly Monosol Rx, LLC) as the real party-in-interest. Pet. 1. Patent Owner identifies Neurelis, Inc. as the real party-in-interest. Paper 6, 2.

*C. Related Proceedings*

The '876 patent was challenged by Petitioner in IPR2019-00449 and IPR2019-00450. Institution of *inter partes* review in both cases was denied. IPR2019-00449, Paper 7; IPR2019-00450, Paper 8.

Patent Owner also indicates that it filed a tort suit against Petitioner in which it cited Petitioner's IPR petitions "as evidence of a pattern of tortious behavior" against Patent Owner. Paper 29, 2 (citing *Neurelis, Inc. v. Aquestive Therapeutics, Inc.,* No. 37-00064665-CU-BT-CTL (Super. Ct. Cal., San Diego)).

*D. The '876 Patent*

The '876 patent is directed to nasally administered pharmaceutical solutions containing one or more benzodiazepine drugs. Ex. 1001, 9:14–17. The '876 patent explains that solubility challenges associated with benzodiazepine drugs previously hindered the development of formulations intended for oral, rectal, or parenteral administration. *Id.* at 1:53–57, 19:12–15. According to the'876 patent, it was discovered, however, that vitamin E (which includes tocopherols and tocotrienols) is an effective carrier for benzodiazepine drugs, as these compounds are soluble, or at least partially soluble, in vitamin E. *Id.* at 33:8–13, 33:42–45. The '876 patent also reports that vitamin E "can have the added benefit of either avoiding irritation of sensitive mucosal membranes and/or soothing irritated mucosal membranes." *Id.* at 33:47–49.

The '876 patent discloses that one or more lower alcohols, such as ethanol and benzyl alcohol, may be used in the formulation. Ex. 1001, 2:57–64, 33:55–67 (noting that to "avoid the drawbacks of emulsions," the disclosed solutions contain vitamin E and "one or more lower alkyl alcohols"). In addition, an alkyl glycoside may be added to the formulation to act as a penetration enhancer. *Id.* at 34:2–9.

*E. Illustrative Claim*

Petitioner challenges claims 1–36 of the '876 patent. Claim 1, which is the only independent claim of the '876 patent, is illustrative of the challenged claims, and is reproduced below:

> 1. A method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising:

> administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of
>
> a benzodiazepine drug,
>
> one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);
>
> ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and
>
> an alkyl glycoside.

Ex. 1001, 63:26–34 (formatting added). Challenged claims 2–36 depend from claim 1, either directly or indirectly.

*F. Instituted Grounds of Unpatentability*

We instituted trial to determine whether claims 1–36 of the ’876 patent are unpatentable based on the following grounds:

| Claims Challenged | 35 U.S.C. § | References/Basis |
|---|---|---|
| 1–16, 24–36 | 103(a) | Gwozdz,[2] Meezan ’962[3] |
| 17–23 | 103(a) | Gwozdz, Meezan ’962, Cartt ’784[4] |

Inst. Dec. 5.

[2] PCT Pub. No. WO 2009/120933 A2, published October 1, 2009 (Ex. 1014, “Gwozdz”).
[3] U.S. Pub. No. 2006/0046962 A1, published March 2, 2006 (Ex. 1011, “Meezan ’962”).
[4] U.S. Pub. No. 2008/0279784 A1, published November 13, 2008 (Ex. 1015, “Cartt ’784”).

## II. ANALYSIS

We have reviewed the parties' respective briefs as well as the relevant evidence discussed in those papers. For the reasons discussed in detail below, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–36 of the '876 patent are unpatentable under 35 U.S.C. § 103 as having been obvious.

### *A. Principles of Law*

To prevail in its challenges to the patentability of all claims of the '876 patent, Petitioner must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e) (2018); 37 C.F.R. § 42.1(d) (2019). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

Regarding obviousness, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness as set forth in *Graham v. John Deere Co*., 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is reasonably likely to be unpatentable as obvious under 35 U.S.C. § 103(a)

as: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417. It is generally obvious to those skilled in the art to substitute one known equivalent for another. *See In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1374 (Fed. Cir. 2007) ("[T]his court finds no . . . error in [the] conclusion that it would have been obvious to one skilled in the art to substitute one ARC [alkaline reactive compound] for another."); *see also Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (the combination of known elements and substitution of one well known agent for another is obvious).

When there is a range disclosed in the prior art, and the claimed invention falls within that range, or the disclosed range overlaps with the claimed range, there is a presumption of obviousness. *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness."); *see also In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (noting that a

claimed range overlaps with a prior art range if the two ranges share a common endpoint (e.g., claim range of 50–100 Å overlaps with prior art range of 100–600 Å)). This presumption may be rebutted by showing the criticality of the claimed range, that the prior art taught away from the claimed range, or that the parameter was not recognized as "result-effective." *E.I. DuPont de Nemours & Company v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018); *Iron Grip*, 392 F.3d 1322.

We analyze Petitioner's asserted grounds of unpatentability in accordance with the above-stated principles.

*B. Level of Ordinary Skill in the Art*

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art ("POSA" or "POSITA"), and thus begin with the level of ordinary skill in the art. The level of ordinary skill in the art is "a prism or lens through which . . . the Board views the prior art and claimed invention" to prevent hindsight bias. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

The parties dispute the level of ordinary skill in the art. Petitioner asserts that, as of the earliest priority date, a person of ordinary skill in the art would have been:

> a medicinal chemist, pharmaceutical chemist, chemist, or biologist involved in the research and development of pharmaceutical formulations and/or delivery. The POSITA would have at least a bachelor's degree in chemical, biological, or pharmaceutical sciences or a medical degree, and several years of experience in the field of transmucosal (including intranasal, rectal, vaginal, ocular, lacrimal, nasolacrimal, buccal, sublingual, urethral, inhalation, and auricular) pharmaceutical formulation development and/or delivery, the amount of post-graduate experience depending upon the level

> of formal education. The individual would also have some experience in design and testing of formulations for mucosal delivery (and particularly in intranasal formulations) of systemic-acting drugs.

Pet. 4. Dr. Peppas also recites this definition in his Declaration. Ex. 1041 ¶ 74.

In response, Patent Owner disputes certain aspects of Petitioner's description of the level of ordinary skill in the art. *See* PO Resp. 15–17. First, Patent Owner, with supporting testimony from Dr. Gizurarson, asserts that "the formulation of a benzodiazepine for intranasal administration is a difficult and complex science requiring a higher skill set and knowledge than a POSA with a bachelor's degree 'with several years of experience.'" *Id.* at 15 (citing Ex. 2012 ¶¶ 28–29). Specifically, according to Patent Owner and Dr. Gizurarson, "the POSA would be working against physiological constraints of active ingredient uptake due to the nasal anatomy, as well as the very low solubility of benzodiazepines in formulating the pharmaceutical composition disclosed in the '876 patent." *Id.* at 15–16 (citing Ex. 2012 ¶¶ 28–29). Therefore, Patent Owner asserts that "a POSA would at least have held a Master's degree with many years of experience, or a Ph.D. or Pharm.D[.] degree with several years of experience, or its equivalent research experience." *Id.* at 16 (citing Ex. 2012 ¶ 29).

Second, Patent Owner contends that a person of ordinary skill in the art would not include a medicinal chemist because "[c]hemists are primarily concerned with chemical structures and synthesizing new chemical compounds" and it is not clear "what role a medicinal chemist would play in the research and development of benzodiazepine pharmaceutical formulations for intranasal administration – especially where, as here, the

chemical structures were all known." PO Resp. 16 (citing Ex. 2012 ¶ 30). Instead, according to Patent Owner, "a POSA would have had knowledge of benzodiazepine structure and function, including solubility issues with benzodiazepines in general." *Id.* (citing Ex. 2012 ¶ 31). Patent Owner also asserts that the "POSA would further have knowledge and practical experience working with intranasal formulations, including knowledge of the physiology and anatomy of the nasal cavity, with relevant experience in developing intranasal formulations." *Id.* at 16–17 (citing Ex. 2012 ¶ 31).

Patent Owner further contends that "[Petitioner] and Dr. Peppas' description of a POSA having experience in 'rectal, vaginal, ocular, lacrimal, nasolacrimal, buccal, sublingual, urethral, inhalation, and auricular' delivery as 'related fields' does not take into consideration the differences in formulating an intranasal product and complexities of the intranasal pathway." PO Resp. 17 (citing Ex. 2012 ¶ 32; Ex. 2011, 118:18–120:19).

Petitioner disagrees with Patent Owner's definition of a person of ordinary skill in the art and contends that such a person would also have experience working with "transmembrane" formulations in addition to "intranasal" formulations. Reply 12 (citing Ex. 2012 ¶¶ 31, 32; Ex. 1150[5] ¶¶ 20–22).

In determining the level of ordinary skill, various factors may be considered, including "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4)

[5] Throughout the Reply, Petitioner sometimes refers to Ex. 1100 when citing to the Declaration of Dr. Wermeling. Because there is no Ex. 1100 in the record and because the Declaration of Dr. Wermeling is Ex. 1150, we have used Ex. 1150 to indicate Petitioner's citations to the Wermeling Declaration.

rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). These factors are "merely a guide," and the weight or significance ascribed to each depends on the particular case. *Id.*

Based on our consideration of the full record, we find that, overall, Patent Owner's definition is more specifically tailored to the claimed subject matter of the '876 patent. We also find that the factors recited above, overall, demonstrate that knowledge of and experience with transmembrane formulations, as suggested by Petitioner, would also be relevant. *See* Ex. 1014, 8:32–9:18; Ex. 1011 ¶¶ 9–13. Therefore, we find that such a person of ordinary skill in the art would have been a pharmaceutical chemist, chemist, or biologist involved in the research and development of pharmaceutical formulations and/or delivery. We also find that the person of ordinary skill in the art would have at least a Master's degree with many years of experience, or a Ph.D. or Pharm.D. degree with several years of experience. In addition, the person of ordinary skill in the art would have had knowledge of benzodiazepine structure and function and would further have knowledge and practical experience working with intranasal and transmembrane formulations, including knowledge of the physiology and anatomy of the nasal cavity, with relevant experience in developing intranasal and transmembrane formulations.

Although we agree with and have primarily adopted Patent Owner's definition for an ordinarily skilled artisan in this proceeding, our analysis and conclusions herein would not change even under Petitioner's definition. The parties also do not appear to indicate that the outcome would differ

based on the definition of the person of ordinary skill in the art. *See* Pet. 4; PO Resp. 15–17; Reply 12.

*C. Claim Construction*

Having defined the ordinarily skilled artisan, we now turn to claim construction. In this *inter partes* review, claim terms are construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b). Under this claim construction standard, claim terms are given their ordinary and customary meaning as would have been understood by one of ordinary skill in the art at the time of the invention. *See id*; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). A patentee may define a claim term in a manner that differs from its ordinary and customary meaning; however, any special definitions must be set forth in the specification with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In the Petition, Petitioner provides proposed constructions for the terms "vitamin E," "bioavailability," "% (w/w)," "% (w/v)," and "about 56.47% (w/v) vitamin E." Pet. 11–14. Patent Owner does not propose its own construction for these terms.

In the Patent Owner Response, Patent Owner proposes constructions for the terms "consisting of" and "in a combined amount." PO Resp. 12–15. Petitioner disagrees with Patent Owner's construction of "consisting of" and does not provide any comments on the proposed construction of "in a combined amount." Reply 9–11. Furthermore, Petitioner proposes a construction for "pharmaceutical solution," which Patent Owner opposes. Reply 11; PO Sur-Reply 4, 18–19.

Upon review of the parties' arguments and the evidence of record, we determine that no terms of the '876 patent require express construction for purposes of this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.")).

*D. Priority Claim of the '876 patent*

The '876 patent was filed as U.S. Application No. 14/527,613 ("the '613 application") on October 29, 2014. Ex. 1001, codes (21), (22). The '876 patent is a continuation of U.S. Application No. 13/495,942 ("the '942 application") (issued as U.S. Patent No. 8,895,546) ("the '546 patent"), filed on June 13, 2012, which is in turn a continuation-in-part ("CIP") of U.S. Application No. 12/413,439 ("the '439 application"), filed on March 27, 2009. *Id.* at code (63). The '876 patent also claims priority to provisional applications 61/040,558 ("the '558 provisional"), 61/497,017 ("the '017 provisional"), and 61/570,110 ("the '110 provisional"), filed on March 28, 2008; June 14, 2011; and December 13, 2011, respectively. *Id.* at code (60).

