

21-1038

**United States Court of Appeals
for the Federal Circuit**

NEURELIS, INC.,
Appellant,

v.

AQUESTIVE THERAPEUTICS, INC.,
Appellee.

*Appeal from the United States Patent and Trademark Office, Patent
Trial and Appeal Board in Inter Partes Review No. IPR2019-00451*

**CORRECTED BRIEF FOR APPELLEE
AQUESTIVE THERAPEUTICS, INC.**

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REPRESENTATIVE CLAIMS

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.

27. The method of claim 1, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

[inside cover]

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel for Appellee Aquestive Therapeutics, Inc. certifies that:

1. The full name of every entity represented by me is: Aquestive Therapeutics, Inc.
2. The full names of all real parties in interest for the entity, not including the entity, are: None.
3. The full names of all parent corporations for the entity and all publicly held companies that own 10% or more stock in the entity is: None.
4. The names of all law firms, partners, and associates that (a) appeared for the entity in the originating agency or (b) are expected to appear in this court for the entity, not including those who have already entered an appearance in this court, are James F. Harrington and Mathew Solow, both of Hoffmann & Baron, LLP.
5. The case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeals is: None.
6. Information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees) is: None.

Date: March 31, 2021

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STATEMENT OF RELATED CASES

This *inter partes* review of U.S. Patent No. 9,763,876 was not previously before this or any other appellate court. No other case is known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal.

JURISDICTIONAL STATEMENT

This appeal arises from an *inter partes* review proceeding, Case No. IPR2019-00451, filed by Aquestive Therapeutics, Inc. challenging all claims of Neurelis, Inc.'s U.S. Patent No. 9,763,876 pursuant to 35 U.S.C. § 6 and 35 U.S.C. §§ 311 *et seq.* Pursuant to 35 U.S.C. § 318(a), the Patent Trial and Appeal Board of the U.S. Patent and Trademark Office issued a Final Written Decision. This Court has jurisdiction for direct review of the Final Written Decision under 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. §§ 141(c), 319.

STATEMENT OF THE ISSUES

1. Whether substantial evidence supports the PTAB's finding that U.S. Provisional Patent Application No. 61/040,558, filed March 28, 2008 ("the '558 provisional") fails to provide adequate written description in accordance with 35 U.S.C. § 112, for the alkyl glycosides, in general, and dodecyl maltoside, specifically, limitations recited in the claims of U.S. Patent No. 9,763,876 ("the '876 patent"), so that the '876 patent is not entitled to the benefit of the filing date of the '558 provisional, and thus Gwozdz¹ and Cartt² are prior art under 35 U.S.C. § 102(e)(1).

2. Whether substantial evidence supports the PTAB's finding that claims 1-16 and 24-36 of the '876 patent are obvious over the combination of Gwozdz and Meezan³.

3. Whether substantial evidence supports the PTAB's finding that claims 17-23 of the '876 patent are obvious over the combination of Gwozdz, Meezan³ and Cartt².

¹ WO 2009/120933 A2, entitled *Pharmaceutical Solutions and Methods for Solubilizing Therapeutic Agents*, published October 1, 2009 ("Gwozdz"). Appx8018-8033.

² US 2008/0279784, *Nasal Administration of Benzodiazepines*, Serial No. 12/116,842, published November 13, 2008 ("Cartt²784"). Appx8034-8072.

³ US 2006/0046962, *Absorption Enhancers for Drug Administration*, Serial No. 11/127,786, published March 2, 2006 ("Meezan³962"). Appx7946-7967

INTRODUCTION

This case relates to nasally administered pharmaceutical solutions containing benzodiazepine drugs and Neurelis, Inc.’s (“Neurelis”) patent covering the use of the solution to treat any patient with a disorder treatable with a benzodiazepine drug.

In August 2020, the Patent Trial and Appeal Board (“PTAB” or “Board”) issued a Final Written Decision (“Decision”) holding claims 1-36 of the ‘876 patent unpatentable. Appx1-70. Substantial evidence supports the PTAB’s findings that the ‘558 provisional fails to provide adequate written description support for the “alkyl glycoside” limitation recited in each of the challenged claims. Relying on the testimony of Aquestive Therapeutics, Inc.’s (“Aquestive”) experts, Dr. Wermeling and Dr. Peppas, the PTAB determined that the ‘558 provisional even with the incorporation of about 150 biological detergents listed in the SIGMA catalog did not provide the required adequate written description.

The PTAB noted that biological detergents constituted just one small subset of the numerous enhancing agent classes discussed in the ‘558 provisional, and that of the about 150 biological detergents, only 12 were alkyl glycosides. The PTAB found that the disclosure of the various acceptable enhancers in the ‘558 provisional, including the 150 biological detergents listed in the SIGMA catalog failed to provide adequate written description support for claims 1-36 of the ‘876

patent. Appx14-Appx19; Appx23; *see, e.g.*, Appx9164 (¶68); Appx10572-10576 (¶¶171-177). Lacking sufficient written description for the “alkyl glycoside” limitation, the PTAB determined that Gwozdz and Cartt’784 are Section 102(e)(1) prior art. Appx23.

