UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

Case No. IPR2025-00464
Patent 8,895,546

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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1001	U.S. Patent No. 8,895,546, Administration Of Benzodiazepine Compositions, filed June 13, 2012 ("'546 Patent")
1002	File History for '546 Patent, Ser. No. 13/495,942 ("'546 FH") Part 1: Pages 1-350 Part 2: Pages 351-700 Part 3: Pages 701-1050 Part 4: Pages 1051-1400 Part 5: Pages 1401-1750 Part 6: Pages 1751-2100 Part 7: Pages 2101-2450 Part 8: Pages 2451-2681
1003	U.S. Patent No. 9,763,876, Administration Of Benzodiazepine Compositions, filed October 29, 2014 ("'876 Patent")
1004	File History for 9,763,876 Patent, Ser. No. 14/527,613 ("'876 FH") Part 1: Pages 1-270 Part 2: Pages 271-530
1005	Provisional Patent Application No. 61/497,017, filed June 14, 2011 ("'017 Provisional")
1006	Provisional Patent Application No. 61/570,110, filed December 13, 2011 ("'110 Provisional")
1007	File History for Non-Provisional Patent Application Serial No. 12/413,439, filed March 27, 2009 ("'439 FH") Part 1: Pages 1-400 Part 2: Pages 401-800 Part 3: Pages 801-1200 Part 4: Pages 1201-1600 Part 5: Pages 1601-2000 Part 6: Pages 2001-2400 Part 7: Pages 2401-2800 Part 8: Pages 2801-3200 Part 9: Pages 3201-3488
1008	Provisional Patent Application No. 61/040,558, filed March 28, 2008 ("'558 Provisional")
1009	Gwozdz et al., WO 2009/120933, Pharmaceutical Solutions And Method For Solubilizing Therapeutic Agents, published October 1, 2009, International Filing Date March 27, 2009 (PCT/US2009/038518) ("Gwozdz")
1010	Meezan et al., U.S. Patent Application Publication No. US 2006/0046962, Absorption Enhancers for Drug Administration, Serial No. 11/127,786, published March 2, 2006 ("Meezan")

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1017	PDR 54th Edition 2000, DIASTAT® (diazepam rectal gel); MIACALCIN® (Calcitonin Nasal Spray); VALIUM® (diazepam injection), Physicians' Desk Reference ("PDR")
1018	Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. Br J Clin Pharmacol. 2002; 53: 501-507 ("Knoester")
1019	Florida Regional Common EMS Protocols Field Guide, Jones and Barlett Publishers, MA (2005) ("EMS")
1020	Valium® Tablet Label, Roche, January 2008 ("Valium label")
1021	Wolfe T, Macfarlane T. Intranasal midazolam therapy for pediatric status epilepticus. Am J Emerg Med 2006; 24:43-346 ("Wolfe")

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1038	USP 26/NF 21 2003, The Official Compendia of Standards, Ethanol, Copyright 2002 (“USP 26/ NF 21”)
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1040	Final Written Decision issued in IPR 2019-00451 filed against U.S. Patent No. 9,763,876, August 6, 2020 (“IPR 2019-00451 Final Written Decision”)
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1060	U.S. Patent No. 5,661,130 to Meezan and Pillion ("Meezan II")
1061	U.S. Patent No. 6,610,271 to Wermeling ("WermelingIV")
1062	Declaration of Dr. Maureen Donovan, Ph.D.
1063	Complaint filed in Neurelis, Inc. v. Padagis LLC et al., Civil Action No. 1:24-cv-11637 (D. Mass) (complaint filed on June 25, 2024).
1064	U.S. Provisional Patent App. No. 61/040,281 ("'281 Provisional")
1065	NOT USED
1066	NOT USED
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1068	Neurelis, Inc. v. Aquestive Therapeutics, Inc., No. 2021-1038, (Fed. Cir. Oct. 7, 2021)
1069	Chart comparing claims 1-22 of the '546 Patent to claims 1- 16 and 24-36 of the '876 Patent

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1070	Declaration of Chad Landmon in Support of Being a Provisionally Recognized PTAB Attorney
1071	US Patent No. 9,763,876 to Cartt ("'876 Patent")
1072	Expert Declaration of Professor Sveinbjorn Gizurarson in Support of Patent Owner's Response to Petition for *Inter Partes* Review of U.S. Patent No. 9,763,876
1073	Lim et al., *Physiological Factors Affecting Nasal Drug Delivery, in* ENHANCEMENT IN DRUG DELIVERY (Elka Touitou & Brian W. Barry, 2007)
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1075	File History for Non-Provisional Patent Application Serial No. 11/127,786, Response to Office Action and Amendments filed August 13, 2007
1076	File History for Non-Provisional Patent Application Serial No. 13/371,274, Declaration of Dr. Edward T. Maggio filed September 19, 2013
1077	Certified Transcript of Deposition of Marc Brown, Ph.D. in *Padagis US LLC vs. Neurelis, Inc.*, IPR2025-00464, IPR2025-00465, IPR2025-00466 (March 17, 2026)
1078	Supplemental Declaration of Dr. Maureen Donovan
1079	Panico et al., A GUIDE TO IUPAC NOMENCLATURE OF ORGANIC COMPOUNDS, Recommendations (1993) ("IUPAC")
1080	US Patent No. 8,278,292 to Brown ("'292 Patent")
1081	Appellant Neurelis Inc.'s Opening Brief, *Neurelis, Inc. v. Aquestive Therapeutics, Inc.*, No. 2021-1038 (Fed. Cir. Feb. 2, 2021).
1082	Appellant Neurelis Inc.'s Reply Brief, *Neurelis, Inc. v. Aquestive Therapeutics, Inc.*, No. 2021-1038 (Fed. Cir. Feb. 2, 2021).
1083	Stipulation Regarding Claim Construction, *Neurelis, Inc. v. Padagis LLC et al.*, 1-24-cv-00562 (D.Del. May 8, 2024).