Petitioner contends that Meezan '962 qualifies as prior art to the claims of the '876 patent under 35 U.S.C. § 102(b) and that Gwozdz and Cartt '784 qualify as prior art at least under 35 U.S.C. § 102(e)(1). Pet. 6–8. Petitioner asserts that Cartt '784 is prior art based on its May 7, 2008, filing date and its November 13, 2008, publication date. *Id.* at 8. Petitioner also contends that Gwozdz qualifies as prior art based on the March 28, 2008, filing date of its U.S. Provisional Application No. 61/040,281 ("Gwozdz

provisional") (Ex. 1046). *Id.* at 6. Petitioner has shown that the claims of Gwozdz are supported by the Gwozdz provisional, "at least because Gwozdz's claims are literally identical to the claims filed in [the] Gwozdz provisional." *Id.* (citing Ex. 1014, 14–15; Ex. 1046, 19–20); *see* Ex. 1014, 4–10; Ex. 1046, 9–15. Patent Owner does not contest that Gwozdz is entitled to this filing date. *See* PO Resp. 17–23. Therefore, we find that Petitioner has satisfied its burden to show that Gwozdz is entitled to the filing date of the Gwozdz provisional. *See Dynamic Drinkware*, 800 F.3d. at 1381 (holding that "[a] reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of the provisional application provides support for the claims in the reference patent in compliance with § 112, ¶ 1.").

Petitioner asserts that the claims of the '876 patent are not entitled to the priority date of the '558 provisional and have an effective filing date of no earlier than the March 27, 2009 filing date of the '439 application. Pet. 18–20. Specifically, Petitioner contends that the '558 provisional does not provide adequate support for the "alkyl glycoside" limitation recited in the challenged claims[6] because the presence of any alkyl glycoside is not disclosed, described, or enabled by the '558 provisional. *Id*. at 19–20. Petitioner further contends that the '558 provisional's "generic disclosure of 'surface active agents (especially non-ionic materials)' . . . does not disclose, describe, and/or enable alkyl glycosides in general (or dodecyl maltoside in particular)." *Id*. at 20 (citing Ex. 1008 ¶ 152; Ex. 1041 ¶ 68).

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[6] Claim 1 requires "an alkyl glycoside." Ex. 1001, 63:34. Since all of the remaining claims of the '876 patent depend, directly or indirectly, from Claim 1, they also require the presence of "an alkyl glycoside."

Patent Owner argues that Gwozdz and Cartt '784 are not prior art to the challenged claims of the '876 patent because the claims are properly supported by the '558 provisional, which was filed on March 28, 2008. PO Resp. 1, 17–18.

Patent Owner argues that the '558 provisional does disclose alkyl glycosides as part of the formulation claimed. PO Resp. 10. Specifically, Patent Owner points to the following disclosure from the '558 provisional:

> In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer . . . . In some embodiments, enhancing agents that are appropriate include . . . acyl glycerols, fatty acids and salts, tyloxapol and ***biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference).***

*Id.* (quoting Ex. 1008 ¶¶ 150–152 (emphasis added)). Patent Owner contends that the excerpt from the 1988 SIGMA catalog ("SIGMA catalog") referenced in the '558 provisional includes alkyl glycosides such as n-Dodecyl β-D-Maltoside, n-Dodecyl β-D-Glucopyranoside, n-Heptyl β-D-Glucopyranoside, n-Hexyl β-D-Glucopyranoside, n-Nonyl β-D-Glucopyranoside, n-Octyl β-D-Glucopyranoside, and Octyl β-D-Thioglucopyranoside, amongst others. *Id*. at 10–11 (citing Ex. 2006, 319–320). Patent Owner, with supporting testimony from Dr. Gizurarson, asserts that "a POSA would have recognized and understood that alkyl glycosides were disclosed and supported in the '558 Provisional through this incorporation by reference." *Id.* at 19 (citing Ex. 2012 ¶ 68).

Patent Owner also asserts that:

> A POSA would have understood that in the context of pharmaceutical formulations, biological detergents would have been limited to detergents appropriate for administering to the

> nasal cavity of a human or other animal subject – which, in such a case, would have been non-ionic detergents.

PO Resp. 11 n.5 (citing Ex. 2012 ¶ 70). According to Patent Owner, "of the 10 non-ionic biological detergents listed on page 316 of the SIGMA catalog, 9 of them are alkyl glycosides." *Id.* at 11 (citing Ex. 2012 ¶ 71). Patent Owner also asserts that, of the non-ionic detergents listed on pages 316–321 of the Sigma catalog, alkyl glycosides "were prominently represented." *Id.* at 19 (citing Ex. 2012 ¶¶ 71–72).

Petitioner, with supporting testimony from Dr. Wermeling, responds that "a POSA <u>would not</u> have understood that the '558 provisional was providing a written description of alkyl glycosides." Reply 5 (citing Ex. 1150 ¶¶ 171–177). According to Petitioner, paragraphs 150–152 of the '558 provisional generically refer to "absorption enhancers" and define the term "enhancer" as "any material which acts to increase absorption across the mucosa and/or increase bioavailability," and describe 15 classes falling within this broad "absorption enhancer" class. *Id.* (citing Ex. 1150 ¶¶ 171, 172). Petitioner also contends that "the recited 'enhancers' can include mucolytic agents, degradative enzyme inhibitors, 'compounds which increase permeability of the mucosal cell membranes' [150], only identifying lysophospholipids and acyl carnitines as <u>preferred</u> candidates [151]." *Id.* at 5–6 (citing Ex. 1150 ¶¶ 171–173). According to Petitioner, paragraph 152 also identifies six additional "enhancer" classes: (i) chelating agents, (ii) surface active agents (especially non-ionic materials), (iii) acyl glycerols, (iv) fatty acids and salts, (v) tyloxapol and (vi) the biological detergents listed on six pages of the SIGMA catalog. *Id.* at 6 (citing Ex. 1150 ¶ 172; Ex. 2006).

Petitioner further asserts that there are approximately 150 different compounds on the cited SIGMA catalog pages divided among four discrete sub-classes: (i) anionic, (ii) cationic, (iii) zwitterionic (amphoteric) and (iv) nonionic (polar). Reply 6 (citing Ex. 2006, 316–321). According to Petitioner and Dr. Wermeling, "[w]ithin the 'non-ionic' biological detergent sub-class are (i) about a dozen alkyl glycoside species and (ii) over eighty non-alkyl glycoside species." *Id.* (citing Ex. 1150 ¶ 175). Petitioner and Dr. Wermeling further contend that "[t]he '558 provisional provides absolutely no information regarding alkyl glycosides, apart from generally listing them among approximately 150 other biological detergents appearing in the SIGMA catalog." *Id.* (citing Ex. 1150 ¶¶ 175–177). Petitioner and Dr. Wermeling conclude:

> In fact, nothing in the '558 provisional would reasonably lead a POSA to any particular sub-class, let alone specific species (compounds) identified in the SIGMA catalog, nor does the '558 provisional suggest that alkyl glycosides might be of special interest, or be significant to the claims. Rather, the '558 Provisional directs the POSA to lysophospholipids and acyl carnitines; all other enhancers being in a "kitchen sink" listing.

*Id.* at 6–7 (citing Ex. 1150 ¶ 176).

*1. Analysis of Priority*

"[T]he hallmark of written description is disclosure," and "the test [for satisfaction of the written description requirement] requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written description "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed,'" and "reasonably" convey to those

skilled in the art "that the inventor had possession of the claimed subject matter as of the filing date." *Id.* (alteration in original, internal citations omitted). Stated another way, "one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). "Whether a claim satisfies the written description requirement is a question of fact." *Nalpropion Pharms., Inc. v. Actavis Labs. Fl, Inc.*, 934 F.3d 1344, 1348 (Fed. Cir. 2019) (citing *Ariad*, 598 F.3d at 1351).

Furthermore, as the Board explained in *Polaris Wireless, Inc. v. TruePosition, Inc.*, IPR2013-00323, Paper 9 (PTAB Nov. 15, 2013), there is no presumption of earlier priority where the specifications of the earlier applications are not the same. *See id.* at 29; *Power Oasis, Inc. v. T-Mobile USA, Inc.,* 522 F.3d 1299, 1305 (Fed. Cir. 2008). Patent Owner does not dispute that the specification of the '876 patent differs from the specification of the '558 provisional.

When faced with a prior art challenge to a claim, the burden of production—alternatively called the burden of going forward—is on the Patent Owner to show that the claim is entitled to a filing date prior to the date of the alleged prior art. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). Thus, "Patent Owner must come forward with evidence and argument . . . showing why the challenged claim is supported by the written description of the priority application." *Nintendo of Am. Inc. v. iLife Techs.*, IPR2015-00106, Paper 12 at 16 (PTAB Apr. 29, 2015). After considering all the cited evidence of record on this priority issue, we find that the evidence favors Petitioner's position. As explained

below, we find that the challenged claims are not sufficiently supported by the written description of the ’558 provisional.

We do not find that the ’558 provisional’s incorporation by reference to six pages of the SIGMA catalog, which includes about 12 alkyl glycosides in a list of about 150 biological detergents, is sufficient to provide written description support for the claims.[7] *See* Ex. 2006; Ex. 1150 ¶ 175. Furthermore, the listing of biological detergents in the SIGMA catalog is just a subset of the numerous possible “enhancing agents” that are discussed in the ’558 provisional. *See* Ex. 1008 ¶¶ 150–152; Ex. 1150 ¶¶ 171–177. There is nothing in the disclosure of the ’558 provisional that directs one of skill in the art to the relatively small number of alkyl glycosides disclosed in the SIGMA catalog. *See* Ex. 1150 ¶ 176*; Purdue Pharma*, 230 F.3d at 1326-27 (“[O]ne cannot disclose a forest in the original application and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.”); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) (“In the absence of such blazemarks, simply describing a large genus of compounds

[7] In our Decision on Institution, we found that reliance on the SIGMA catalog as adequate support for the “alkyl glycoside” limitation recited in the claims was an improper incorporation by reference of essential material under 37 C.F.R. § 1.57(d) (“Rule 57”). Inst. Dec. 9–10. Patent Owner challenges the propriety of applying Rule 57 in this context. *See, e.g.*, PO Resp. 21–23. For purposes of this Decision, we do not need to decide the Rule 57 issue because, even assuming the material in the SIGMA catalog was properly incorporated by reference, we find that this disclosure is not sufficient to provide written description support for the “alkyl glycoside” limitation in the claims.

is not sufficient to satisfy the written description requirement as to particular species or subgenuses.”).

Patent Owner asserts that a POSA would have understood that “in the context of pharmaceutical formulations, biological detergents would have been limited to detergents appropriate for administering to the nasal cavity,” which would have been non-ionic detergents. PO Resp. 11 n.5 (citing Ex. 2012 ¶ 70). However, nothing in the ’558 provisional’s disclosure restricts the “biological detergents” listed in the SIGMA catalog to non-ionic detergents and, furthermore, the ’558 provisional lists ionic and non-ionic enhancing agents so there is no disclosure directing a POSA to use only non-ionic detergents.[8] Reply 7–8 (citing Ex. 1150 ¶ 175, n.5, 6). *See Ariad*, 598 F.3d 1336 at 1352 (“A description that merely renders the invention obvious does not satisfy” the written description requirement.); *see Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (“It is not sufficient for purposes of the written description requirement of § 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to the modifications that the inventor might have envisioned, but failed to disclose.”).

Patent Owner argues that Petitioner never met its burden to establish a facially reasonable likelihood of unpatentability because they did not address the incorporation by reference to the SIGMA catalog in the Petition and, therefore, this *inter partes* review should be terminated. *See* PO Resp. 18–

[8] Even if the SIGMA catalog’s disclosure was limited to only the non-ionic compounds listed therein, according to Dr. Wermeling, this list would still include over 100 compounds with no guidance in choosing the alkyl glycosides over other non-ionic compounds. *See* Ex. 1150 ¶ 176.

21. This argument is unavailing. Petitioner clearly challenged the '876 patent priority claim in contending that "the presence of any alkyl glycosides (either generally or particularly) – regardless of amount – was not disclosed, described, or enabled by [the] '558 Provisional." Pet. 20. Furthermore, with supporting testimony from Dr. Peppas, Petitioner further asserted that the '558 provisional's "generic disclosure of 'surface active agents (especially non-ionic materials)' . . . does not disclose, describe, and/or enable alkyl glycosides…" *Id.* (citing Ex. 1008 ¶ 152; Ex. 1041 ¶ 68). We do not agree that Petitioner's failure to specifically address the '558 provisional's incorporation by reference to the SIGMA catalog results in a failure to establish a reasonable likelihood of unpatentability. Petitioner's assertion, with supporting testimony from Dr. Peppas, that the '558 provisional failed to describe or enable alkyl glycosides was sufficient, in our view, to provide a reasonable likelihood of prevailing with respect to at least one of the challenged claims.[9]

As discussed above, although the petitioner has the ultimate burden of persuasion to prove unpatentability, a patent owner must demonstrate entitlement to a priority date when the patent owner relies on that priority date to overcome an anticipation or obviousness argument. *See Dynamic Drinkware*, 800 F.3d at 1379–80 (discussing burdens in *inter partes* review to show entitlement to provisional filing dates and relying on infringement cases involving continuation-in-part applications); *In re NTP, Inc.*, 654 F.3d

[9] Petitioner's argument and evidence challenging the priority claim of the '876 patent in the Petition was, at minimum, sufficient to meet a threshold burden of proceeding, requiring Patent Owner to produce argument and evidence to the contrary, which it had an opportunity to do during trial. *See Dynamic Drinkware*, 800 F.3d at 1379–80.