The PTAB’s finding of inadequate written description is supported by substantial evidence, and has forced Neurelis to attempt to recast the PTAB’s Decision as somehow evidencing a failure by the Board to consider the 150 biological detergents listed in the SIGMA catalog as being incorporated into the ‘558 provisional. The reason behind Neurelis’ attempt to reframe the Decision’s written description analysis into a “failure to incorporate” dispute is evident - standard of review. Compliance with the written description requirement of Section 112 is a question of fact that is reviewed for substantial evidence. In contrast, whether and to what extent material is incorporated by reference (an issue not on appeal) is a question of law which this Court reviews *de novo*. At bottom, the PTAB’s written description analysis was correctly predicated on the incorporation of the SIGMA catalog’s biological detergents into the ‘558 provisional. *See, e.g.*, Appx19, n.7.

The PTAB carefully detailed support for the factual underpinnings of its obviousness findings with citations to documentary evidence of record, including the testimony of Aquestive’s experts (Dr. Peppas and Dr. Wermeling) and

Neurelis' expert (Dr. Gizurarson) and the logical conclusions that could be drawn from that evidence were clearly explained. The PTAB found that all of the cited prior art dealt with solving problems in connection with optimizing the administration of drugs at the nasal mucosa so as to, *inter alia*, increase the bioavailability of the drug. The PTAB also found that the '876 patent claim limitations lack criticality and that there was no evidence of unexpected results.

Further, Neurelis' reliance on secondary considerations such as long-felt need is insufficient due to: (i) an absence of any nexus; and (ii) the presence of methods and products fulfilling the alleged long-felt need, and such reliance is therefore inadequate to overcome the substantial evidence of primary considerations rendering claims 1-36 obvious.

Collectively, this provides more than sufficient substantial evidence to support the PTAB's findings relating to the obviousness of the claims of the '876 patent, and that Aquestive has demonstrated by a preponderance of evidence that claims 1-36 are unpatentable under 35 U.S.C. § 103(a).

STATEMENT OF THE CASE

The PTAB determined that substantial evidence supported the finding that all claims of the ‘876 patent unpatentable as obvious in view of Gwozdz, Meezan‘962 and Cartt‘784. Appx25-60; Appx68-69. Gwozdz and Cartt‘784 are Section 102(e)(1) prior art because of the ‘558 provisional’s failure to comply with the written description requirement for the ‘876 patent’s “alkyl glycoside” limitation so that the ‘876 patent is not entitled to the effective filing date of its earliest application.

A. The ‘876 Patent And Technology

The claims of the ‘876 patent are directed to methods of treating any disorder treatable with any benzodiazepine drug by administering the drug in a solution to the nasal mucosa. Appx84 (9:14-17). Benzodiazepines share similar neuropharmacologic properties beyond only treating seizures, including anxiety reduction, sedation, sleep induction and muscle relaxation. Appx11003. For example, lorazepam can be used as a sedative and to treat anxiety. Appx10592 (¶211).

Claim 1, the only independent claim, 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.

Appx111.

All claims of the '876 patent require that the solution "consist[] of" four components, namely (1) a benzodiazepine (*e.g.*, diazepam); (2) one or more natural or synthetic tocopherols or tocotrienols (*e.g.*, vitamin E); (3) ethanol and benzyl alcohol; and (4) an alkyl glycoside (*e.g.*, dodecyl maltoside). Appx111-112 (63:25-65:30). Some dependent claims vary the proportions of the components or further identify the component (diazepam, vitamin E or dodecyl maltoside). Some dependent claims also provide dose, dosing, formulation (sprayable solutions) and bioavailability limitations. Appx111-112.

Nasal administration of drugs involves providing the drug at the nasal mucosa in sufficient concentration, with, if necessary, an additional mucosal penetration/absorption enhancer, so as to provide sufficient bioavailability for the drug to be effective. If a portion of the drug is not absorbed in the nasal cavity, it can be absorbed in the gut after swallowing, *i.e.*, nasal oral absorption or nas-oral absorption. Appx10551-10553 (¶¶123-126); Appx10922-10923 (¶¶58-59). Moreover, because of nas-oral absorption, the overflow from a diazepam solution administered to the nose would be absorbed in the gut resulting in about 100%

bioavailability of the diazepam. See Appx10510 (¶65, n.1). Diazepam, *e.g.*, has a 100% absolute bioavailability. Appx10503 (¶55); Appx9891; see Appx9886-9890; Appx9892-9893.

B. There Is No Written Description Support For The Alkyl Glycoside Limitation

Suitable alkyl glycosides can act as penetration enhancers when in contact with the nasal mucosa, thereby increasing the absorption of the benzodiazepine through the mucosa. Appx96 (34:2–19); see *infra*, at 13, 15. All claims require an alkyl glycoside, with dependent claims 27-28 and 30-33 specifically requiring that the alkyl glycoside be “dodecyl maltoside”. Appx111-112 (63:25-65:29).