I. INTRODUCTION

Patent Owner's Response (POR) largely seeks to relitigate issues that have already been decided. Most notably, Patent Owner is collaterally estopped from disputing obviousness over Gwozdz in view of Meezan. In IPR2019-00451, affirmed by the Federal Circuit, the Board held materially indistinguishable claims—including claims reciting dodecyl maltoside—unpatentable over that same prior art combination. Patent Owner identifies no difference here that materially alters the unpatentability analysis, and it therefore cannot reassert most of the arguments advanced in its Response.

To the extent the Board left a few discrete issues open, none change the result. First, any argument that Gwozdz should be excluded as prior art under 35 U.S.C. §103(c)(2) is now moot. The Board denied Patent Owner's request to file a certificate of correction that would have added joint-research-agreement language to the '546 patent, and without that correction the patent as issued does not satisfy the statutory disclosure requirement on which Patent Owner's theory depends. Second, Patent Owner's dispute over whether Gwozdz's reference to a "penetration enhancer" is supported by the provisional is immaterial. That issue does not bear on whether a person of ordinary skill would have been motivated to combine Gwozdz and Meezan, because the Board has already determined that such a motivation

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existed, and Petitioner's obviousness showing does not depend on that phrase in any event.

Thus, claims 17 and 22 of the '546 patent are unpatentable on the grounds set forth in the Petition (Pet.).

II. REPLY ARGUMENTS

A. Collateral Estoppel Precludes Patent Owner From Disputing Obviousness Over Gwozdz in View of Meezan

Patent Owner's response disputes that Gwozdz in view of Meezan renders the claims obvious despite the Board's Final Written Decision in IPR2019-00451 (the '451 IPR) to the contrary that was affirmed by the Federal Circuit. *See* EX1040, 68-69; EX1068, 1-2. Patent Owner tries to escape the preclusive effect of collateral estoppel by arguing that U.S. Pat. No. 9,763,876 ("the '876 Patent") was previously adjudicated and not the '546 Patent. POR, 46. But Federal Circuit precedent confirms collateral estoppel applies to identical issues across different patents and claims so long as the differences "do not materially alter" the question of unpatentability. *Finjan LLC v. SonicWall, Inc.*, 84 F.4th 963, 969 (Fed. Cir. 2023). Patent Owner is not able to identify any difference in the previously adjudicated claims of the '876 Patent and currently challenged claims of the '546 Patent that would "materially alter" the question of unpatentability.

Indeed, the only difference in the claims that Patent Owner points to is the limitation reciting "dodecyl maltoside" in the '546 Patent. In making this argument,

Patent Owner falsely states that "the Board in the 451 IPR only addressed claims reciting 'alkyl glycoside.'" POR, 50. However, "dodecyl maltoside" was recited in claims 26-28 and 30-33 of the '876 Patent. The Board expressly addressed claims 26-28 and 30-33 reciting DDM and found them obvious in the '451 IPR:

> Claim 26 depends from claim 25 and specifies that the alkyl glycoside is dodecyl maltoside…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)…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.

EX1040, 33-35, (emphasis added)[1] and 37-47 (discussing motivation to combine); *see also* Ex. 1003 at 64:54-65:17 ('876 Patent claims 26-28 and 30-33 recite DDM). Patent Owner extensively litigated obviousness for claims reciting DDM in the '451 IPR.

Most telling, in its unsuccessful appeal from the '451 IPR, Patent Owner expressly raised the DDM claims in its appeal:

[1] Emphasis always added unless otherwise noted.

- "2: Did the Board prejudicially err in misconstruing '876 patent claims 26-28 and 30-33 as requiring generic 'alkyl glycoside' rather than the claimed 'dodecyl maltoside', and then denying these claims priority to the '558 provisional application" and
- "3. Did the Board prejudicially err in holding all '876 patent claims obvious"

EX1081, 1; *see also id.* at 40-51 (addressing motivation to combine prior art under issue 3). Indeed, Patent Owner expressly argued on appeal that "Gwozdz are [sic] not available as prior art for at least claims 26-28 and 30-33, because Neurelis is entitled to the '558 provisional application's priority date for dodecyl maltoside." *Id*. at 40.