1268, 1276 (Fed. Cir. 2011) ("[A] patent's claims are not entitled to an earlier priority date because the patentee claims priority. Rather, for a patent's claims to be entitled to an earlier priority date, the patentee must demonstrate that the claims meet the requirements of 35 U.S.C. § 120." (citations omitted)); *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 870–71 (Fed. Cir. 2010); *Tech. Licensing*, 545 F.3d at 1327–29; *Power Oasis*, 522 F.3d at 1305–06.

As explained in *Dynamic Drinkware*, a petitioner has the initial burden of going forward to show that there is invalidating prior art. *Dynamic Drinkware*, 800 F.3d at 1379. As discussed above, Petitioner satisfied its initial burden of production on the issue of whether Gwozdz is prior art by establishing that Gwozdz is entitled to the effective filing date of the Gwozdz provisional. Therefore, Gwozdz is prior art to the '876 patent under 35 U.S.C. § 102(e)(1) unless Patent Owner can show that the '876 patent is entitled to the effective filing date of the '558 provisional. As discussed above, Petitioner also presented arguments as to why the "alkyl glycoside" limitation was not sufficiently described or enabled in the '558 provisional application. Thus, the burden of production shifts to Patent Owner, who must show not only the existence of earlier applications, but also how the written description in the earlier applications supports the challenged claims. *Dynamic Drinkware*, 800 F.3d at 1379–80. "[T]o gain the benefit of the filing date of an earlier application under 35 U.S.C. § 120, each application in the chain leading back to the earlier application must comply with the written description requirement of 35 U.S.C. § 112." *Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378 (Fed. Cir. 2007) (quoting *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir.

1997)); *see also In re Hogan*, 559 F.2d 595, 609 (CCPA 1977) ("[T]here has to be a continuous chain of copending applications each of which satisfies the requirements of § 112 with respect to the subject matter presently claimed." (alteration in original) (quoting *In re Schneider*, 481 F.2d 1350, 1356 (CCPA 1973))).

In view of the above, and after reviewing all of the evidence, we find that the '558 provisional does not provide adequate written description support for the "alkyl glycoside" limitation. Therefore, the claims of the '876 patent are not entitled to the benefit of priority to the '558 provisional. Accordingly, we determine that Gwozdz and Cartt '784 are § 102(e)(1) prior art to the claims of the '876 patent.

*E. Obviousness of Claims 1–16 and 24–36 over Gwozdz and Meezan '962*

Petitioner contends that the subject matter of claims 1–16 and 24–36 of the '876 patent would have been obvious over the combined disclosures of Gwozdz and Meezan '962. Pet. 23–86. Patent Owner opposes. PO Resp. 23–38; PO Sur-Reply 12–18. Having considered the totality of the arguments and evidence, we find that Petitioner has shown by a preponderance of the evidence that claims 1–16 and 24–36 are unpatentable as having been obvious over Gwozdz and Meezan '962.

*1. Gwozdz*

Gwozdz is directed to the use of tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing hydrophobic or lipophilic therapeutic agents, in order to provide increased bioavailability. Ex. 1014, 4:29–33, 7:3–8. Such therapeutic agents include benzodiazepines, including diazepam. *Id*. at 8:6–

10. Specifically, Gwozdz discloses a "pharmaceutical solution comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combinations thereof." *Id*. at 4:14–17.

Gwozdz teaches that the combination of a tocopherol and an alcohol "is much less irritating to the skin and/or mucous membranes than pure alcohol solutions and generally provides higher loading of a therapeutic agent than emulsions, liposomes, encapsulations, or cyclodextrins." Ex. 1014, 5:2–7. Gwozdz also recognizes that "diluting a tocopherol or tocotrienol with an alcohol or glycol dramatically reduces the inherent viscosity of the tocopherol or tocotrienol thereby allowing for generation of sprayable formulations." *Id*. at 6:29–7:2. Gwozdz further discloses methods of treatment with these pharmaceutical solutions, including via intranasal administration, and states that such solutions are "particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa." *Id*. at 4:24–27, 9:2–8, 9:19–21.

Examples of alcohols for use in the compositions disclosed in Gwozdz include "ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combination thereof." Ex. 1014, 6:16–19. Gwozdz discloses that, "[i]n some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol(s) and/or glycol(s) is in an amount from about 1% to about 70% (w/w)." *Id*. at 4:17–21. Gwozdz also discloses that ethanol can constitute 1% to 40% or 10% to 30% of the pharmaceutical solution and that the tocopherol and ethanol can be used in ratios of approximately 95:5, 90:10, 85:15, 80:20, 75:25, 70:30, 65:35, or 60:40, respectively. *Id*. at 7:20–28.

*2. Meezan '962*

Meezan '962 discloses using an alkyl glycoside and/or saccharide alkyl ester to improve the bioavailability of drug molecules. Ex. 1011 ¶ 4. According to Meezan '962, the compositions of the invention can be used with "small molecule organic drug molecules" and can be delivered nasally. *Id*. The active drug used in its formulations can include many different types of active ingredients, including anti-seizure agents. *Id.* ¶¶ 52, 136.

*3. Limitations of Independent Claim 1*

Petitioner contends that the combination of Gwozdz and Meezan '962 discloses or suggests each element of claim 1. Pet. 37–41. Petitioner presents arguments mapping the language of claim 1 to the disclosures of each reference. Pet. 37–41, 65–69; Ex. 1041, 225–229. We have reviewed Petitioner's arguments and, for the reasons articulated below, find that a preponderance of the evidence supports Petitioner's contentions.

*a.* Claim 1

Claim 1 recites "[a] method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug." Ex. 1001, 63:26–30. Petitioner presents evidence that Gwozdz teaches methods of treating a patient with pharmaceutical solutions, which may be administered intranasally, and can include benzodiazepines. Pet. 37, 65–66 (citing Ex. 1014, 4:24–26, 8:6–13, 9:19–21).

Claim 1 also recites "one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w)." Ex. 1001, 63:30–32. Petitioner presents evidence that

Gwozdz teaches the use of tocopherols or tocotrienols in amounts of about 30–99%. Pet. 38–39, 67 (citing Ex. 1014, 4:18–19, 5:12–14, 7:8–10). The percentage range for tocopherols/tocotrienols disclosed by Gwozdz (about 30–99%) significantly overlaps with the claimed range of about 30–95%. Furthermore, Petitioner contends that Patent Owner never demonstrated any criticality with respect to the amount of tocopherols. *Id*. at 39–40. Patent Owner has not argued, nor do we find that Patent Owner has established, that a range of about 30% to about 95% (w/w) of tocopherols/tocotrienols achieves unexpected results. *See E.I. du Pont*, 904 F.3d at 1006 (explaining that prior art ranges that overlap with a claimed range create "a presumption of obviousness," which may be rebutted if the patentee comes forward with evidence showing, *inter alia*, that the claimed invention achieves unexpected results).

Claim 1 also recites "ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w)." Ex. 1001, 63:33–34. Petitioner and Dr. Peppas present evidence that Gwozdz teaches the use of ethanol, benzyl alcohol, and combinations thereof[10] wherein "[t]he alcohol (or combinations of alcohols) may be present in amounts of about 1-70%" and "[e]thanol may be present in amounts of 1-40% or 10-30%." Pet. 40, 68 (citing Ex. 1014, 4:19–21, 7:10–11, 7:20–24). Therefore, the range of

[10] Dr. Peppas testifies that the combination of ethanol and benzyl alcohol was also used (along with other ingredients) in diazepam formulations such as the rectal gel Diastat and the injectable solution Valium. *See* Ex. 1041 ¶ 133 (citing Ex. 1042, 2, 10). Dr. Peppas also cites to other prior art references discussing the preference for using a drug solvent system containing benzyl alcohol and ethanol. *See id.* ¶¶ 134, 135 (citing Ex. 1018, 3:52–54, 4:7–23; Ex. 1019, 3:65–4:1, 5:5–7, 5:64–6:51).

combined alcohol in Gwozdz overlaps with the claimed range. Furthermore, Petitioner contends that Patent Owner never demonstrated any criticality with respect to the amount of alcohol(s). *Id*. Patent Owner has not argued, nor do we find that Patent Owner has established, that a range of ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w) achieves unexpected results. *See E.I. du Pont*, 904 F.3d. at 1006.

Claim 1 also recites "an alkyl glycoside." Ex. 1001, 63:34. Petitioner presents evidence that Meezan '962 discloses the use of alkyl glycosides in pharmaceutical solutions, including nasal sprays. Pet. 41, 69 (citing Ex. 1011 ¶¶ 4, 8, 12–13, 63, 70, 73).

We determine that Petitioner has shown, by a preponderance of the evidence, that the combination of Gwozdz and Meezan '962 teaches or suggests each and every limitation of claim 1.

*4. Limitations of Dependent claims 2–16 and 24–36*

Having decided that the combination of Gwozdz and Meezan '962 teaches or suggests each and every limitation of claim 1, we turn to claims 2–16 and 24–36 of the '876 patent, which all depend, directly or indirectly, from claim 1. As discussed below, we find that Petitioner also shows by a preponderance of the evidence that Gwozdz and Meezan '962 account for the limitations in these claims. *See* Pet. 41–63; 69–86. We have also reviewed Dr. Peppas' testimony and find that a preponderance of the evidence supports his opinion that the cited references collectively disclose or suggest each and every limitation of claims 2–16 and 24–36. *See* Ex. 1041, 229–247.

Patent Owner does not present separate arguments for any of the dependent claims. *See generally* PO Resp. 23–38.

*a.* Claim 2

Claim 2 depends from claim 1 and further requires that "the natural or synthetic tocopherols or tocotrienols is Vitamin E." Ex. 1001, 63:35–36. Petitioner, with supporting testimony from Dr. Peppas, presents evidence that Gwozdz discloses vitamin E. Pet. 41, 69 (citing Ex. 1014, 6:1–2; Ex. 1041 ¶ 373).

*b.* Claims 3–4

Claim 3 depends from claim 1 and further requires that "the benzodiazepine drug is selected from the group consisting of" twenty-two different benzodiazepines, including diazepam "or any pharmaceutically-acceptable salts thereof, and any combinations thereof." Ex. 1001, 63:37–44. Claim 4 depends from claim 3 and specifies that the benzodiazepine drug is diazepam (or salt thereof). *Id*. at 63:45–47. Petitioner, with supporting testimony from Dr. Peppas, presents evidence that Gwozdz discloses the use of benzodiazepines such as diazepam as well as ten other benzodiazepines that are recited in claim 3. Pet. 42, 69–70 (citing Ex. 1014, 8:9–13; Ex. 1041 ¶ 376).

*c.* Claims 5–6

Claim 5 depends from claim 1 and further requires that "the solution contains about 1 to about 20% (w/v) of benzodiazepine." Ex. 1001, 63:48–49. Claim 6 depends from claim 5 and requires that the benzodiazepine is diazepam. *Id*. at 63:50–51. Petitioner, with supporting testimony from Dr. Peppas, presents evidence that Gwozdz teaches "that it is possible to make diazepam solutions of 6.67% (in ethanol); in combinations of tocopherol and alcohol (ethanol), it is possible to make diazepam solutions of 'greater than or equal to 8%', 'greater than or equal to 9%', and

'approaching the 10% level.'" Pet. 43, 70–71 (citing Ex. 1014, 7:12–19; Ex. 1041 ¶ 379).

*d.* Claim 7

Claim 7 depends from claim 1 and requires that the one or more tocopherols or tocotrienols are selected from a group of nine different tocopherols or tocotrienols, including α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol, or any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof. Ex. 1001, 63:52–58. Petitioner, with supporting testimony from Dr. Peppas, presents evidence that Gwozdz teaches use of α-tocopherol, β-, γ-, and δ-tocopherol, as well as isomers thereof and esters thereof. Pet. 43–44, 71 (citing Ex. 1014, 6:2–13; Ex. 1041 ¶ 382).

*e.* Claims 8 and 15

Claim 8 depends from claim 1 and requires that "the solution contains ethanol from 1 to 25% (w/v) and benzyl alcohol from 1 to 25% (w/v)." Ex. 1001, 63:59–61. Claim 15 depends from claim 1 and requires that "the solution comprises ethanol from 10 to 22.5% (w/v) and benzyl alcohol from 7.5 to 12.5% (w/v)." Ex. 1001, 64:15–17.