It is not disputed that the alkyl glycoside limitation is one of the “essential limitations” that must be clearly supported, in accordance with 35 U.S.C. § 112, 1st paragraph, in every priority application in the chain leading up to the ‘876 patent. See, *e.g.*, *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002) (“for the non-provisional utility application to be afforded the priority date of the provisional application, . . . the written description of the provisional must adequately support the claims of the non-provisional application”). However, before the PTAB, Neurelis failed to provide any support evidencing that each application in the chain complied with the written description requirements of Section 112, or that the ‘558 provisional itself contains the

necessary written description for the recited alkyl glycosides and dodecyl maltoside limitations.

Paragraphs 150-152 of the '558 provisional, reproduced below, describe and disclose a host of acceptable enhancers suitable for increasing absorption across the mucosa and/or increasing bioavailability, including two “preferred” enhancers - lysophospholipids and acyl carnitines. Appx 7814; *see, e.g.*, Appx16; Appx10572 (¶¶171, 173).

[150] In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer. The term “enhancer”, means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an “enhancer” can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

[151] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% w/v.

[152] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), 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). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.

Appx7814 (¶¶150-152) (emphasis supplied); *see* Appx10572-10576 (¶¶171-177); Appx9164 (¶68). Paragraph 152 incorporates the biological detergents listed in six

pages of the SIGMA catalog. Appx10705-10710. Included in those six pages are about 150 biological detergents, in four categories: (i) anionic, (ii) cationic, (iii) zwitterionic (amphoteric) and (iv) non-ionic (polar). Among the host of biological detergents listed, 100 are non-ionic of which only 12 are alkyl glycosides.

Appx10705-10710; Appx10574-10757 (¶175); *see* Appx10572-10576 (¶¶171-177).

Based on the substantial evidence presented, the PTAB concluded:

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.

Appx19. Additionally, the Board concluded that nothing in the '558 provisional would have directed a POSA to the nonionic biological detergents listed in the SIGMA catalog. Appx20 (“nothing in the '558 provisional's disclosure restricts the ‘biological detergents’ listed in the SIGMA catalog to non-ionic detergents”).

Finally, the PTAB found that “[e]ven 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.” Appx20, n.8; *see* Appx10575-10576 (¶176); *see also* Appx9164 (¶68); Appx10574-10575 (¶¶173-175).

Consequently, because the ‘558 provisional does not provide adequate Section 112 written description for the alkyl glycoside limitation, the ‘876 patent claims are not entitled to the ‘558 provisional’s filing date; therefore, Gwozdz and Cartt‘784 are Section 102(e)(1) prior art.

C. All Claims Of The ‘876 Patent Are Obvious

Gwozdz, Meezan‘962 and Cartt‘784 teach or suggest each limitation of the claims of the ‘876 patent. After weighing the evidence presented and considering the arguments advanced by the parties, the PTAB correctly found claims 1-16 and 24-36 of the ‘876 patent obvious over the combination of Gwozdz and Meezan‘962, and claims 17-23 of the ‘876 patent obvious over the combination of Gwozdz, Meezan‘962 and Cartt‘784.

Notably, Neurelis failed to demonstrate any criticality or any unexpected results associated with, *inter alia*, the amounts of tocopherols/tocotrienols, ethanol and benzyl alcohol and alkyl glycosides. *See, e.g.*, Appx27; Appx29-30; Appx32; Appx34-35; Appx47-48; *see* Appx9155-9162 (¶¶49-63); Appx10577-10590 (¶¶178-207).

1. Gwozdz teaches the first three of the four “consisting of” components of all the claims of the ‘876 patent, namely (i) a benzodiazepine; (ii) one or more natural or synthetic tocopherols or tocotrienols and (iii) ethanol and benzyl alcohol

Gwozdz, Appx 8018-8033, teaches increasing the solubility and bioavailability of drugs such as benzodiazepines, for use in nasal administration, by forming a solution of, *e.g.*, benzodiazepine (including diazepam), tocopherols/tocotrienols (including vitamin E), ethanol and benzyl alcohol. Appx23-28; Appx9228-9231 (¶¶192-202); Appx9287 (¶372); Appx9288 (¶375). Thus, Gwozdz teaches the first three of the four “consisting of” components of all the claims of the ‘876 patent, namely (1) a benzodiazepine (*e.g.*, diazepam); (2) one or more natural or synthetic tocopherols or tocotrienols (*e.g.*, vitamin E) and (3) ethanol and benzyl alcohol. *Id.*

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.” Appx8022 (4:14-17); *see* Appx9228-9231 (¶¶192-202). Gwozdz’s solution is described as being used for solubilizing hydrophobic or lipophilic therapeutic agents in order to provide increased bioavailability. Appx23-24; Appx8022 (4:29-33); Appx8025 (7:3-8). The therapeutic agents disclosed in Gwozdz include benzodiazepines, including diazepam. Appx23; *see* Appx8026

(8:6-10). Gwozdz also 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.” Appx8023 (5:2-7). Gwozdz further 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.” Appx8024-8025 (6:29-7:2). Additionally, Gwozdz discloses methods of treatment using 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.” Appx8027 (9:19-21).

Examples of alcohols for use in the compositions described in Gwozdz include “ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combination thereof.” Appx8024 (6:16-19); *see* Appx24. Gwozdz also 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).” Appx8022 (4:17-21); *see* Appx24. Gwozdz further states that ethanol can constitute 1%-40% or 10%-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. Appx8025 (7:20-28); *see* Appx24.