Patent Owner cites an appellee waiver argument to suggest he DDM claims were not litigated in the '451 IPR, but Patent Owner's own Federal Circuit briefing shows the opposite. Patent Owner told the Federal Circuit it had raised "express arguments" in the '451 IPR and "in no way 'concede[d]' the separate patentability of dependent dodecyl maltoside claims 26-28 and 30-33" there. EX1082, 7-8. The '451 IPR record confirms that point. *See* EX2076, 23-38 (applying its motivation argument to all claims, including claims 26-28 and 30-33).

Having told the Federal Circuit it litigated the DDM limitation in claims 26-28 and 30-33, Patent Owner cannot disown that admission here. The issue of whether

a POSA would have been motivated to combine the prior art for claims reciting DDM was litigated and resolved in the ’451 IPR and affirmed by the Federal Circuit. While Patent Owner argues the “issue” for collateral estoppel is limited to the specific arguments Patent Owner actually raised, they provide no case law to support that notion. Indeed, the very purpose of collateral estoppel is to prevent a new argument on an already litigated and decided issue. Unlike the *Purdue* case cited by Patent Owner, there was no waiver of this issue…at most Patent Owner believes it now has a better argument on why it should prevail on this previously litigated issue. POR at 52 (citing *Purdue Pharma L.P. v. Iancu*, 767 F. App’x 918, 922 (Fed. Cir. 2019).

Even if there was some difference in the claims adjudicated in the ’451 IPR claims 17 and 22 of the ’546 Patent, those differences are not material in view of Meezan’s disclosure of “dodecyl-β-D-maltoside” that the Board agreed with. EX1010 ¶ [0156]; EX1040, 34. The Federal Circuit has applied collateral estoppel in circumstances where narrowing language in unadjudicated claims does not materially alter the invalidity analysis. *Ohio Willow Wood Co. v. Alps South*, LLC, 735 F.3d 1333, 1342–43 (Fed. Cir. 2013) (finding collateral estoppel where the unadjudicated claims recite “block copolymer” gel instead of the broader “polymeric” gel recited in the adjudicated claims); *Soverain Software LLC v. Victoria's Secret Direct Brand Mgmt*., LLC, 778 F.3d 1311, 1319 (Fed. Cir. 2015)

(finding collateral estoppel where the unadjudicated claims recited "transmitting a hypertext statement over the Internet, rather than over a generic network").

As such, the Board has already determined that claims reciting "dodecyl maltoside" are obvious over Gwozdz[2] in view of Meezan in IPR2019-00451, and Patent Owner is collaterally estopped from disputing that the claims in this proceeding are obvious over the proposed ground.

B. Level of Ordinary Skill in the Art

Patent Owner offers a different definition of a person of ordinary skill in the art ("POSA") (POR, 8; EX2074, ¶¶60-62) but never argues that Petitioner's definition is wrong. Petitioner's definition is identical to the one the PTAB adopted in the '451 IPR and should be adopted here for consistency.

Dr. Maureen Donovan qualifies as a POSA under either definition, and the claims would be obvious under either one. Patent Owner does not argue otherwise. EX1078, ¶¶ 6-8.

[2] Patent Owner often refers to Gwozdz as "Gwozdz-PCT" in its Response. For the sake of clarity and consistency with the Petition, this Reply references Gwozdz as "Gwozdz" and the provisional to which Gwozdz claims priority as "Gwozdz-Provisional" as the Board does in the Institution Decision.

C. There is No Inconsistency in Claim Construction Between This IPR and the Litigation

Petitioner has withdrawn all of its claim constructions positions in the District Court to ensure consistency with this IPR proceeding in line with the Director's recent precedential and informative decisions on this issue. *See* EX1083, 2-3; *Revvo Techs., Inc. v. Cerebrum Sensor Techs., Inc.*, IPR2025-00632, Paper 20 (Nov. 3, 2025) (precedential); *Tesla, Inc. v. Intellectual Ventures II LLC*, IPR2025-00340, Paper 18 (Nov. 5, 2025) (informative). As such, Petitioner is not "advancing different positions in the two forums." *Revvo Techs*, 5.

Petitioner agreed to adopt Patent Owner's proposed construction in the litigation, "no construction necessary; the scope of 'consisting of' is established by law," which is consistent with the construction proposed in the Petition. EX1083, 1 and 3. Indeed, the Board noted this consistency in the Institution Decision when stating that Petitioner "suggests the transitional phrase 'consisting of' means the claimed pharmaceutical solutions include only those components recited in the claims . . . [s]uch interpretation tracks the conventional meaning of the 'consisting of' transitional phrase in claim drafting." Paper 13, 7, n.5.