Petitioner contends that Gwozdz teaches that the alcohols can be ethanol, benzyl alcohol, and combinations thereof, and that the total alcoholic content can be about 1–70%, of which ethanol can be 1–40%, or 10–30%. Pet. 44 (citing Ex. 1014, 4:19–21, 6:16–19, 7:10–11, 7:20–24). Petitioner further asserts that Patent Owner "never demonstrated any criticality to the amount(s) or types of alcohol(s)" and, therefore, "lacking criticality, [one of ordinary skill in the art] would easily and routinely experiment with various amounts of ethanol between 10-30%, combined

with benzyl alcohol making up the remainder of the total of 1-70% alcohol (i.e., 1-40%)." *Id*. at 44–45. Petitioner contends that these values overlap with or encompass the amounts recited in claims 8 and 15, and, therefore, render the claims obvious. *Id*. at 45.

In our Institution Decision, we expressed skepticism that Petitioner had demonstrated the absence of any unexpected results in using a solution with 1 to 25% (w/v) ethanol and 1 to 25% (w/v) benzyl alcohol or 10 to 22.5% (w/v) ethanol and 7.5 to 12.5% (w/v) benzyl alcohol based on arguments made during prosecution of a counterpart European application. *See* Inst. Dec. 18–19. In response, Petitioner argues, with supporting testimony from Dr. Wermeling, that the data relied on by the European Patent Office ("EPO") does not support unexpected results or criticality because there were no tests done inside or outside the recited ranges to test for criticality or unexpected results and the comparison between a solution and a suspension is improper. Reply 24 (citing Ex. 1150 ¶¶ 178–207). We find Petitioner's argument and Dr. Wermeling's testimony persuasive on this issue. Patent Owner has not argued in this proceeding, nor do we find that Patent Owner has established, that a solution with 1 to 25% (w/v) ethanol and 1 to 25% (w/v) benzyl alcohol or 10 to 22.5% (w/v) ethanol and 7.5 to 12.5% (w/v) benzyl alcohol achieves unexpected results. *See E.I. du Pont*, 904 F.3d. at 1006.

In view of the foregoing, we find that Petitioner has sufficiently shown that there is no persuasive evidence of unexpected results or criticality for the claimed ranges.

*f.* Claims 9–10

Claim 9 depends from claim 8 and requires that the "benzodiazepine drug is present in the pharmaceutical solution in a concentration from about 10 mg/mL to about 250 mg/mL." Ex. 1001, 63:62–64. Claim 10 depends from claim 9 and requires that the benzodiazepine drug concentration is "from about 20 mg/mL to about 50 mg/mL." *Id*. at 63:65–67. Petitioner, with supporting testimony from Dr. Peppas, asserts that these ranges are equivalent to about 1–25% (w/v) and about 2–5% (w/v), respectively. Pet. 46 (citing Ex. 1041 ¶¶ 210, 387–388).

Petitioner presents evidence that Gwozdz teaches "that it is possible to make diazepam solutions of 'greater than or equal to 8%', 'greater than or equal to 9%', and 'approaching the 10% level' in tocopherol/alcohol combinations." Pet. 46, 73 (citing Ex. 1014, 7:14–19). Petitioner, with supporting testimony from Dr. Peppas, further contends that one of ordinary skill in the art "could easily reduce the percentage of dissolved diazepam simply by including less diazepam in the formulation." *Id*. (citing Ex. 1041 ¶¶ 390–391).

*g.* Claims 11–12

Claim 11 depends from claim 1 and requires that "the one or more natural or synthetic tocopherols . . . is in an amount from about 45% to about 85% (w/w)." Ex. 1001, 64:1–4. Claim 12 depends from claim 11 and requires that the amount is "from about 60% to about 75% (w/w)." *Id*. at 64:5–8.

Petitioner presents evidence that "Gwozdz teaches that tocopherols may be present in amounts of about 30-99%. Alpha-tocopherol may be present in amounts of 60-99% or 70-90%." Pet. 47 (citing Ex. 1014, 4:17–

19, 7:8–10, 7:20–25; Ex. 1041 ¶ 395). The tocopherol percentage ranges disclosed by Gwozdz overlap with the claimed ranges. Furthermore, Petitioner contends that Patent Owner never demonstrated any criticality to the amounts of tocopherols. *Id.* Patent Owner has not argued, nor do we find that Patent Owner has established, that a tocopherol range of from about 45% to about 85% (w/w) or from about 60% to about 75% (w/w) achieves unexpected results. *See E.I. du Pont*, 904 F.3d. at 1006.

*h.* Claims 13–14

Claim 13 depends from claim 1 and requires that "the ethanol and benzyl alcohol is in a combined amount from about 15% to about 55% (w/w)." Ex. 1001, 64:9–11. Claim 14 depends from claim 13 and requires "a combined amount from about 25% to about 40% (w/w)." *Id*. at 64:12–14. Petitioner presents evidence that "Gwozdz teaches that the alcohols can be ethanol, benzyl alcohol, and combinations thereof" and the "[t]otal alcoholic content can be about 1-70%." Pet. 47–48 (citing Ex. 1014, 4:19–21, 6:16–19, 7:10–11).

The range of combined alcohol in Gwozdz fully encompasses the claimed ranges. Furthermore, Petitioner contends that Patent Owner never demonstrated any criticality with respect to the amount of alcohol(s). Pet. 48. Patent Owner does not argue, nor do we find after considering the evidence of record, that a range of ethanol and benzyl alcohol in a combined amount from about 15% to about 55% (w/w) or from about 25% to about 40% (w/w) achieves unexpected results. *See E.I. du Pont*, 904 F.3d. at 1006.

*i.* Claim 16

Claim 16 depends from claim 1 and requires that "the solution is in a pharmaceutically-acceptable spray formulation." Ex. 1001, 64:18–19.

Petitioner, with supporting testimony from Dr. Peppas, presents evidence that Gwozdz teaches "that the combination of a tocopherol and an alcohol can result in sprayable formulations." Pet. 48–49, 75 (citing Ex. 1014, 6:29–7:2; Ex. 1041 ¶ 401).

*j.* Claims 24–26

Claim 24 depends from claim 1 and requires that "the solution contains at least about 0.01% (w/w) of an alkyl glycoside." Ex. 1001, 64:50–51. Claim 25 depends from claim 24 and requires that "the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside." *Id*. at 64:52–53. Claim 26 depends from claim 25 and specifies that the alkyl glycoside is dodecyl maltoside. *Id*. at 64:54–55. Petitioner presents evidence that "Meezan '962 teaches that alkyl glycosides are present in amounts of about 0.1-2%, about 0.01-1%, and most preferably about 0.01-0.125% by weight." Pet. 55, 76–77 (citing Ex. 1011 ¶ 70). Petitioner also argues that Meezan '962 discloses dodecyl maltoside as "a preferred alkyl glycoside." *Id.* at 55 (citing Ex. 1011 ¶¶ 56, 58, 61, 92, 155–158, Table 1).

*k.* Claims 27 and 29

Claim 27 depends from claim 1 and requires that "the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside." Ex. 1001, 64:56–58. Claim 29 also depends from claim 1 and requires that "the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol." Ex. 1001, 64:63–65. Petitioner, with supporting testimony from Dr. Peppas, presents evidence that "Gwozdz teaches dissolving diazepam in a combination of tocopherols (i.e., vitamin E) and alcohols, including ethanol and benzyl alcohol." Pet. 55–56, 77 (citing Ex. 6:16–19, 7:3–19; Ex. 1041 ¶ 422). Petitioner also contends that

Meezan ’962 discloses the use of an alkyl glycoside, e.g., dodecyl maltoside, in the solution. *Id.* at 56 (citing Ex. 1011 ¶¶ 56, 58, 61, 92, 155–158, Table I).

*l.* Claim 28

Claim 28 depends from claim 1 and requires that “the solution consists of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25% (w/v) dodecyl maltoside, q.s. dehydrated ethanol.” Ex. 1001, 64:59–62. As pointed out by Petitioner, this claim requires about 22.78% of ethanol. Pet. 56.

Petitioner presents evidence that Gwozdz teaches that tocopherols may be present in amounts of about 30–99% and alpha-tocopherol may be present in amounts of 60–99% and contends that Patent Owner never demonstrated any criticality to the amount of tocopherols. Pet. 57, 78 (citing Ex. 1014, 4:17–19, 7:8–10, 7:20–22). Petitioner also presents evidence that Gwozdz teaches “that in combinations of tocopherol and alcohol (ethanol), it is possible to make diazepam solutions ‘approaching the 10% level.’” *Id*. at 58, 79 (citing Ex. 1014, 7:12–19). Petitioner also presents evidence that “Meezan ’962 teaches that 0.25% is a preferred amount of alkyl glycoside,” “dodecyl maltoside is a specifically preferred alkyl glycoside,” and “0.25% dodecyl maltoside is also specifically disclosed.” *Id*. (citing Ex. 1011 ¶¶ 56, 61, 150, 151, 158, 167, Table I, Fig. 1; Ex. 1041 ¶¶ 365–367).

With respect to the percentages of benzyl alcohol and ethanol required by claim 28, Petitioner argues that Patent Owner never demonstrated any criticality for the amounts or types of alcohols; therefore, “Gwozdz’s disclosure of: (i) alcohols, including combinations of ethanol and benzyl alcohol, and (ii) total alcoholic content of about 1-70%, and ethanol content

of 1-40% or 10-30%, renders obvious the alcohol amounts/combination recited in Claim 28." Pet. 57. For the reasons stated *supra* with regard to claims 8–10 and 15, Petitioner's assertion that Patent Owner never showed any unexpected results with respect to the amount of ethanol and benzyl alcohol is sufficiently supported by the evidence of record.

*m.* Claims 30–33

Claim 30 depends from claim 1 and requires that "the solution consists of diazepam from 5 to 15% (w/v), dodecyl maltoside from about 0.01 to 1% (w/v), vitamin E from 45 to 65% (w/v), ethanol from 10 to 25% (w/v) and benzyl alcohol from 5 to 15% (w/v)." Ex. 1001, 64:66–65:3. Claim 31 depends from claim 1 and is similar to claim 30 but does not include "about" with respect to dodecyl maltoside. *Id*. at 65:4–8. Claim 32 depends from Claim 1 and requires that "the solution consists of diazepam from 9 to 11% (w/v), dodecyl maltoside from 0.1 to 0.5% (w/v), vitamin E from 50 to 60% (w/v), ethanol from 15 to 22.5% (w/v) and benzyl alcohol from 7.5 to 12.5% (w/v)." *Id*. at 65:9–13. Claim 33 depends from claim 1 and is similar to claim 32 but limits the amounts to: 10% diazepam, 0.15–0.3% dodecyl maltoside, 50–60% vitamin E, 17–20% ethanol, and 10–12% benzyl alcohol. *Id*. at 65:14–17.

In arguing the obviousness of these claims, Petitioner makes arguments similar to those made for claim 28. *See* Pet. 59–61. For the reasons stated *supra* with regard to claims 8–10, 15, and 28, Petitioner's assertion that Patent Owner never showed any unexpected results is sufficiently supported by the evidence of record.

*n.* Claims 34–36

Claim 34 depends from claim 1 and requires "wherein said treatment achieves bioavailability that is from about 80 to 125% of that achieved with the same benzodiazepine administered intravenously." Ex. 1001, 65:18–21. Claim 35 depends from claim 34 and requires 90 to 110% bioavailability and claims 36 depends from claim 35 and requires 92.5 to 107.5% bioavailability. *Id*. at 65:22–29.

Petitioner contends that Gwozdz teaches that the combination of tocopherols and alcohol(s) "increased bioavailability of the therapeutic agent." Pet. 61 (citing Ex. 1014, 7:3–8). Petitioner further contends that one of ordinary skill in the art would readily understand how to determine bioavailability and that it was known in the art that bioavailability levels of about 100% should be targeted in order to obtain FDA approval. *Id*. at 61–62 (citing Ex. 1023; Ex. 1044, 7). According to Petitioner, in order to achieve such levels of bioavailability, one of ordinary skill in the art, aware of Gwozdz, "would turn to Meezan '962, which had successfully improved the bioavailability of intranasally administered drugs." *Id*. at 62.

Petitioner also contends, with supporting testimony from Dr. Peppas, that one of ordinary skill in the art would have turned to Meezan '962 because it "increased bioavailabilities of intranasally administered drugs from 3% up to 98% with alkyl glycosides" and that one of ordinary skill in the art "would be motivated to routinely experiment with a combination of Gwozdz's and Meezan '962's teachings to arrive at a desired bioavailability approaching 100%." Pet. 63 (citing Ex. 1041 ¶¶ 424–425, 428–430, 434). Petitioner asserts that "[s]uch routine experimentation would be well within

the skill" of one of ordinary skill in the art. *Id*. (citing Ex. 1041 ¶¶ 424–425, 428–430, 434).