2. Meezan‘962 describes the use of alkyl glycosides, the last of the four “consisting of” components of all the claims of the ‘876 patent

Meezan‘962, Appx7946-7967, teaches using an alkyl glycoside, including dodecyl maltoside, as an absorption enhancer in a solution to improve the bioavailability of drug molecules, including small organic molecules and anti-seizure agents, for use in nasal administration. Appx25; Appx7950-7955 (¶¶4, 8, 12-13, 36, 52, 58, 63, 70, 73); Appx9238-9239 (¶¶222-223). Supported by the testimony of Aquestive’s expert, the PTAB found that Meezan‘962’s reference to “small organic molecules and anti-seizure agents” encompassed benzodiazepines, which includes diazepam. *See* Appx46; Appx9238-9239 (¶¶222-223); *see also* Appx10565 (¶150). Thus, Meezan‘962 teaches the fourth of the “consisting of” components, namely an alkyl glycoside (*e.g.*, dodecyl maltoside). *See* Appx9238-9239 (¶¶222-224); Appx9241-9247 (¶¶227, 229-237).

Meezan‘962 also provides that the 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.” Appx7955 (¶70). Finally, 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.”

Appx7953-7954 (¶¶ 56, 58, 61); Appx7957 (¶92); Appx7962-7963 (¶¶150-151, 155-159); *see* Appx9286 (¶¶ 365-367).

3. Cartt‘784 teaches the dose, dose volume and dosing regimen limitations of the ‘876 patent

Cartt‘784, Appx8034-8072, teaches dosing amounts, volumes, regimens for nasal administration of benzodiazepines, and methods for increasing bioavailability by using absorption enhancers. *See, e.g.*, Appx8036(¶¶14-19); Appx8038 (¶31); Appx8040-8042 (¶¶33-36); Appx8043 (¶39), Appx8045-8046 (¶42); *see* Appx55.

Cartt‘784 also describes, *inter alia*, liquid nasal sprays for the administration of benzodiazepines which may be formed from solutions containing vitamin E, ethanol, and benzyl alcohol, all as disclosed in Gwozdz, and the use of alkyl glycosides, as disclosed in Meezan‘962. Thus, Cartt‘784 teaches dose and dosing claim limitations suitable for use with Gwozdz and Meezan‘962. *See* Appx9248-9253 (¶¶243-252).

In particular, 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.” Appx8037 (¶28). While generally directed to intranasal particulate formulations, Cartt‘784 does disclose that the formulations can be liquid nasal sprays and that the drug may be in solution. Appx8036 (¶¶138-144); *see* Appx9251 (¶247); *see* Appx55. Cartt‘784

provides a list of solvents including ethanol and benzyl alcohol, as well as nonionic surfactants including dodecyl maltoside. Appx8048-8050 (¶¶47-48); Appx8061 (¶130); Appx8067 (¶182); *see* Appx9251 (¶¶248-249); Appx55.

As referred to above, Cartt‘784 teaches the use of absorption enhancers to increase bioavailability. Appx8060 (¶124); Appx9250-9251 (¶250). In fact, Cartt‘784 expressly discloses numerous alkyl glycosides, including n-dodecyl β - D-maltoside (a dodecyl maltoside). Appx8060-8061 (¶¶128-129); *see* Appx55; Appx9252 (¶251); *see also infra*, at 60-61.

D. In Addition To Gwozdz, Meezan‘962 And Cartt‘784, The Prior Art Contains Numerous Examples Of Intranasal Administration Of Benzodiazepines

The prior art is replete with numerous disclosures of nasally administered benzodiazepines, including for the treatment of seizures. *See, e.g.*, Appx10144-10149, Appx10214-10259; *see* Appx10522-10524 (¶¶82-87); Appx53-54.

Some prior art methods for the intranasal administration of benzodiazepines included spraying off-the-shelf intravenous (“IV”) preparations of benzodiazepines into the nose by using a mucosal atomization device (“MAD”). Appx10260-10266. A picture of a mucosal atomization device is reproduced below.



Appx10262; Appx10512 (¶68).

One prior art example is the intranasal administration of a lorazepam IV solution drawn into a syringe attached to a mucosal atomization device and then squirted rapidly into a nostril. Appx10253; Appx10524 (¶87).

Another example involves the directions given to Florida EMS workers at least as early as 2005 (Appx9691-9694) to use the intranasal administration of benzodiazepines to treat, *e.g.*, seizures, by using a MAD nasal sprayer to administer the IV solutions. See Appx10525-10526 (¶88); Appx10542-10544 (¶¶111-112). The instructions for treating seizure disorders directed the intranasal use of any of three benzodiazepines, Diazepam (Valium®), or Lorazepam (Ativan®) or Midazolam (Versed®), specifically directing that the dose be the

same for IV and intranasal. “Intranasal administration of benzodiazepines requires the use of a mucosal atomization device (same as IV dose)”. Appx9779; see Appx9720. It is noteworthy that Diazepam (Valium®) IV solutions contain, *inter alia*, diazepam, ethyl alcohol and benzyl alcohol. Appx9587; see Appx10525-10527 (¶88).