D. Gwozdz is Prior Art Under 35 U.S.C. §102(e)

1. *There is a Different Inventive Entity Between Gwozdz and the '546 Patent, which is Prima Facie Evidence that Gwozdz is "By Another"*

Patent Owner asserts that Petitioner has failed to establish that Gwozdz meets the "by another" requirement of Section 102(e), because inventors Gwozdz, Loxley, and Mitchnick recited on Gwozdz are also named inventors on the '546 patent. POR, 15. Under pre-AIA 35 U.S.C. §102(e), a reference is *prima facie* "by another" whenever the inventive entities are not identical; overlap in inventors does not matter, and a difference of even one inventor is enough. *Merck Serono S.A. v. Hopewell Pharma Ventures, Inc.*, Nos. 2025-1210, 2025-1211, slip op. at 22 (Fed. Cir. Oct. 30, 2025) (any incongruity in the inventive entity renders the prior disclosure "by another"). The '546 patent recites Cartt, Medeiros, Gwozdz, Loxley, Mitchnick, Hale, and Maggio as inventors, (EX1001) while Gwozdz recites only Gwozdz, Loxley, and Mitchnick as inventors (EX1009). That difference is enough, and Gwozdz is "by another" under the provisions of Section 102(e).[3]

[3] Patent Owner has never asserted that the entirety of the inventive concept in the '546 Patent was provided by Gwozdz, Loxley, and Mitchnick.

2. *Whether Gwozdz-Provisional Explicitly Supports Inclusion of a "Penetration Enhancer" is Irrelevant*

Patent Owner argues Gwozdz is not prior art under §102(e) because its reference to "penetration enhancers" lacks support in the Gwozdz-Provisional, which does not use that exact phrase. POR, 16–17 (comparing EX1064 and EX1009 and arguing "[t]here is no disclosure of 'penetration enhancers' in Gwozdz-Provisional"). Patent Owner also alleges that it is the recitation of "penetration enhancer" in Gwozdz that is the "basis" for the motivation to combine. POR, 16-17. But that is plainly inaccurate.

As discussed *infra* Section II(F)(2)(i)-(iv), the motivation to combine Gwozdz and Meezan is established irrespective of whether Gwozdz discloses a "penetration enhancer" as prior art. And the Board agreed. *See*, Paper 13, 18-20. Further, not once does Petitioner or Dr. Donovan assert that the motivation is based on Gwozdz's disclosure of "penetration enhancer." Instead, Petitioner cites to a paragraph in Gwozdz that discusses the inclusion of "other pharmaceutically acceptable additives" to establish that Gwozdz contemplated additional excipients to enhance efficacy. Pet., 27; EX1062, ¶98. Consequently, even if Gwozdz does not qualify as prior art for the "penetration enhancer" term, the result is the same – a motivation nonetheless existed to combine Gwozdz and Meezan.

3. *Gwozdz Qualifies as Prior Art Under §311(b)*

Patent Owner acknowledges that patent applications qualify as prior art under 35 U.S.C. §§311(b) under *Lynk Labs, Inc. v. Samsung Elecs. Co.*, 125 F.4th 1120, but notes only that *Lynk* sought *certiorari* to preserve the issue. POR, 18 n.4. Petitioner agrees that Gwozdz is prior art and notes that *certiorari* was denied on March 9, 2026.

E. Gwozdz is Not Excluded as Prior Art Under 35 U.S.C. §103(c)(2)

By the Patent Owner's own admission, the safe harbor exemption of §103(c)(2) requires that the patent discloses the names of the parties to the joint research agreement ("JRA"). POR, 19. Per the Board's Decision dated March 20, 2026 (Paper 37, 15), the Board has denied Patent Owner's request for rehearing for leave to file a petition for a certificate of correction ("CoC") seeking to add language about a joint research agreement into the '546 Patent. As such, Patent Owner's argument that Gwozdz is precluded as Section 102(e) prior art under the provisions of Section 103(c)(2) (POR, 18-25) lacks any basis because the '546 Patent as issued does not disclose the names of the parties to the JRA.

Nonetheless, even if a CoC were to be entered to reflect the JRA between Questcor and Particle Sciences, Inc. ("PSI"), the JRA would still not disqualify

Gwozdz as prior art.[4] The provisions of 35 U.S.C. §103(c) relied upon by Patent Owner may only disqualify prior art under Sections 102(e), (f), and (g) "where the subject matter and the claimed invention were, at the time the claimed invention was made, ***owned by the same person or subject to an obligation of assignment to the same person***." 35 U.S.C. §103(c)(1). As Patent Owner admits in its January 5, 2026 Patent Owner Response, the '558 Provisional (the earliest asserted priority application for the '546 Patent) was "owned by Questcor," and the provisional that is the priority application for Gwozdz (the "Gwozdz-Provisional") was "owned by PSI," which are not the same person under the statute. POR, 24 (citing EX2040).

The inventors of the '546 Patent and Gwozdz themselves recognized and deliberately addressed this lack of common ownership. Their declarations submitted with the Patent Owner Response admit that the '558 Provisional and the Gwozdz-Provisional were intentionally filed on the same day (March 28, 2008) specifically "so that neither application would create an impediment to the other." EX2045, ¶28; EX2046, ¶20. These statements prove the inventors knew the '558 Provisional and

[4] Patent Owner's refusal to agree to strike the three declarations related to this issue shows intent to further challenge or appeal the Board's decision denying leave to file a CoC. As such, the Board should address this independent basis showing why Gwozdz is prior art to provide a full record for any appeal and avoid piecemeal resolution of the issues.