In our Decision on Institution, we expressed skepticism that Petitioner sufficiently showed that a POSA would have reasonably expected to achieve the bioavailabilities recited in claims 34–36. *See* Inst. Dec. 27–31. In response, Petitioner and Dr. Wermeling assert that:

> at least with respect to diazepam (which has oral bioavailability of about 100%) – and due to the fact that there is always an oral absorption phase during intranasal administration – a POSA would have expected to achieve bioavailabilities approaching 100% (which falls within the ranges recited in Claims 34-36).

Reply 26–27 (citing Ex. 1150 ¶¶ 188–190).

Other than the general arguments regarding motivation to combine and reasonable expectation of success discussed *infra*, Patent Owner does not make any specific arguments regarding these claims.

In view of the foregoing, we find that Petitioner has sufficiently shown that one of ordinary skill in the art would have reasonably expected success in achieving the bioavailabilities recited in claims 34–36 of the '876 patent based on the disclosures of Gwozdz and Meezan '962.

In view of the above and the evidence of record, we determine that Petitioner has shown, by a preponderance of the evidence, that the combination of Gwozdz and Meezan '962 teaches or suggests each and every limitation of claims 2–16 and 24–36.

5. *Motivation to combine/reasonable expectation of success*

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of

ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). We address motivation to combine and reasonable expectation of success in turn below.

*a) Motivation to combine*

Petitioner, with supporting testimony from Dr. Peppas, asserts that a person of ordinary skill in the art would have had reason to combine the teachings of Gwozdz and Meezan '962. Pet. 33–34 (citing Ex. 1041 ¶¶ 193–194, 225–226, 257–260, 364, 424). Petitioner contends that "Gwozdz relates to solving generally-recognized problems associated with, *inter alia*, intranasal administration of low-solubility drugs" and was "directed to using solvents to increase the dissolved drug percentage." *Id*. at 33 (citing Ex. 1014, 4:29–33, 9:22–28; Ex. 1041 ¶¶ 193–194). According to Petitioner, one of ordinary skill in the art, "seeking to optimize and improve upon Gwozdz would be motivated to modify Gwozdz with the teachings of another reference that solved the same general problems." *Id*. Petitioner contends that a POSA "would be motivated to look to Meezan '962" because it is "similarly directed to solving generally-recognized problems associated with, e.g., intranasal administration of drugs" and it recognized the utility of including solvents. *Id.* (citing Ex. 1011 ¶¶ 2–3, 74, 146; Ex. 1041 ¶¶ 225–226).

According to Petitioner, Meezan '962 solves the intranasal drug administration problems differently than Gwozdz in that "Meezan '962

recognized that alkyl glycosides 'stabilize[] the biological activity and increase[] the bioavailability of the drug'" and, therefore, "solved the known problems by increasing the drug amount available to the body, instead of increasing the % of drug that was dissolved and administered." Pet. 33–34 (citing Ex. 1011 ¶ 5; Ex. 1041 ¶ 226). Petitioner concludes that "a POSITA would seek to combine the teachings of the references in an effort to successfully increase the bioavailable amount of drug." *Id.* at 34 (citing Ex. 1041 ¶¶ 257–260, 364, 424).

Patent Owner asserts that Petitioner has failed to demonstrate a motivation to combine the disclosure of Gwozdz with Meezan '962. *See* PO Resp. 27–29, 35–38. Patent Owner and Dr. Gizurarson assert that a POSA would not look to both (1) increase drug solubility and (2) use penetration enhancers to increase the permeability of the nasal mucosa in order to increase the permeation problems associated with intranasal administration. *Id.* at 27–28 (citing Ex. 1041 ¶¶ 121–168; Ex. 2012 ¶ 79). Patent Owner contends that "a POSA would not recognize the solutions as necessarily compatible and instead would look to pursue one or the other." *Id.* (citing Ex. 2012 ¶ 79).

On this point, we credit the testimony of Dr. Peppas discussed *supra* and are not persuaded that a person of ordinary skill in the art would have been deterred from looking to both increase drug solubility and use penetration enhancers as ways to overcome problems associated with intranasal administration of low-solubility drugs. Dr. Gizurarson provides no reason or evidence as to why these two solutions would be mutually exclusive. Furthermore, as pointed out by Petitioner, a patent application on which Dr. Gizurarson is named as an inventor, discusses the use of alkoxy-

polethylene glycol as a solubilizer for poorly soluble therapeutic agents and also discloses adding additional compounds such as ethanol and benzyl alcohol to enhance solubility as well as adding surfactants, i.e., enhancing agents. Reply 13–14 (citing Ex. 1070 ¶¶ 17, 60–62). Patent Owner asserts that Dr. Gizurarson testified that the components disclosed in the patent application "were chosen based on the targeted mucosal route." PO Sur-Reply 15. We are not persuaded by this argument because the patent application lists intranasal administration as a type of mucosal administration and Dr. Gizurarson testified that the disclosure does not exclude intranasal administration in its discussion of using solubilizers such as alcohols with enhancing agents. *See* Ex. 1070 ¶¶ 4, 60–62; Ex. 1149, 115:1–117:19.

Patent Owner also contends that Gwozdz provides no motivation to modify its disclosed formulations. PO Resp. 28. Specifically, Patent Owner asserts that Gwozdz dealt with the issue of bioavailability of benzodiazepines for intranasal administration by focusing on solubility and "left no room for modification in its precipitation sensitive formulations." *Id.* (citing Pet. 28; Ex. 1041 ¶ 194). In support of its arguments, Patent Owner cites to the following disclosure from Gwozdz:

> . . . the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.

*Id.* at 29 (citing Ex. 1014, 7).

Based on this disclosure, Patent Owner asserts:

> A POSA, knowing that Gwozdz's solubility level for diazepam is close to the same amount as the clinical dose needed for therapeutic effect (10 mg), and combined with the above statement, would understand that increasing the amount of tocopherol and decreasing the amount of ethanol increases the solubility and approaches diazepam's saturation concentration.

PO Resp. at 29 (citing Ex. 2012 ¶ 83). According to Patent Owner, this brings the formulation of Gwozdz close to risk of precipitation in the humid nasal cavity and "a POSA would learn from the teachings of Gwozdz that adding less tocopherol reduces the solubility of diazepam." *Id.* (citing Ex. 2012 ¶¶ 65, 82–83).

Patent Owner contends that "a POSA would have no motivation – and instead would be turned away from – adjusting the formulation any further (let alone adding any additional excipient such as benzyl alcohol or an alkyl glycoside to the mix)." PO Resp. 29–30 (citing Ex. 2012 ¶¶ 80–85). According to Patent Owner:

> A POSA would understand that doing so would potentially take away from the amount of either or both of the tocopherol and ethanol and, in turn, *decrease* the solubility of diazepam – *i.e.*, he would not sacrifice drug solubility by removing or reducing a co-solvent necessary for maximizing solubility of the benzodiazepine drug.

*Id.*

On this point, we credit the testimony of Dr. Peppas and Dr. Wermeling that a person of ordinary skill in the art would have been motivated to use tocopherol along with a combination of alcohols such as ethanol and benzyl alcohol, as disclosed in Gwozdz. *See* Ex. 1041 ¶¶ 103 n.9, 131–136, 192–203, 363; Ex. 1150 ¶¶ 129–156. We are not persuaded that a POSA would have been deterred based on a single specific example in Gwozdz cited by Patent Owner. In fact, the example discussed by Patent

Owner is described as a "non-limiting example" and Gwozdz also discloses the use of tocopherol with ***combinations*** of different alcohols including ethanol and benzyl alcohol. *See* Ex. 1014, 4, 6, 7; Ex. 1150 ¶¶ 129–142. Furthermore, as Dr. Wermeling testified, a "POSA would have recognized that the addition of benzyl alcohol to a tocopherol+ethanol co-solvent system – as suggested by Gwozdz – would result in a ternary co-solvent system with different solubility characteristics" and a POSA "would adjust the amounts of the three solvents to maximize solubility of the drug." Ex. 1150 ¶ 139.

Dr. Wermeling concludes:

> Indeed, a POSA would have been very motivated to routinely experiment with a ternary system, which would inherently require that at least one of the two co-solvents in the binary system be reduced in order to make room for the third co-solvent (i.e., to create the ternary system). Combining and adjusting three solvents to maximize solubility of any water-insoluble drug (such as diazepam) is a simple, well-known, and routine technique that a POSA could (and would) easily do when directed (as by Gwozdz) to use three solvents (especially when the three solvents are specifically identified, as by Gwozdz).

Ex. 1150 ¶ 141.

Even assuming, *arguendo*, that the example cited by Patent Owner was considered a preferred embodiment, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971). Furthermore, a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Labs.,* 874 F.2d 804 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989).

We also find that Petitioner, along with the testimony of Dr. Peppas and Dr. Wermeling, has persuasively shown that a person of ordinary skill in the art would have been motivated to combine tocopherol with ethanol and benzyl alcohol. As discussed *supra*, Dr. Peppas testifies that the combination of ethanol and benzyl alcohol was also used (along with other ingredients) in diazepam formulations such as the rectal gel Diastat and the injectable solution Valium. *See* Ex. 1041 ¶ 133 (citing Ex. 1042, 2, 10). Dr. Peppas also cites to other prior art references discussing the preference for using a drug solvent system containing benzyl alcohol and ethanol. *See Id.* ¶¶ 134, 135 (citing Ex. 1018, 3:52–54, 4:7–23; Ex. 1019, 3:65–4:1, 5:5–7, 5:64–6:51). Similarly, Dr. Wermeling testifies that a "POSA would know that there are historic and commercial examples that combined benzyl alcohol with ethanol and diazepam, along with other solvents" such as Diastat and Valium and "benzyl alcohol and ethanol were known to be readily miscible." Ex. 1150 ¶ 146 (citing Ex. 1031, 10; Ex. 1042, 2, 10; Ex. 1076, 11).

Furthermore, with regard to Patent Owner's argument that a POSA would not have used another excipient due to fear of precipitation, the disclosure of Gwozdz is not limited to administration in one nostril and administration in more than one nostril would allow for a lower concentration of drug in solution being administered in each nostril, which would avoid the potential for diazepam to precipitate out of the solution. *See* Reply 14–15 (citing Ex. 1150 ¶¶ 130–132; Ex. 1149, 38:9–18).

Patent Owner argues that Petitioner overlooks the label for Nayzilam, a commercialized intranasal diazepam formulation, which requires to dose one nostril, wait at least 10 minutes, and then dose the other nostril if the

patient has not responded. PO Sur-Reply, 17 (citing Ex. 1072, 1). We are not persuaded by this argument. The fact that a nasal diazepam product, approved in 2019, includes such dosing instructions does not indicate that one of ordinary skill in the art in 2009 would have been deterred from providing administration in both nostrils. *See* Ex. 2018. In fact, as discussed *infra*, Cartt '784 discloses (in 2008) that intranasal solutions of benzodiazepines can be administered in one nostril, in both nostrils sequentially, or in one nostril, then the second nostril, and then the first nostril again (and, optionally, in the second nostril again). *See* Ex. 1015 ¶¶ 31, 33, 35, 39, 42, 45; Ex. 1150 ¶¶ 144–145. Dr. Wermeling and Dr. Gizurarson agree that a POSA would reduce the diazepam concentration and apply a lower concentration to both nostrils in order to avoid precipitating, while still achieving the desired therapeutic effect. *See* Ex. 1149, 38:9–18; Ex. 1150 ¶¶ 143, 144.

Patent Owner also asserts that Petitioner shows no motivation to combine the formulations of Gwozdz with the formulations of Meezan '962. *See* PO Resp. 35–38. Specifically, Patent Owner contends that Petitioner "provides no motivation for a POSA to increase bioavailability of Gwozdz's intranasal formulation with addition of a penetration enhancer." *Id.* at 35–36. According to Patent Owner, Gwozdz "distinguishes itself from prior art solutions containing surfactants or micellar formulations and exemplifies a maximized tocopherol formulation necessary for achieving increased solubility." *Id.* at 36 (citing Ex. 2012 ¶ 82). Therefore, Patent Owner asserts that there would have been no motivation for a POSA to modify Gwozdz by adding a surfactant such as an alkyl glycoside. *Id.*

Patent Owner further contends that one of skill in the art would not have been motivated to combine the formulations of Gwozdz and Meezan ’962 because Meezan ’962 was concerned with “increasing absorption and decreasing adverse effects of ***water-soluble*** therapeutic drugs” and “increasing stability of its peptide and protein formulations by addition of surfactants” such as alkyl glycosides. PO Resp. 36 (citing Ex. 2012 ¶ 96; Ex. 1011 ¶ 4). Patent Owner also asserts that Meezan ’962 does not disclose benzodiazepines (directly or indirectly) and concludes that “a POSA would not find Meezan ’962 relevant to poorly water-soluble therapeutic agents such as benzodiazepines.” *Id.* at 26, 37 (citing Ex. 2012 ¶ 97).