E. The *Inter Partes* Review Proceedings

1. Aquestive’s Petition

Aquestive’s Petition asserted that (1) claims 1-16 and 24-36 of the ‘876 patent are unpatentable based on Gwozdz and Meezan’962; and (2) claims 17-23 are unpatentable based on Gwozdz, Meezan’962 and Cartt’784. *See generally* Appx210-211; Appx241; Appx269-297. The PTAB instituted *inter partes* review on both grounds. *See* Appx388-389.

The foundation of Aquestive’s unpatentability argument is that Gwozdz and Cartt’784, with effective filing dates of March 28, 2008 and May 7, 2008, respectively, are prior art pursuant to Section 102(e)(1) because the effective filing date of the ‘876 patent is no earlier than March 27, 2009. Appx211-212; *see* Appx13-17. Neurelis does not dispute that: (1) Gwozdz and Cartt’784 are entitled to the above filing dates; (2) absent adequate written description support for the alkyl glycoside limitations in the ‘558 provisional, the ‘876 patent’s effective filing

date is no earlier than March 27, 2009; and (3) Meezan'962 is prior art under Section 102(b).

In the Petition, Aquestive maintained that Gwozdz was entitled to the effective filing date of its provisional. Appx211-212; see Appx13-14. Then, Aquestive and its expert Dr. Peppas noted that the '558 provisional failed to provide sufficient written description support for the "alkyl glycoside" limitation recited in all the challenged claims, which included the "dodecyl maltoside" limitation found in dependent claims 27-28 and 30-33: Appx225; see Appx9164 (¶68) ("the '558 Provisional does not mention, disclose, or provide written support for alkyl glycosides (or any particular species thereof, e.g., dodecyl maltoside."); see Appx220-223; Appx9142-9144 (¶29); Appx9162-9165 (¶¶64-70).

2. Patent Owner's Preliminary Response

Neurelis filed a Patent Owner's Preliminary Response attempting to address Aquestive's position that there was insufficient written description in the '558 provisional so that the claims of the '876 patent were not entitled to the filing date of the '558 provisional. Importantly, Neurelis urged that the Petition should be denied because Aquestive did not expressly discuss the SIGMA catalog identified in paragraph 152 of the '558 provisional. Appx342. Relying on nothing more than attorney argument, Neurelis argued that the SIGMA catalog "would have

reasonably conveyed to the artisan that the inventor had possession at that time of the claimed alkyl glycosides.” Appx343.

3. PTAB’s Decision To Institute, Neurelis’ Requests For Rehearing And Precedential Opinion Panel Review

In its Decision to Institute, the PTAB found Neurelis’ arguments unpersuasive and instituted *inter partes* review of claims 1-36 of the ‘876 patent. *See, e.g.*, Appx388-389. In particular, the PTAB rejected Neurelis’ written description argument and concluded, after discussing the parties’ arguments and evidence regarding alkyl glycosides, generally, and dodecyl maltoside, specifically, that there was insufficient written description support in the ‘558 provisional for the “alkyl glycosides” limitations recited in the claims of the ‘876 patent. *See* Appx354-358. The PTAB also stated that 37 C.F.R. §1.57 (“Rule 57”) would also preclude the ‘876 patent from incorporating the “alkyl glycoside” essential limitation, if present, from the SIGMA catalog. Appx357-358.

Dissatisfied, Neurelis requested rehearing of the Decision to Institute arguing, *inter alia*, the PTAB had erred because its decision to institute was allegedly predicated on the Board’s application of Rule 57.

In denying Neurelis’ Request for Rehearing of its Decision to Institute, the PTAB reviewed the parties’ respective burdens of production and persuasion

associated with a priority dispute. Appx457-460. Specifically, the PTAB observed that after Aquestive satisfied its initial burden showing that the ‘558 provisional did not provide adequate written description support for the “alkyl glycoside” limitations, the burden shifted to Neurelis. Appx458. At that point, Neurelis was required to produce evidence demonstrating that the ‘558 provisional provided the necessary written description support in order to eliminate Gwozdz (and Cart’784) as prior art. Appx457-459; *see Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1380 (Fed. Cir. 2015).

However, the PTAB found that Neurelis had limited its arguments to attacking the alleged deficiencies in Aquestive’s showing of inadequate written disclosure in the ‘558 provisional for the claimed alkyl glycoside limitations, and had not provided any “analysis demonstrating that every patent application along the priority chain conveys with reasonable clarity to those skilled in the art that the inventors were in possession of each limitation of each of the challenged claims, as well as the claimed invention as a whole”. Appx458-460. The Board made clear that its comments regarding Rule 57 were not the basis for institution:

Given Patent Owner’s failure to satisfy its burden of production to show that all of the ‘876 patent claims are supported throughout the priority chain, we need not address Patent Owner’s additional arguments regarding the application of 37 C.F.R. § 1.57 at this time.

Appx460.