Gwozdz-Provisional were not commonly owned and that one could serve as prior art against the other (*i.e.*, an "impediment"). Their strategic same-day filing was a calculated attempt to mitigate—but not eliminate—the risks of separate ownership.[5]

Without co-ownership, the safe harbor of Section 103(c)(2) cannot apply.[6]

F. The Challenged Claims are Obvious Over Gwozdz in view of Meezan[7]

1. *The Combination of Gwozdz and Meezan Discloses the "Consisting Of" Limitation*

Patent Owner asserts that, in view of Petitioner's alleged claim construction argument that "consisting of" requires a "zero-impurity" formulation, that Petitioner has failed to establish that Gwozdz or Meezan meets this claim limitation, because ethanol "indisputably contains water." POR, 26-27. However, as discussed supra Section II(C), per the Director's recent guidance, and to eliminate any doubt,

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[5] Patent Owner has refused to make its fact witness declarants available for depositions, including Messrs. Hale, Mitchnick, and Cartt, depriving Petitioner of the opportunity to inquire further regarding the facts associated with these filings.

[6] As Dr. Donovan opined, the '558 provisional does not disclose or support the "dodecyl maltoside" limitation, and the earliest priority date is March 28, 2009. *See* EX1062, ¶¶42-54; EX1078, ¶¶11-13.

[7] As discussed above, the Board should determine that Patent Owner is collaterally estopped from raising these arguments.

Petitioner has withdrawn its District Court claim construction position for the "consisting of" term, including all associated briefing and declarations in support of its briefing. EX1083, 1-3.

Petitioner's analysis in the Petition has only ever applied the plain and ordinary meaning of "consisting of" to the prior art, specifically noting that "Gwozdz and Meezan render obvious a pharmaceutical solution for nasal administration 'consisting of' (i.e., **containing only**) the claimed benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and an alkyl glycoside." Pet., 41; EX1062, ¶138-139; EX1078 ¶¶14-17. The Petition correctly notes that "consisting of" requires that the claimed formulation contains only those components expressly recited in the body of the claims, consistent with the well-established meaning of "consisting of" that excludes any elements, steps, or ingredients not specified in the claim. *See, e.g., Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016); *AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001). And the Board preliminarily agreed, noting in its Institution Decision that Petitioner's interpretation "tracks the conventional meaning of the 'consisting of' transition phrase." Paper 13, 7 n.5.

And in the '451 IPR, which used the same "consisting of" transition phrase, the Board determined that "no terms of the '876 patent require express construction

for purposes of this Decision." EX1040, 12-13. Thus, Petitioner provided no construction of "consisting of" in this IPR because Petitioner has only ever advocated that the term have its plain and ordinary meaning, and the Board has expressly stated that the term (as present in the nearly identical claims of the '876 patent) does not require construction.

Gwozdz discloses the claimed "ethanol" requirement. Pet., 43-45; EX1009, 6:16-19, 4:17-21; 7:8-11; 7:20-27; EX1062, ¶147-149. The Board reached the same conclusion in IPR2019-00451, finding that Gwozdz teaches the "ethanol" component of the '876 patent, which is identical to the term recited in the '564 claims. EX1040, 26-27. Similarly, in this proceeding, the Board noted in its Institution Decision that "Patent Owner is collaterally estopped from contesting obviousness of the claimed pharmaceutical solution recited in claims 1-22 of the '546 patent based on materially identical issues that were already adjudicated in IPR2019-00451." Paper 13, 16-17. Just as the Board in IP2019-00451 determined that Gwozdz teaches the claimed "ethanol," the Board in this proceeding should confirm the same, as Patent Owner is collaterally estopped from arguing otherwise.

Even if "consisting of" requires a "zero-impurity" formulation, Gwozdz discloses this limitation. A reference qualifies as prior art for all that is disclosed therein. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("a reference…is prior art for all that it teaches."). Gwozdz explicitly

states that the ethanol is desirably 90-100% ethanol. EX1009, 6:28-29. Ethanol at "100%" contains no additional components and thus satisfies even Patent Owner's "zero-impurity" interpretation.

Patent Owner further argues that Gwozdz's disclosure of "penetration enhancer" supplies the motivation to combine with Meezan and that, because that discussion appears in a section on injectable formulations that may contain water, the Gwozdz formulation must also contain water. POR, 27-28. As an initial matter, as discussed infra Section II(F)(2)(i)-(iv), Gwozdz's disclosure of "penetration enhancer" is not the lynchpin that establishes the motivation to combine with Meezan – numerous other rationales exist for why a POSA was motivated to combine the references. Nowhere in Gwozdz does it state that water is a required component of the formulation. In fact, when describing the "present invention," Gwozdz states that it is "directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agent." EX1009, 4:29-33. And, regarding Patent Owner's focus on injection formulations, Gwozdz explicitly clarifies that formulations suitable for parenteral (i.e., injection) administration can be aqueous or **non-aqueous**. Id., 11:17-18. Patent Owner fails to account for the non-aqueous embodiments in Gwozdz.