Further, according to Patent Owner, Meezan ’962 “disclosed the use of surfactants in an ***aqueous*** setting” and a “POSA would need more information (outside of either Gwozdz or Meezan’962 disclosure) in order to determine how the alkyl glycosides of Meezan’962 would function including, e.g., ‘[s]olubility of the glycoside in other solvents, [] other carriers . . . [p]robably a number of other parameters; pH, pH sensitivity, concentrations’ etc.” PO Resp. 37 (citing Ex. 2012 ¶ 98; Ex. 1011 ¶¶ 146–172; Ex. 2011, 141:8–11, 141:14–18). Patent Owner asserts that Petitioner fails to discuss how alkyl glycosides function in a non-aqueous environment and Meezan ’962 “discloses alkyl glycosides as a stabilizer *only* in aqueous formulations.” PO Sur-Reply 15 (citing Ex. 2011, 140:20–23).

According to Patent Owner, “[b]ecause independent claim 1 of the ’876 patent excludes water from its benzodiazepine solution – through its ‘consisting of’ language – it does not provide a vehicle for which a surfactant such as alkyl glycoside could work to stabilize or act as a traditional penetration enhancer in a solution.” PO Resp. 38 (citing

Ex. 2011, 138:12–139:23). Patent Owner concludes that, for these reasons, "a POSA would have been discouraged from selecting the alkyl glycoside as disclosed and used in Meezan'962 to add to the non-aqueous formulations of Gwozdz." *Id.*

As discussed *supra*, we are not persuaded that a POSA would have been deterred from modifying the one specific example in Gwozdz cited by Patent Owner. We, furthermore, credit the testimony of Dr. Peppas and Dr. Wermeling that a POSA would have been motivated to look at multiple ways of increasing intranasal delivery of drugs. For example, Dr. Wermeling testifies that "a POSA would understand the benefits from using a penetration enhancer, even in situations of already-high bioavailability, as penetration enhancers would (among other things) be useful in adjusting the rate and amount of drug absorbed purely intranasally." Ex. 1150 ¶ 146 n.4. Also, while Meezan '962 does not specifically reference benzodiazepines, it does refer to small organic molecules and anti-seizure agents, which encompass benzodiazepines. *See* Ex. 1011 ¶¶ 3, 4, 130; Ex. 1041 ¶ 222; Ex. 1150 ¶ 150.

Furthermore, contrary to the arguments of Patent Owner, Meezan '962 is not limited to water soluble therapeutic drugs and discloses using alkyl glycosides in aqueous or non-aqueous systems:

> Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A 'pharmaceutically acceptable carrier' is an aqueous or **non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof**, and can contain a surfactant,…a solvent,… Pharmaceutically acceptable carriers are well known in the art and include, for example,…**oils** such as olive oil or injectable organic esters…A pharmaceutically acceptable carrier can also be selected from substances such as…**benzyl alcohol**,….

Ex. 1011 ¶ 74 (emphasis added). Given this disclosure, we credit the testimony of Dr. Wermeling that "a POSA would be motivated to increase the solubility of diazepam given its lower potency as compared to other benzodiazepines and in recognition of limited water solubility." Ex. 1150 ¶ 152.[11]

Thus, Petitioner demonstrates, by a preponderance of the evidence, that a person of ordinary skill in the art would have had reason to add alkyl glycoside as a penetration enhancer, as disclosed in Meezan '962, with a formulation of benzodiazepine, tocopherol, ethanol, and benzyl alcohol, as disclosed in Gwozdz.

*b) Reasonable Expectation of Success*

We next consider whether Petitioner has shown by a preponderance of the evidence that the skilled artisan would have had a reasonable expectation of success in achieving the method claimed in the '876 patent. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Petitioner's declarant, Dr. Peppas, testifies that Patent Owner never demonstrated any criticality for the amount of ingredients in the claims; therefore, a POSA would have easily been able to experiment with different amounts and types of tocopherols, alcohols, benzodiazepines, and alkyl

[11] Dr. Gizurarson also testified that he was unaware of any documents to support the position that alkyl glycosides could not be used in non-aqueous solutions and that he was unaware of any documents to support the position that alkyl glycosides could not be used with benzodiazepines. *See* Ex. 1149, 85:2–3, 94:9–18; Ex. 1150 ¶¶ 162–165.

glycosides with an expectation of success. Ex. 1041 ¶¶ 363, 368. He also testifies that "[b]ased on Meezan'962's teachings, the POSITA would add an alkyl glycoside to Gwozdz's teachings with an expectation of successfully increasing the bioavailability." *Id.* ¶ 364.

Patent Owner asserts that Petitioner's theory of obviousness lacks a showing of a reasonable expectation of success in modifying Gwozdz to include ethanol, benzyl alcohol, tocopherol or tocotrienol, and alkyl glycosides. PO Resp. 30. First, Patent Owner asserts that Petitioner has not shown a reasonable expectation of success in adding a penetration enhancer such as alkyl glycoside to the Gwozdz formulation. *Id.* at 31. According to Patent Owner, alkyl glycosides are known nonionic surfactants and "[t]he Handbook of Pharmaceutical Excipients ("Handbook") (Ex. 1031) teaches that non-ionic surfactants interact to the detriment of the disclosed solvents." *Id.* For example, the Handbook states that "[e]thanol is inactivated in the presence of nonionic surfactants and is ineffective against bacterial spores." *Id.* (citing Ex. 1031, 4). The Handbook also states that "antimicrobial activity is reduced in the presence of nonionic surfactants…" *Id.* (citing Ex. 1031, 10). Patent Owner concludes that:

> A POSA would recognize that especially when dealing with multidose intranasal use, the inactivation of microbial activity of ethanol and/or benzyl alcohol could have consequences in the successful approval of an intranasal formulation. EX2012, ¶¶ 88–89. A POSA by 2008 would have been aware of such interactions and, thus, less likely to look to a nonionic surfactant to combine with a formulation that already included ethanol and benzyl alcohol. *Id.*

*Id.*

We do not find this argument persuasive. First, Dr. Wermeling and Dr. Gizurarson testify that ethanol is not known to be used as an

antibacterial agent in benzodiazepine formulations. *See* Ex. 1149, 78:15–21; Ex. 1150 ¶ 154. Furthermore, according to Dr. Wermeling, the benzodiazepine formulation in the final package has to be aseptic so there are no bacteria to kill. Ex. 1150 ¶ 155. Therefore, we credit Dr. Wermeling's testimony and agree with Petitioner that "whether or not the antimicrobial properties are inactivated is irrelevant and a POSA would not be led away from considering nonionic surfactants." Reply 17 (citing Ex. 1150 ¶ 155). Even if such antimicrobial properties were important, we credit the testimony of Dr. Wermeling that "a POSA would not expect that the very small amounts of nonionic surfactants being used would be sufficient to inactivate the antimicrobial properties of high concentrations of ethanol and/or benzyl alcohol being used here." Ex. 1150 ¶ 156.

Patent Owner also contends that Petitioner has not shown a reasonable expectation of success in adding additional solvents such as benzyl alcohol to the Gwozdz formulation. PO Resp. 33. According to Patent Owner, the Handbook entry for benzyl alcohol provides the following regarding the combination of benzyl alcohol with fats:

> Benzyl alcohol is incompatible with oxidizing agents and strong acids. ***It can also accelerate the autoxidation of fats.***

*Id.* (citing Ex. 1031, 10). Based on this disclosure, Patent Owner asserts:

> A POSA relying on the Handbook would have at least been cautioned not to combine benzyl alcohol with tocopherols or tocotrienols. EX2012, ¶¶ 86–87. A POSA would recognize that doing so would negate the anti-oxidation properties of tocopherols and, as a result, degrade the compound such that undesirable by-products could be introduced into the formulation. *Id.*

*Id.*

In addition, according to Patent Owner, a POSA as of 2008 would also have been aware that solvents such as benzyl alcohol were known irritants to the nasal cavity. PO Resp. 33–34 (citing Ex. 1041 ¶ 103(b); Ex. 2012 ¶ 90). Therefore, Patent Owner asserts that "a POSA would understand that because of the presence of benzyl alcohol, which is used as a preservative in pharmaceutical formulations, injectable compositions containing benzyl alcohol could not be used in intranasal formulations." *Id.* at 34.

We do not find this argument persuasive and credit the testimony of Dr. Wermeling that a POSA would not be concerned about potential auto-oxidation of fats by the benzyl alcohol because oxygen is absent in these single-use emergency rescue products. *See* Ex. 1150 ¶ 134 n.2. We also find persuasive the testimony of Dr. Wermeling that the Handbook, relied on by Patent Owner, does not provide any conditions necessary for such autoxidation to occur, nor does it indicate that tocopherols would autoxidize in the presence of benzyl alcohol. *See id.* We also find persuasive Dr. Wermeling's testimony that, "in cases of acute life-threatening indications such as epileptic seizures, a relatively high local irritation to the mucosa is acceptable." *Id.* ¶ 211.

Upon review of the record as a whole, we find that one of ordinary skill in the art would have had a reasonable likelihood of success in combining the disclosures of Gwozdz and Meezan '962 to achieve the claimed invention. *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985) ("Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness.").

Therefore, we determine that Petitioner has demonstrated by a preponderance of the evidence that each limitation of claims 1–16 and 24–36 are taught or suggested by the combination of Gwozdz and Meezan '962 and further that the skilled artisan would have had reason to make the suggested combination with a reasonable expectation of success.

6. *Objective indicia of non-obvious*

In determining whether a claim is obvious in light of the prior art, we also consider any relevant evidence of secondary considerations of non-obviousness. *See Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have suggested to one of ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of non-obviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Patent Owner presents evidence of failure of others and long-felt need. *See* PO Resp. 40–44.

Patent Owner argues that, as of 2008 and 2009, "there was a well-known need in the market for immediate treatment of epileptic seizures – with intranasal administration of benzodiazepines – and more specifically, diazepam – proving to be a promising solution." PO Resp. 41 (citing Ex. 2012 ¶¶ 111–112). According to Patent Owner, "while the ability to administer therapeutic drugs intranasally was first realized as early as 1980 (EX2008, 1240), intranasal formulation of benzodiazepines has been hampered by technical challenges posed by benzodiazepines." *Id.* at 41–42.

Patent Owner further asserts that the fact that the industry had failed to develop the benzodiazepine formulation of the '876 patent is evident from

the fact that, before Patent Owner's invention, no company had ever commercialized an intranasal benzodiazepine formulation and only one company has ever done so (i.e., Nayzilam, a midazolam formulation), which was released in 2019. PO Resp. 43 (citing Ex. 2012 ¶ 75; Ex. 2018). Patent Owner also asserts that, "to address this unmet need," it submitted a New Drug Application ("NDA") with the Food and Drug Administration ("FDA") for Valtoco, which it refers to as "diazepam nasal spray that is representative of the '876 patent claims." *Id.* (citing Ex. 2024). According to Patent Owner, "the fact that Neurelis, with the Valtoco® formulation, met this long-felt but unmet need – especially in light of the failure of others – confirms the non-obviousness of the '876 patent." *Id.* at 44 (citing Ex. 2012 ¶ 113).

Objective evidence of nonobviousness is relevant only if there is a nexus between this evidence and the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). A presumption of nexus applies if the asserted objective evidence "is tied to a specific product and that product 'embodies the claimed features, and is coextensive with them.'" *Id.* (quoting *Polaris Indus., Inc. v. Artic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018)). To the extent that a presumption of nexus does not apply, Patent Owner may still prove nexus "by showing that the evidence of secondary considerations is the 'direct result of the unique characteristics of the claimed invention.'" *Id.* (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

At the outset, we give Patent Owner's arguments about failure of others and long-felt need very little weight in our obviousness analysis. Patent Owner relies on Valtoco as meeting the alleged long-felt need, yet

Patent Owner does not allege (or even mention) any "nexus" with respect to that formulation in its briefing. *See* PO Resp. 40–44; PO Sur-Reply 19–26. Although Patent Owner asserts that Valtoco "is representative of the '876 patent claims"[12] and "met [the] long-felt but unmet need," it provides no description of the Valtoco formulation as compared to the claims of the '876 patent. As pointed out by Petitioner, "Dr. Gizurarson testified he did not know Valtoco's formulation. Absent that information, [Patent Owner] did not establish the required nexus connecting the '876 patent claims to Valtoco." Reply 28; Ex. 1149, 18–19.

When asked about nexus at the Oral Hearing, Patent Owner appeared to change their position and Patent Owner's counsel stated that they "don't argue a nexus between VALTOCO…and the claims" and that "[i]t is the formulation of the claim and the disclosure of the patent that meets the needs, not the product itself." Tr. 50:20–26. Patent Owner's counsel also cited to Paragraph 113 of the Gizurarson Declaration (Tr. 51:7–12); however, that paragraph also does not specifically tie the limitations of the '876 patent claims to the presented evidence of failure of others or long-felt need. Rather, the secondary consideration evidence presented is broadly directed to an intranasal benzodiazepine formulation rather than to the specific formulation recited in the claims of the '876 patent. *See* Ex. 2012 ¶ 113.