After its request for rehearing was denied (Appx455-461), Neurelis requested Precedential Opinion Panel (“POP”) review of the Rule 57 issue and of whether the PTAB improperly shifted the burden of proof regarding priority. Neurelis’ request for POP review was also denied. Appx518-519.

4. Neurelis’ Patent Owner’s Response

Neurelis’ Patent Owner’s Response offered Neurelis an opportunity to address the PTAB’s determination of insufficient written description. Neurelis argued: (1) Aquestive failed to expressly address the SIGMA catalog in its Petition; (2) that the ‘558 provisional’s reference to the SIGMA catalog and its list of about 150 biological detergents, including 12 alkyl glycosides, provided sufficient written description support; and (3) the PTAB improperly relied on Rule 57 in instituting review.

Neurelis also argued that a POSA would not have been motivated to combine Gwozdz, Meezan’962 and Cartt’784, and that long-felt need overcame any *prima facie* case of obviousness.

5. Aquestive's Reply

In support of its Reply, Aquestive relied on Dr. Peppas' original declaration, as well as the declaration of Dr. Wermeling.⁴ Dr. Wermeling's declaration focused on, *inter alia*, his first-hand experience working with benzodiazepines and the development of intranasal sprays, *i.e.*, an area in which Neurelis alleged that Dr. Peppas had insufficient first-hand experience. *See, e.g.*, Appx10492-10494 (¶¶34-35, ¶38); Appx10495 (¶40); Appx10530 (¶93); Appx10537-10540 (¶¶102-107).

Through, *inter alia*, the expert testimony of Dr. Wermeling, Aquestive refuted and rebutted Neurelis' assertion that the mere appearance of 150 biological detergents in the SIGMA catalog was sufficient to satisfy the requirements of Section 112. Unlike Neurelis' expert Dr. Gizurarson, Dr. Wermeling analyzed the entirety of the '558 provisional's ¶¶150-152's description of acceptable enhancers together with all the 150 biological detergents listed in the SIGMA catalog.

In particular, Dr. Wermeling opined that a POSA would not have understood that the '558 provisional with the SIGMA catalog incorporation provided written

⁴ Aquestive was permitted in its reply to respond to issues addressed not only in Neurelis' response but also those discussed in the PTAB's Decision to Institute, and to submit corresponding rebuttal arguments and evidence. *See* Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019), *available at* <https://www.uspto.gov/TrialPracticeGuideConsolidated>, at 73. Appx61-62, n.13.

description support for alkyl glycosides. Appx10572-10576 (¶¶171-177).

Dr. Wermeling testified that paragraphs 150-152 of the ‘558 provisional generically refer to “absorption enhancers” (*i.e.*, “any material which acts to increase absorption across the mucosa and/or increase bioavailability”) and describe 15 separate classes falling within this broad category of absorption enhancers. Appx10572-10574 (¶¶171-172); *see* Appx7814 (¶¶150-152). Further, Dr. Wermeling observed that the ‘558 provisional refers to both ionic and non-ionic enhancers and expressly states that lysophospholipids and acyl carnitines are “preferred.” Appx10574 (¶173); *see* Appx7814 (¶151). Thus, the other enhancers described and disclosed in the ‘558 provisional, including the 150 listed SIGMA catalog compounds, must be non-preferred enhancers. Appx10575-10576 (¶¶173-175).

Dr. Wermeling concluded:

Again, from reading the ‘588 [*sic*] Provisional (including ¶¶ [150]-[152]) and the Sigma catalogue, it is my opinion that the inventors did not have any particular enhancing agent in mind as part of their invention (other than ¶ [151]’s preference for lysophospholipids and acyl carnitine alternatives). It is my further opinion that a POSA would have understood the ‘588 [*sic*] Provisional application as not disclosing alkyl glycosides.

Appx10576 (¶177).

Consequently, nothing in the ‘558 provisional would have reasonably lead a POSA to any particular sub-class, let alone specific species (such as alkyl glycosides or sub species such as dodecyl maltoside), nor does the ‘558 provisional suggest that alkyl glycosides generally or any alkyl glycoside specifically might be of special interest, or be significant to the claims. *See generally* Appx10572-10576 (¶¶171-177).

6. Neurelis’ Sur-reply

Neurelis’ Sur-reply afforded yet another opportunity to address its failure to provide evidence supporting its priority claim.⁵ Instead, Neurelis again tried to improperly shift the burden to Aquestive, arguing that Aquestive had the burden not only to identify that the ‘558 provisional lacked adequate support for the alkyl glycoside limitations pursuant to §112 (which Aquestive met), but also that Aquestive had to go into detail and prove that alkyl glycosides as claimed in the ‘876 patent were not disclosed in paragraphs 150-152 of the ‘558 provisional, which at that stage was Neurelis’ burden. Appx643-646.

⁵ Any suggestion that Neurelis’ procedural rights were violated is baseless. *See* Blue Br. 31-34. For example, in a conference with the PTAB, Neurelis argued, *inter alia*, that Dr. Wermeling’s entire declaration was new evidence. In response the Board increased the word count of Neurelis’ Sur-reply by 1000 words to address any complaints Neurelis had with Dr. Wermeling’s Declaration. Appx11141 (19:14-18); Appx11146 (24:4-6). Additionally, Neurelis took Dr. Wermeling’s deposition, relied on it in its Sur-reply, and had the opportunity to address any purported new issues at trial.