Similarly, Patent Owner asserts the examples of Meezan all include peptides dissolved in water, which Patent Owner apparently interprets as requiring water in the formulation. POR, 28. As discussed infra Section II(F)(2)(iii), however, Meezan explicitly states that its alkyl glycosides may be used in either aqueous or non-aqueous systems.

2. *There Were Ample Reasons and Motivation to Combine Gwozdz and Meezan*

In asserting a lack of motivation to combine Gwozdz and Meezan, and no expectation of success, Patent Owner primarily rehashes the same arguments asserted in the ’451 IPR. In that proceeding, the Board found Patent Owner’s arguments unpersuasive, concluding that there was a motivation to combine the teachings of Gwozdz and Meezan with a reasonable expectation of success. EX1040, 37-54. The Board should make the same finding here.

(i) Petitioner’s Obviousness Position is Based on Known Problems, not Hindsight, and Motivation Existed to Modify Gwozdz with Meezan

Patent Owner argues Petitioner improperly borrowed the “problem” from the ’546 patent and then used hindsight to improve an already successful Gwozdz formulation. POR, 29-33. That characterization ignores both the Petition’s record citations and settled Federal Circuit law. As an initial matter, “[a]dmissions in the specification regarding the prior art are binding on the patentee for purposes of a

later inquiry into obviousness." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007). The '546 Patent explicitly states in the background that prior art benzodiazepine formulations (including oral, rectal, and parenteral) had limited use due to solubility challenges. Pet., 25-26; EX1001, 1:47-2:13. This is the precise type of admission envisioned by *PharmaStem Therapeutics* that is binding on the patentee and relevant to the obviousness inquiry.

Patent Owner further asserts that Gwozdz solved the solubility and bioavailability issues associated with diazepam, and there was no need to further modify the Gwozdz formulation. POR, 29-33. But, as explained in the Petition, Gwozdz teaches that the pharmaceutical solutions described therein may further incorporate additional pharmaceutically acceptable additives. Pet., 26-27; EX1009, 10:9-16; EX1062, ¶98. A POSA in the field of pharmaceutical dosage form development is motivated to pursue better physicochemical properties, including solubility, stability, and bioavailability. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364–67 (Fed. Cir. 2007) (optimization for improved physicochemical properties, including bioavailability-related properties, is an obvious target for the skilled artisan). While Gwozdz focused on improving solubility of drugs with solubility issues (primarily by the use of solvent systems containing alcohols in combination with tocopherol compounds), a POSA would have nonetheless been motivated to look to additional strategies to modify the Gwozdz formulations to

increase absorption and bioavailability, *e.g.*, by incorporating an absorption enhancer. Pet., 27-28; EX1062, ¶98-100, 104-110. Meezan provides this specific guidance, disclosing the inclusion of absorption enhancers to enhance bioavailability. *Id*. Consequently, a motivation existed to modify Gwozdz with Meezan.

This same argument was asserted by Patent Owner in IPR2019-00451. EX1040, 23-60. The Board rejected it, finding a motivation to modify Gwozdz with the teachings of Meezan (EX1040, 40-44), and should do so here.

(ii) Interactions Between Excipients Do Not Negate Motivation

Patent Owner asserts that there was no motivation to combine Gwozdz and Meezan because the antimicrobial activity of the benzyl alcohol and ethanol components of Gwozdz would be reduced in the presence of a nonionic surfactant like dodecyl maltoside. POR, 34. However, this would not impact a POSA's motivation to include the nonionic surfactant of Meezan (dodecyl maltoside) in the Gwozdz formulation. EX1078, ¶¶30-33.

A POSA would have understood that an intranasal formulation (i.e., a nasal spray) as contemplated by Gwozdz would require a formulation in a final package that has virtually no bacteria present in the formulation. *Id*., ¶31. Consequently, for a one-time use product like a diazepam nasal spray (used for emergency treatment

of seizure), whether or not the antimicrobial properties of ethanol and benzyl alcohol are decreased or inactivated would not be seen as a limitation. *Id*.

Even if a diazepam nasal spray formulation were intended to be used more than once, this would not impact the motivation to combine. A POSA would not expect that the very low concentrations of dodecyl-β-D-maltoside disclosed by Meezan (e.g., 0.25%, 0.375%, and 0.5%) would be sufficient to completely inactivate the antimicrobial properties of the relatively high concentrations of the combination of ethanol and benzyl alcohol utilized in the Gwozdz formulation. *Id.*, ¶32-33.

Once again, this same argument was asserted by Patent Owner in IPR2019-00451, and the Board again rejected this argument, finding that any decrease in antimicrobial activity would be irrelevant given the aseptic final packaging of the benzodiazepine nasal spray, as well as small amount of nonionic surfactant being used. EX1040, 48-49.