Moreover, even if nexus had been shown, the objective evidence of nonobviousness identified by Patent Owner provides only limited support for nonobviousness of the challenged claims. For example, Petitioner has

[12] This assertion comes up only once in a brief, unsupported parenthetical.

presented persuasive evidence that benzodiazepines were delivered intranasally prior to 2009, which undercuts Patent Owner's arguments of failure of others and long-felt need. *See* Ex. 1150 ¶¶ 82–87 (citing Exs. 1121, 1136–1144).

For these reasons, we are not persuaded by Patent Owner's arguments that failure of others and long-felt need weigh toward the non-obviousness of the claimed subject matter.

*7. Conclusions as to obviousness of claims 1–16 and 24–36 over Gwozdz and Meezan '962*

In sum, we find that the combination of Gwozdz and Meezan '962 teaches or suggests each and every element of claim 1–16 and 24–36. We find that an ordinarily skilled artisan would have been motivated to combine Gwozdz with Meezan '962, and would have had a reasonable expectation of success in achieving the claimed invention. On this record, we also find that the evidence of secondary considerations of non-obviousness is weak, at best. As discussed above, we find that Patent Owner has not established the requisite nexus between the challenged claims and any of the asserted secondary considerations. We are therefore unable to accord them any substantial weight. *Fox Factory*, 944 F.3d at 1373.

Thus, after carefully considering the arguments and evidence, we determine that Petitioner has shown by a preponderance of evidence that claims 1–16 and 24–36 of the '876 patent would have been obvious over Gwozdz and Meezan '962.

*F. Asserted Obviousness of Claims 17–23 over Gwozdz, Meezan '962, and Cartt '784*

Petitioner contends that the subject matter of claims 17–23 of the '876 patent would have been obvious over the combined disclosures of Gwozdz,

Meezan ’962, and Cartt ’784. Pet. 49–54, 87–92. Patent Owner opposes. PO Resp. 23–39; PO Sur-Reply 12–19. Having considered the totality of the arguments and evidence, we find that Petitioner has shown by a preponderance of the evidence that claims 17–23 are unpatentable as having been obvious over Gwozdz, Meezan ’962, and Cartt ’784.

*1. Cartt ’784*

Cartt ’784 discloses “nasal formulations for administering benzodiazepine drugs, such as diazepam, lorazepam or midazolam, to a patient in need of therapeutic treatment with a benzodiazepine drug.” Ex. 1015 ¶ 28. Cartt ’784 is directed to intranasal particulate formulations but discloses that the formulations can be liquid nasal sprays and that the drug may be in solution. *Id*. ¶¶ 9, 138–139, 141. Cartt ’784 also discloses a list of solvents including ethanol and benzyl alcohol, as well as nonionic surfactants including dodecyl maltoside. *Id*. ¶¶ 47, 48, 130, 182. Cartt ’784 also provides different dosing amounts, volumes, and regimens for the benzodiazepine formulations. *Id*. ¶¶ 7, 31, 33–36, 39, 42, 45, 47, 55–56, 64, 71–72, 79–80, 87–88, 95–96, 104–105, 112–113, 144.

*2. Limitations of Claims 17–23*

*a.* Claims 17–18

Claim 17 depends from claim 16, which depends from claim 1, and requires the pharmaceutically-acceptable spray formulation of claim 16 “wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.” Ex. 1001, 64:19–23. Claim 18 depends from claim 17 and requires that “said pharmaceutical solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 µL to about 200 µL.” *Id*. at 64:24–26. Petitioner presents evidence that

Cartt '784 discloses that diazepam may be present in amounts of about 1 to about 20 mg per dose, and discloses "diazepam volumes include 25-250 µl, preferably 50-150 µl, and especially about 100 µl." Pet. 49, 87–88 (citing Ex. 1015 ¶¶ 63–64).

*b.* Claims 19–22

Claim 19 depends from claim 18 and requires that the method "comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril." Ex. 1001, 64:27–30. Claim 20 also depends from claim 18 and requires spraying the "benzodiazepine into each nostril." *Id*. at 64:31–34. Claim 21 depends from Claim 20 and recites the optional step of "spraying a third quantity of the pharmaceutical solution into the first nostril." *Id*. at 64:35–41. Claim 22 depends from Claim 21 and recites the optional step of "administering at least a fourth quantity of the pharmaceutical solution to the second nostril." *Id*. at 64:42–45. Petitioner, with supporting testimony from Dr. Peppas, presents evidence that Cartt '784 discloses the dosing regimen elements of claims 19–22. *See* Pet. 51–52, 88–91 (citing Ex. 1015 ¶¶ 31, 33, 35, 39, 42, 45; Ex. 1041 ¶ 451).

*c.* Claim 23

Claim 23 depends from claim 21 and requires "wherein the nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which is treatable with the pharmaceutical solution." Ex. 1001, 64:46–49. Petitioner, with supporting testimony from Dr. Peppas, presents evidence that Cartt '784 discloses the use of benzodiazepines for treating symptoms before and/or after they start. Pet. 52–54, 91–92 (citing Ex. 1015 ¶¶ 3, 60, 61, 68, 69; Ex. 1041 ¶ 455).

We determine that Petitioner has shown, by a preponderance of the evidence, that the combination of Gwozdz, Meezan '962, and Cartt '784 teaches or suggests each and every limitation of claims 17–23.

*3. Motivation to combine/reasonable expectation of success*

Petitioner argues that, since neither Gwozdz nor Meezan '962 provide specific dosing regimens for benzodiazepines/diazepam, one of ordinary skill in the art would look to the similar reference of Cartt '784, titled "Nasal Administration of Benzodiazepines," for these teachings. Pet. 34. Petitioner, with supporting testimony from Dr. Peppas, further argues that one of ordinary skill in the art "would not be deterred from incorporating the teachings of Cartt '784, even though it is not specifically directed to solutions (instead disclosing intranasal particulate formulations)" and "would easily adapt" these teachings "to the Gwozdz/Meezan '962 combination." *Id*. at 34–35 (citing Ex. 1041 ¶¶ 257–260).

Patent Owner argues that Petitioner fails to demonstrate a motivation to combine the formulation of Cartt '784 to the Gwozdz and/or Meezan '962 formulations. PO Resp. 38–40. First, Patent Owner asserts that "Gwozdz distinguished its non-aqueous lipophilic and hydrophobic formulations from Cartt '784 by stating, '[a]dvantageously, the resulting pharmaceutical solution is not an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions.'" *Id.* at 39 (citing Ex. 1014, 4–5; Ex. 2012 ¶ 107). Patent Owner further asserts that Cartt '784 applies to particulate formulations of benzodiazepines so "a POSA would not find particulate formulations of benzodiazepines as easily translatable to solutions of benzodiazepines, especially as it relates to dosing regimens." *Id.* (citing Ex. 2011, 145:13–17).

We find that Petitioner has persuasively shown that a person of ordinary skill in the art would have been motivated to combine the disclosures of Gwozdz and Meezan '962 with Cartt '784. Cartt '784 recognized the:

> need for benzodiazepine formulations that are capable of providing to the nasal mucosa sufficient quantity of benzodiazepine in a small enough volume to provide therapeutically effective blood plasma concentration of benzodiazepine within a short period after administration of the formulation to the nasal mucosa.

Ex. 1015 ¶ 8. Cartt '784 also:

> provides methods of administering a benzodiazepine to a patient, comprising nasally administering an effective amount of the benzodiazepine to the patient, wherein the effective amount of the composition is effective to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure.

*Id.* ¶ 28.

Although Cartt '784 discusses benzodiazepines in particulate form, it states that the dosage form may be "a nasal spray or nasal drop, although presently preferred embodiments are nasal sprays…[which] may be liquid or solid nasal sprays" and acknowledges that "[i]t is also possible for the drug to be fully soluble in the liquid." Ex. 1015 ¶¶ 138–139. Cartt '784 also states that the dosage form may be in the form of liquid droplets which "may be formed from solutions…" *Id.* ¶ 139. The solution may be a combination of the drug in a "non-aqueous medium." *Id.* Dr. Peppas testified that tocopherol would be such a non-aqueous medium. *See* Ex. 1041 ¶ 248. Cartt '784 also "classifies both ethanol and benzyl alcohol as useful solvents." *Id.* ¶ 249 (citing Ex. 1015 ¶ 182). Cartt '784 further discloses the

use of absorption enhancers, including alkyl glycosides. *See* Ex. 1015 ¶¶ 128–129; Ex. 1041 ¶¶ 250–252.

Based on these disclosures, we credit the testimony of Dr. Peppas that the teachings of Gwozdz, Meezan ’962, and Cartt ’784 are “naturally combinable” because they “all recognized that there are benefits to administering active agents intranasally” and “sought to provide solutions to these difficult problems” with “different potential solutions.” *See* Ex. 1041 ¶¶ 257–258. We also credit the testimony of Dr. Wermeling that a “POSA would have looked to Cartt’784 for its disclosure of dosing regimens (including dosing amounts and volume amounts) for benzodiazepines (including diazepam)” and would have combined this disclosure with Gwozdz’s disclosure of “intranasal benzodiazepine (diazepam) in ternary solvent systems, and further with Meezan’962’s disclosure of alkyl glycosides (penetration enhancers).” Ex. 1150 ¶ 170.

On this record, and upon review of Petitioner’s arguments and supporting evidence, we determine that Petitioner sufficiently explains why one of ordinary skill in the art would have looked to Cartt ’784’s disclosure when seeking dosing regimens for the compositions disclosed in Gwozdz and Meezan ’962, and would have had a reasonable expectation of success in achieving the claimed invention. Petitioner also sufficiently explains how the combined disclosures of Gwozdz, Meezan ’962, and Cartt ’784 would have taught or suggested the subject matter of claims 17–23. As discussed *supra*, we also find that the evidence of secondary considerations of non-obviousness is weak, at best.

Thus, after carefully considering the arguments and evidence, we determine that Petitioner has shown by a preponderance of evidence that

claims 17–23 of the ’876 patent would have been obvious over Gwozdz, Meezan ’962, and Cartt ’784.

## III. PATENT OWNER’S IDENTIFICATION OF ALLEGEDLY IMPROPER REPLY ARGUMENTS AND EVIDENCE

Patent Owner previously requested permission to file a Motion to Strike portions of Petitioner’s Reply and the Declaration of Dr. Daniel P. Wermeling, Pharm.D. (Ex. 1150). We denied this request, but authorized the parties to file a joint chart identifying the Reply arguments and evidence Patent Owner believes are improper and providing Petitioner’s response to Patent Owner’s arguments. Paper 26 (“Objec.”). We address the issues the parties identify below.

### *A. Claim Construction*

Patent Owner contends that Petitioner provided new claim constructions for the terms “ethanol,” “consisting of,” and “solution.” Objec. 1–2. As discussed *supra*, upon review of the parties’ arguments and the evidence of record, we determine that no terms of the ’876 patent require express construction for purposes of this Decision. Therefore, Patent Owner’s arguments regarding Petitioner’s new claim construction arguments are moot.

### *B. Person of Ordinary Skill in the Art*

The Petition provides a definition of one of ordinary skill in the art and supports that definition with testimony from Dr. Peppas. Pet. 4; Ex. 1041 ¶ 74. Patent Owner disagrees with this definition in its Response, providing testimony of Dr. Gizurarson to support its arguments. PO Resp. 15–17; Ex. 2012 ¶¶ 27–33. Dr. Wermeling responds to the definition of a POSA provided by Patent Owner and testifies that it is necessary to add

transmembrane experience to the definition provided by Dr. Gizurarson. Ex. 1150 ¶¶ 20–22.

Patent Owner objects to page 12 of the Reply and paragraphs 20–22 of Dr. Wermeling's Declaration as allegedly offering new opinions on the level of skill in the art that are not in the Petition. Objec. 2.

Neither Petitioner's Reply nor Dr. Wermeling's Declaration testimony seek to change the proposed definition of one of ordinary skill in the art set forth in the Petition. Dr. Wermeling, instead, addresses the specific arguments made in Patent Owner's Response and Dr. Gizurarson's Declaration and asserts that the POSA would also need transmembrane experience. Petitioner and Dr. Wermeling's assertion that transmembrane experience is needed is also consistent with Petitioner and Dr. Peppas's assertion that a POSITA would have experience with transmucosal pharmaceutical formulation development and/or delivery. *See* Pet. 4–5; Ex. 1041 ¶ 74. As such, we find that Dr. Wermeling's testimony related to the level of ordinary skill in the art constitutes proper rebuttal.