7. The PTAB's Final Written Decision

After fully considering the evidence proffered by the parties, including the testimony of the parties' respective experts, the PTAB rejected Neurelis' arguments and evidence to the contrary, and found that there was substantial evidence demonstrating challenged claims 1-36 to be *prima facie* obviousness.

a. The PTAB's findings of inadequate written description

The PTAB rejected Neurelis' argument that Aquestive failed to meet its burden to establish a lack of written description as "unavailing." Appx20-21. Rather, the PTAB found that Aquestive "clearly challenged the '876 patent priority claim." Appx21. Thus, because Aquestive "satisfied its initial burden on the issue of whether Gwozdz is prior art," the PTAB concluded that Neurelis was required "to produce argument and evidence to the contrary, which it had an opportunity to do during trial," and noted the burden of production shifted to Neurelis to demonstrate "how the written description in the ['558 provisional] supports the challenged claims." Appx21 n.9; Appx22. The same reasoning applied to Cartt'784. Appx23. The PTAB also stated that, even though it was "assuming the material in the SIGMA catalog was properly incorporated by reference," that disclosure "is not sufficient to provide written description support for the 'alkyl glycosides' limitation in the claims." Appx19, n.7. The PTAB also determined

“[t]here 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.” Appx19. Additionally, the PTAB found that the “biological detergents in the SIGMA catalog is just a subset of the numerous possible ‘enhancing agents’ that are discussed in the ‘558 provisional.” Appx19; *see* Appx7814 (¶¶150-152); Appx 10572-10576 (¶¶171-177).

Rejecting Neurelis’ argument that a POSA, faced with the numerous enhancers described in paragraphs 150-152 of the ‘558 provisional, would have focused on the “non-ionic detergents,” the PTAB concluded “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.” Appx20.

b. The PTAB’s Obviousness Findings

Based on the evidence provided by Aquestive, including the testimony of Dr. Peppas, the PTAB found that the combination of Gwozdz and Meezan’962 teaches or suggests every limitation of claim 1 of the ‘876 patent. Appx23-27. For example, Gwozdz discloses a solution and teaches methods of treating a patient with intranasally administered solutions of benzodiazepines, including in order to increase bioavailability. Appx25. Gwozdz also teaches the use of tocopherols or

tocotrienols in amounts of about 30-99% which significantly overlaps with the range of 30-95% recited in claim 1. Appx26.

Again, the PTAB observed there was no evidence of any criticality or unexpected results associated with the claimed amount of tocopherols. Appx26. Next, the PTAB held that Gwozdz teaches the use of ethanol, benzyl alcohol and combinations thereof, and the alcohol (or combinations of alcohols) may be present in amounts of about 1-70%, and ethanol may be present in amounts of 1-40% or 10-30%, again overlapping with the combined amount of alcohols recited in claim 1. Appx26-27. Additionally, the PTAB observed that no evidence was proffered demonstrating any criticality or unexpected results associated with the range of ethanol and benzyl alcohol. Appx27. Finally, the Board concluded that because Meezan'962 discloses the use of alkyl glycosides in pharmaceutical solutions, including nasal sprays, Gwozdz and Meezan'962 teach or suggest each limitation of claim 1. Appx27.

The PTAB next addressed dependent claims 2-16 and 24-36. Appx27-37. The PTAB found that a preponderance of the evidence demonstrates that the cited references collectively disclose or suggest each limitation of claims 2-16 and 24-36. Appx27; Appx37. Notably, based on Neurelis' submissions, the PTAB found that Neurelis "d[id] not present separate arguments for any of the dependent claims." Appx27 (emphasis supplied).

The PTAB concluded that a POSA would have had reason to make the suggested combination of Gwozdz and Meezan'962 with a reasonable expectation of success. Appx37-51. In arriving at its conclusion, the PTAB credited the substantial evidence of Aquestive's experts, Dr. Peppas (Appx9180 (¶103, n.9); Appx9196-9198 (¶¶131-136); Appx9228-9231 (¶¶192-203), and Dr. Wermeling (Appx10554-10567 (¶¶129-156)), over the evidence proffered by Neurelis' expert, Dr. Gizurarson. *See, e.g.*, Appx39; Appx41; Appx46; Appx47; Appx49; Appx50.

The PTAB also found claims 17-23 obvious over Gwozdz, Meezan'962 and Cartt'784. Appx54-60. The PTAB concluded that in addition to the disclosures of Gwozdz and Meezan'962, Cartt'784 discloses: (1) nasal formulations for administering benzodiazepines such as diazepam, (2) liquid nasal sprays, including that the drug may be in solution, (3) solvents such as ethanol and benzyl alcohol, (4) alkyl glycosides, and (5) dosing amounts, volumes, and regimens for the benzodiazepine formulations. Appx55.