Patent Owner also appears to argue that, because tocopherols were known to be generally unstable and sensitive to degradation, a POSA would use caution in modifying the tocopherol-containing formulation of Gwozdz. POR, 35. But this argument is undercut by the very disclosure of Gwozdz, teaching formulations containing one or more tocopherols and one or more alcohols. EX1009, 4:13-17. Additionally, Gwozdz expressly teaches that additional pharmaceutically acceptable

additives can be added to the solution. EX1009, 10:9-16. Thus, based on the express teachings of Gwozdz, the alleged instability and sensitivity of tocopherols would not impact the motivation to combine Gwozdz and Meezan.

(iii) The Absence of "Penetration Enhancer" in Gwozdz Does Not Defeat the Motivation to Combine

Patent Owner asserts that (1) the disclosure of "penetration enhancer" in Gwozdz (which Patent Owner argues is not supported by Gwozdz-Provisional and is not prior art) is the sole basis for the motivation to combine; and (2) the remaining disclosure in Gwozdz related to the inclusion of "other pharmaceutically acceptable additives" is not sufficient to support the motivation to combine. POR, 35-36. Both of these arguments fail.

Even assuming, *arguendo*, that Gwozdz's "penetration enhancers" language lacks provisional support under Section 102(e), that does not undermine the well-established motivation to combine Gwozdz and Meezan established by Petitioner. In particular, Petitioner has established a motivation to combine based on at least (1) the known water solubility issues associated with diazepam, limiting delivery of sufficient amount of drug to the desired tissue (Pet., 25-27; EX1062 ¶¶95-97); (2) Meezan's teachings that alkyl glycosides increase bioavailability for nasal administration (Pet., 27, 30-32; EX1062, ¶¶103-107); and (3) Meezan's alkyl glycosides being compatible with non-aqueous solvent systems, such as those

disclosed in Gwozdz (Pet., 32; EX1062, ¶¶108-110). None of these rationales rely on, or cite to, Gwozdz's discussion of "penetration enhancers," and the motivation to combine is established independent of this disclosure. Indeed, in its Institution Decision in this proceeding, the Board agreed. Paper 13, 19-20.

Additionally, Patent Owner fails to consider the full scope of Gwozdz's disclosure. Gwozdz states that the pharmaceutical compositions may contain "other pharmaceutically acceptable additives" including "acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and ***wetting*** or other biocompatible ***materials***" to improve the efficacy. Pet., 26-27; EX1009, 10:9-16; EX1062, ¶98. Although Patent Owner asserts that the "penetration enhancer" term is not supported by the Gwozdz-Provisional, the "wetting…material" term is explicitly recited in the text of the Gwozdz-Provisional. *See* POR, 17 (chart highlighting language in Gwozdz-Provisional and Gwozdz, including the phrase "wetting or other biocompatible materials" present in both disclosures); EX1064, 10:10-17. Additionally, Meezan states that the absorption enhancers described therein are surfactants, and that "[t]he term 'surfactant' is any surface active agent that modifies interfacial tension of water…Broadly, the group includes soaps, detergents, emulsifiers, dispersing and ***wetting agents***, and several groups of antiseptics." EX1010, ¶0053. Consequently,

Gwozdz's disclosure of the inclusion of a "pharmaceutically acceptable additive," including a "wetting material" further supports the motivation to combine the teachings of Gwozdz and Meezan, as laid out in the Petition and the supporting declaration of Dr. Donovan. Pet., 26-27; EX1062, ¶98; EX1078 ¶¶18-29.

Further, Patent Owner argues that, because Petitioner has allegedly advocated that the claims be construed to exclude all water, a POSA would be dissuaded from these teachings because the "other pharmaceutically acceptable additives" language is in a portion of the Gwozdz specification discussing injectable solutions, which may include added saline or water. POR, 36-37. However, as noted *supra* Section II(F)(1), nowhere in Gwozdz does it state that water is a required component of the formulation, and Gwozdz explicitly clarifies that formulations suitable for parenteral (i.e., injection) administration can be aqueous or ***non-aqueous***. EX1009, 11:17-18. Thus, Gwozdz's disclosure regarding "other pharmaceutically acceptable additives" is not confined to water-containing formulations.

Patent Owner also argues that Gwozdz's discussion of the inclusion of "other pharmaceutically acceptable additives" is not for nasal formulations specifically, and therefore cannot support the motivation to combine. POR, 37. However, Patent Owner's position again ignores the full disclosure of Gwozdz. A reference may be relied upon for all that it would have reasonably suggested to a POSA. *Merck & Co v. Biocraft Labs*., 874 F.2d 804, 807 (Fed. Cir. 1989). Gwozdz discloses that "[the]

pharmaceutical compositions of the present invention can be administered by any of the following nonlimiting exemplary routes," including intranasal administration. EX1009, 9:2-9. Even if Gwozdz discusses "pharmaceutically acceptable additives" in the section focused on injectables, that disclosure is part of the reference's overall teaching, and is understood to apply across the various nonlimiting routes of administration, including intranasal.