*C. General Rebuttal Arguments and Evidence*

Patent Owner also objects to multiple portions of the Reply and Dr. Wermeling's testimony as advancing new theories and relying on new evidence. Objec. 2–7. Upon review of Patent Owner's objections and Petitioner's responses to those objections, we are persuaded that the identified portions of the Reply and Dr. Wermeling's testimony represent proper rebuttal arguments intended to respond to arguments raised by Patent

Owner, opinions Dr. Gizurarson presented in his declaration, and/or statements made in the Decision on Institution.[13]

Patent Owner is correct that some exhibits Dr. Wermeling discusses are not addressed in the Petition. As our reviewing court has instructed, however, "the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings and, as long as the opposing party is given notice of the evidence and an opportunity to respond to it, the introduction of such evidence is perfectly permissible under the [Administrative Procedure Act]." *Genzyme Therapeutic Prod. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F. 3d 1360, 1366 (Fed. Cir. 2016). Here, Patent Owner deposed Dr. Wermeling after receiving his reply Declaration, had an opportunity to respond to his arguments and supporting evidence in a Sur-Reply, and has filed a Motion to Exclude his testimony on relevance and prejudice grounds. *See Yeda Research v. Mylan Pharms, Inc.*, 906 F.3d 1031, 1040 (Fed. Cir. 2018). Thus, we find that the portions of the Reply and Dr. Wermeling's testimony and supporting documentary evidence cited by Patent Owner are not improper. *See Apple Inc. v. Andrea Elecs. Corp.*, 949 F.3d 697, 706-07 (Fed. Cir. 2020).

## IV. MOTIONS TO EXCLUDE

Both parties moved to exclude evidence in this proceeding.

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[13] "[T]he Board will permit the petitioner, in its reply brief, to address issues discussed in the institution decision." Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019) ("Consolidated Trial Practice Guide"), *available at* https://www.uspto.gov/TrialPracticeGuideConsolidated, at 73.

*A. Petitioner's Motion to Exclude*

Petitioner moved to exclude Exhibits 2001–2010 and 2013–2024 generally for relevancy under Fed. R. Evid. 402, confusion, waste, and prejudice under Fed. R. Evid. 403, hearsay under Fed. R. Evid. 802, and lack of authentication under Fed. R. Evid. 901. Pet. MTE. Petitioner also moved to exclude portions of Ex. 2012 (Declaration of Dr. Gizurarson) for relevancy under Fed. R. Evid. 402, confusion, waste, and prejudice under Fed. R. Evid. 403, improper lay testimony under Fed. R. Evid. 701, unqualified expert testimony under Fed. R. Evid. 702, hearsay under Fed. R. Evid. 802, and improper summary without underlying documents under Fed. R. Evid. 1006. *Id.* at 6–7. Our conclusions in this Final Written Decision do not rely upon any of the evidence in Exhibits 2001–2005, 2007–2010, and 2013–2024 that Petitioner seeks to exclude. Accordingly, Petitioner's Motion to Exclude these exhibits is *dismissed* as moot.

*1. Exhibit 2006*

With regard to Exhibit 2006, the 1988 SIGMA catalog, Petitioner argues that the exhibit is offered to prove the truth of the matter asserted without meeting any hearsay exception and that Patent Owner failed to provide evidence sufficient to establish that the exhibit is what it is purported to be. Pet. MTE, 4.

First, we do not rely on Ex. 2006 for the matter asserted but rather for what it described to an ordinary artisan. Therefore, it is not hearsay under Fed. R. Evid. 801(c). Furthermore, Patent Owner provided library affidavits (Ex. 2025, Ex. 2026) authenticating Ex. 2006. Therefore, Ex. 2006 is properly authenticated. Thus, we *deny* the Motion to Exclude Exhibit 2006.

*2. Exhibit 2012*

With regard to Exhibit 2012, the Declaration of Dr. Sveinbjörn Gizurarson, Ph.D., Petitioner argues that we should exclude paragraphs 2, 5, 7, and 67 for relevancy under Fed. R. Evid. 402, and confusion, waste, and prejudice under Fed. R. Evid. 403. Pet MTE, 6. Petitioner also argues that we should exclude paragraphs 2, 3, 5, 28–33, 36, 44, 48, and 50–51 because they "include assertions for which evidence has not been introduced sufficient to show that the witness has personal knowledge of the matters asserted." *Id.* Petitioner further asserts that we should exclude paragraphs 16–25, 26, 28, 31–36, 38–39, 41–43, 48, 50–52, 54–56, 58, 60–61, 67–70, 75, 77–80, 82–87, 89–95, 97, 99–109, and 111–116 under Fed. R. Evid. 701 and 702 because of improper lay testimony and unqualified expert testimony. *Id.* at 6–7. Petitioner further asserts that we should exclude paragraphs 28-33, 44–46, 48, 50–52, 54, 56–61, 63–67, 71–72, 74, 77–78, 83–84, 89, 92, and 111–113 under Fed. R. Evid. 802 as "the exhibit is offered to prove the truth of the matter asserted without meeting any hearsay exception." *Id.* at 7. Lastly, Petitioner asserts that we should exclude paragraphs 28–29, 36, 48, 50–51, 56, 58, 59–60, 79, 85, 87, 89, 95, 100–102, 104–105, 109, and 114–116 under Fed. R. Evid. 1006 because they "constitute improper summary with underlying documents not made available." *Id.*

Our conclusions in this Final Written Decision do not rely upon any of the evidence in paragraphs 2, 3, 5, 7, 16–26, 33–36, 38–39, 41–46, 48, 50–52, 54–61, 63–72, 74, 75, 77–80, 82–87, 89–95, 97, 99–109, and 111–116 of Exhibit 2012. Accordingly, Patent Owner's Motion to Exclude these

paragraphs under Fed. R. Evid. 402, 403, 701, 702, 802, and 1006 is *dismissed* as moot.

With respect to paragraphs 28–32 of the Gizurarson Declaration, in which Dr. Gizurarson provides his opinion regarding the definition of a person of ordinary skill in the art, we find that Dr. Gizurarson has provided sufficient background qualifications to opine on this issue. With regard to Petitioner's hearsay argument, we find that Dr. Gizurarson's opinions in these paragraphs are based on his experience in the field, which has been sufficiently shown. Therefore, these opinions are not predicated on hearsay. Similarly, because the opinions in these paragraphs are based on Dr. Gizurarson's prior experience, they do not constitute an improper summary without underlying documents under Fed. R. Evid. 1006. Accordingly, Petitioner's Motion to Exclude paragraphs 28–32 of Exhibit 2012 under Fed. R. Evid. 402, 403, 701, 702, 802, and 1006 is *denied.*

*B. Patent Owner's Motion to Exclude*

Patent Owner moved to exclude Exhibits 1009, 1013, 1017, 1021, 1022, 1033, 1036, 1038, 1048, 1050, 1065, 1069, 1080, 1081, 1122, portions of Exhibit 1149, and the entirety of, or portions of, Exhibit 1150, generally for relevancy under Fed. R. Evid. 402, confusion, waste, and prejudice under Fed. R. Evid. 403, hearsay under Fed. R. Evid. 802, and lack of authentication under Fed. R. Evid. 901. PO MTE. Patent Owner also moved to exclude paragraphs 29–63, 167–168, 171–191, 264–362, and Appendix A (pp. 197–224) of Exhibit 1041 (Declaration of Dr. Peppas) for relevancy under Fed. R. Evid. 402, confusion, waste, and prejudice under Fed. R. Evid. 403, and outside the scope of expertise and conclusory and unreliable statements under Fed. R. Evid. 602 and 701–702. *Id.* at 2–4. Our

conclusions in this Final Written Decision do not rely upon any of the evidence in Exhibits 1009, 1013, 1017, 1021, 1022, 1033, 1036, 1038, 1048, 1050, 1065, 1069, 1080, 1081, 1122, and 1149 that Patent Owner seeks to exclude. We also do not rely upon any of the evidence at paragraphs 29–63, 167–168, 171–191, 264–362, and Appendix A (pp. 197–224) of Exhibit 1041 (Declaration of Dr. Peppas). Accordingly, Patent Owner's Motion to Exclude is *dismissed* as moot with respect to these Exhibits (or portions thereof).

*1. Exhibit 1150*

With regard to Exhibit 1150, the Declaration of Daniel P. Wermeling, Pharm.D., Patent Owner argues that we should exclude this exhibit or portions thereof, because "it sets forth arguments that were not presented in the Petition, cannot be relevant to it, and consequently serves only to confuse and create unfair prejudice through belated surprise" under Fed. R. Evid. 402–403. PO MTE, 9–11.

As discussed above, we determine that no terms of the '876 patent require express construction for purposes of this Decision. Therefore, Patent Owner's argument that we should exclude paragraphs 23–30 of the Wermeling Declaration because they relate to new claim construction arguments is *dismissed* as moot. Also, as discussed above, we find that the other cited portions of Dr. Wermeling's testimony properly respond to Patent Owner's arguments, the testimony of Dr. Gizurarson, and the Decision on Institution. *See Genzyme*, 825 F. 3d at 1366; Consolidated Trial Practice Guide, 73. Accordingly, Patent Owner's Motion to Exclude Exhibit 1150 or portions thereof under Fed. R. Evid. 402–403 is *denied.*

Patent Owner also asserts that we should exclude paragraphs 59–89 and 90–126 of Exhibit 1150 under Fed. R. Evid. 602 because "Dr. Wermeling testifies outside the scope of his expertise in analyzing regulatory approval and commercialization of drug products." PO MTE, 11. Our conclusions in this Final Written Decision do not rely upon any of the evidence in paragraphs 59–81 or 88–126 of Exhibit 1150. Accordingly, Patent Owner's Motion to Exclude these paragraphs under Fed. R. Evid. 602 is *dismissed* as moot. With respect to paragraphs 82–87, we do not find that these paragraphs discuss regulatory approval or commercialization of drug products. Rather, these paragraphs discuss prior art references that describe intranasal delivery of benzodiazepines for the treatment of seizures prior to 2009, upon which we find Dr. Wermeling qualified to opine. Accordingly, Patent Owner's Motion to Exclude paragraphs 82–87 under Fed. R. Evid. 602 is *denied.*

Patent Owner further asserts that paragraphs 23–30, 59–89, 95–100, 114–118, and 171–177 of Exhibit 1150 should be excluded under Fed. R. Evid. 701–702 because Dr. Wermeling's opinions therein "are conclusory and unreliable as Dr. Wermeling does not disclose the underlying facts or any basis in support of his opinions." PO MTE, 11–12. Our conclusions in this Final Written Decision do not rely upon any of the evidence in paragraphs 23–30, 59–81, 88–89, 95–100, or 114–118 of Exhibit 1150. Accordingly, Patent Owner's Motion to Exclude these paragraphs under Fed. R. Evid. 701–702 is *dismissed* as moot.

With respect to paragraphs 82–87, as discussed above, we find that these paragraphs discuss prior art references that discuss intranasal delivery of benzodiazepines for the treatment of seizures prior to 2009. We find that

these paragraphs are properly supported by citations to the prior art references being discussed. Furthermore, paragraphs 171–177 discuss Dr. Wermeling's opinions with regard to the '558 provisional application and its incorporation by reference to the Sigma Catalog and how such disclosure would be understood by a person of ordinary skill in the art. We find these opinions to be properly supported. Therefore, Patent Owner's Motion to Exclude paragraphs 82–87 and 171–177 under Fed. R. Evid. 701–702 is *denied.*

Patent Owner further contends that we should exclude paragraphs 191–194 and 102–104 of Exhibit 1150 under Fed. R. Evid. 805 and 1006, respectively. PO MTE, 13. Our conclusions in this Final Written Decision do not rely upon any of the evidence in paragraphs 191–194 or 102–104 of Exhibit 1150. Accordingly, Patent Owner's Motion to Exclude these paragraphs under Fed. R. Evid. 805 and 1006 is *dismissed* as moot.

## V. CONCLUSION[14]

Petitioner establishes by a preponderance of the evidence that claim 1–36 of the '876 patent are unpatentable as follows.

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[14] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

| Claims | 35 U.S.C. § | Reference(s)/Basis | Claims Shown Unpatentable | Claims Not Shown Unpatentable |
|---|---|---|---|---|
| 1–16, 24–36 | 103(a) | Gwozdz, Meezan ’962 | 1–16, 24–36 | |
| 17–23 | 103(a) | Gwozdz, Meezan ’962, Cartt ’784 | 17–23 | |
| **Overall Outcome** | | | 1–36 | |

## VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–36 of the ’876 patent have been proven to be *unpatentable*; and

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.

FURTHER ORDERED that Petitioner’s Motion to Exclude is *dismissed* as moot with respect to Exhibits 2001–2005, 2007–2010, 2013–2024, and portions of Exhibit 2012, and *denied* with respect to Exhibit 2006 and paragraphs 28–32 of Exhibit 2012; and

FURTHER ORDERED that Patent Owner’s Motions to Exclude is *dismissed* as moot with respect to Exhibits 1009, 1013, 1017, 1021, 1022, 1033, 1036, 1038, 1048, 1050, 1065, 1069, 1080, 1081, 1122, and portions of Exhibits 1041, 1149, and 1150, and *denied* with respect to Exhibit 1150 and portions thereof.

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