(iv) Meezan is Not Limited to Large Molecule Drugs and Motivation Existed to Combine Meezan with Tocopherol/Alcohol Carriers

Patent Owner asserts that, even if a motivation existed to modify Gwozdz, there was no motivation to modify with the teachings of Meezan. POR, 38. Patent Owner asserts that (1) Meezan is directed to large molecules, and, consequently, there would be no motivation to apply those teachings to small molecule drugs like benzodiazepines (POR, 38-39); and (2) Meezan does not teach compatibility with tocopherols and tocopherol/alcohol carriers (POR, 40-41). But these arguments fail, as they ignore the express teachings of Meezan and Gwozdz, and fail to give consideration to the knowledge of a POSA.

Addressing the issue of small vs. large molecule drug compounds, Meezan teaches that the alkyl glycosides will increase bioavailability of small molecules (less than 1.5 kDaltons). EX1010, ¶130. Diazepam (having a molecular weight of 284.74) is clearly within this range. Pet., 31; EX1062, ¶107. Additionally, Meezan

states that the alkyl glycosides can be used with small organic molecules (EX1010, ¶0130) and anti-seizure agents (EX1010, ¶0052), which encompasses the class of benzodiazepines. EX1062, ¶106-107. Patent Owner further asserts that, because a small molecule drug would already be expected to absorb easily, a further absorption enhancer would be superfluous. POR, 40. But again, this overlooks Meezan's express teachings that the alkyl glycosides described therein "increas[e] absorption of a low molecular weight compound…via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route…. Such low molecular weight compounds include but are not limited to… a small organic molecule." EX1010, ¶0008. Thus, Patent Owner's tenuous position is contrary to the express teachings of Meezan.

Further, Meezan's alkyl glycosides are not limited to water soluble drugs, and may be used in either 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,....

EX1010, ¶74. Meezan discloses that the alkyl glycoside system can be used with "non-aqueous" carriers, which may include mixtures of alcohols (such as benzyl

alcohol) and oleaginous components. While Meezan does not expressly reference "tocopherols" as a potential oil, a non-aqueous carrier containing a mixture of alcoholic and oleaginous components encompasses the Gwozdz carrier containing tocopherol, ethanol, and benzyl alcohol. And, as noted previously, Gwozdz discloses the addition of "pharmaceutically acceptable additives" including "wetting" agents (EX1009, 10:9-16), which Meezan admits is a term that encompasses the alkyl glycoside surfactants. EX1010, ¶0053. Thus, a POSA was motivated to utilize Meezan's alkyl glycosides in non-aqueous carriers containing tocopherols or tocopherols and alcohols.

This same argument was asserted by Patent Owner in IPR2019-00451. EX1040, 23-60. The Board rejected it, finding that Meezan was not limited to water soluble drugs or aqueous carriers (EX1040, 45-47), and should do so here.

3. A POSA Was Motivated to Utilize Dodecyl Maltoside

Patent Owner argues that, even if Gwozdz and Meezan were combined, a POSA still would not have been motivated to use dodecyl maltoside. POR 42-45. Meezan's disclosure of only a few preferred alkyl glycosides defeats that argument.

Meezan identifies three preferred alkyl glycosides: dodecyl maltoside (DDM), tridecyl maltoside, and tetradecyl maltoside (TDM). EX1010, ¶0157. Its examples then focus on only two of them: DDM and TDM. *Id*., ¶¶ 0146-0172.

A POSA need not be steered to only the single "most preferred" option. Where the art discloses a small set of known alternatives, one option's being preferred, optimal, or even somewhat better does not teach away from the others or eliminate motivation to use them. *See In re Fulton*, 391 F.3d 1195, 1200–01 (Fed. Cir. 2004); *In re Gurley*, 27 F.3d 551, 553–54 (Fed. Cir. 1994); *Uber Techs., Inc. v. X One, Inc.*, 957 F.3d 1334, 1340–42 (Fed. Cir. 2020). Meezan does not suggest that DDM is disfavored. To the contrary, it identifies DDM as one of the preferred "more effective" alkyl glycosides. With only two preferred exemplary alkyl glycosides—TDM and DDM—a POSA would have been motivated to use DDM. EX1062 ¶¶ 93-94, 98-99, 104-110; EX1078, ¶¶ 27-29.

Patent Owner argues that DDM was ineffective, but that mischaracterizes the evidence. Testing of DDM at concentrations of 0.25%, 0.375%, and 0.5% all demonstrated a dramatic improvement in efficacy. EX1078, ¶28. A POSA therefore would have been motivated to use DDM at concentrations of 0.25%-0.5%. EX1062 ¶¶ 93-94, 98-99, 104-110; EX1078, ¶¶ 27-29.

III. CONCLUSION

Claims 17 and 22 of the '546 patent are not patentable for the reasons provided in the Petition and further addressed in this Reply.

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CERTIFICATION OF WORD COUNT

Petitioner certifies that the word count in this Reply, including all footnotes, is 5,581 words as counted by the word-processing program (Microsoft Word for Office 365) used to generate this Reply, where such word count excludes the table of contents, mandatory notices, certificate of service, list of exhibits, and this certificate of word count. This Reply is in compliance with the 5,600 word limit set forth in 37 C.F.R. § 42.24(c)(1).

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that a complete copy of the forgoing document and all associated exhibits are being served via electronic mail on March 31, 2026 upon the following:

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