With respect to claims 17-18, the PTAB determined that Cartt'784 describes the relevant diazepam dose and volume. Appx55-56. Supported by Dr. Peppas, the PTAB determined that Cartt'784 discloses the dosing regimen elements recited in claims 19-22. Appx56; *see* Appx9308-9312 (¶¶443-451). As to claim 23, based on the testimony of Dr. Peppas, the PTAB concluded that Cart '784 discloses the

use of benzodiazepines for treating symptoms before and/or after they start.

Appx56; see Appx9312-9313 (¶¶452-455).

As discussed above, the foundation of Neurelis' arguments was not what the references disclosed but, rather that its claims were nevertheless nonobvious based on an alleged lack of motivation to combine, a lack of expectation of success and a long-felt need for the nasal administration of benzodiazepines. The Board addressed these arguments and based on substantial evidence, found them lacking and the claims obvious.

For example, Neurelis argued: (1) a POSA would not look to combine the teachings of increasing drug solubility, as taught by Gwozdz, with the use of enhancers to increase mucosal penetration, as taught by Meezan'962; (2) Meezan'962 would not work in a non-aqueous environment such as Gwozdz; (3) Meezan'962 did not expressly disclose benzodiazepines or provide information sufficient for a POSA to use Meezan'962's alkyl glycosides with Gwozdz' solution; and (4) Cartt'784 was limited to particulate formulations of benzodiazepines and excludes solutions in its teachings. See Appx45-46; Appx57. The Board, supported by the testimony of Aquestive's experts, disagreed. See Appx47-51; Appx58-60.

The PTAB also rejected Neurelis' arguments that secondary considerations supported the non-obviousness of claims 1-36. Appx51-54; Appx59 (as "discussed

supra, we also find that the evidence of secondary considerations of non-obviousness is weak, at best.”).

SUMMARY OF THE ARGUMENT

The PTAB’s Decision finding claims 1-36 of the ‘876 patent unpatentable should be affirmed in its entirety, as Neurelis’ unsupported arguments to the contrary are without merit.

Neurelis offers no persuasive reason or compelling evidence that the PTAB erred in finding that there was inadequate written description support in the ‘558 provisional for the “alkyl glycoside” limitation recited in the challenged claims; therefore, both Gwozdz and Cartt’962 are prior art under 35 U.S.C. § 102(e)(1).

Importantly, Neurelis does not dispute that Gwozdz, Meezan’962 and Cartt’784 disclose every limitation of the ‘876 claims. A POSA would have been motivated to optimize existing technology for the intranasal administration of benzodiazepines and would have had more than a reasonable expectation of success. At bottom, substantial evidence demonstrates that a POSA would have reasons for, and a reasonable expectation of success in, combining the teachings of Gwozdz, Meezan’962 and Cartt’784 to arrive at the subject matter recited in claims 1-36.

Neurelis does not proffer any arguments or evidence supporting criticality or unexpected results with respect to any of the claim limitations that would impact a POSA's motivation to combine or reasonable expectation of success.

Neurelis' claims regarding a purported long-felt need also fails for at least three reasons. First, Neurelis never established the requisite nexus between the '876 patent claims and its VALTOCO® product. Second, the prior art is replete with examples of the intranasal administration of benzodiazepines, including diazepam. Third, Neurelis' so-called long-felt need is not co-extensive with its claims for the intranasal administration of benzodiazepines or diazepam to treat any disorder - not only seizures.

While Neurelis argues the PTAB erred in finding claims 1-36 obvious, only claims 1, 27-28 and 30-33 were expressly addressed in its Opening Brief. However, Neurelis' argument regarding the dodecyl maltoside limitation appearing in claims 27-28 and 30-33 was never advanced below. In fact, the PTAB found, and Neurelis conceded, separate arguments were not presented for any of the dependent claims (*i.e.*, 2-36). Consequently, Neurelis has waived any argument that claims 2-36 are nonobvious.

In sum, the PTAB detailed substantial evidence supporting its decision regarding written description and provided abundant rationale to support its obviousness findings. Neurelis' Opening Brief fails to demonstrate otherwise.

The PTAB did not legally err, and substantial evidence supports the Board’s determination that claims 1-36 of the ‘876 patent are unpatentable under 35 U.S.C. § 103(a).

ARGUMENT

A. Standard Of Review

On appeal, the correctness of the PTAB’s decision can be defended on any ground supported by the record. *Rexnord Indus., LLC v. Kappos*, 705 F.3d 1347, 1356 (Fed. Cir. 2013).

This Court reviews the legal conclusions of the PTAB *de novo* and its factual findings for substantial evidence. *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017). “Substantial evidence is something less than the weight of the evidence but more than a mere scintilla of evidence” meaning that “[i]t is such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.” *In re NuVasive, Inc.*, 842 F.3d 1376, 1379-80 (Fed. Cir. 2016) (internal quotation marks and citations omitted). A decision is supported by substantial evidence even if the record would reasonably support contradictory conclusions. *In re Jolley*, 308 F.3d 1317, 1320 (Fed. Cir. 2002). As observed by this Court, “[i]f two inconsistent conclusions may reasonably be drawn from the evidence in record, the PTAB’s decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial

evidence.” *Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1357 (Fed. Cir. 2018) (internal quotation marks, brackets, and citations omitted).

Whether a patent claim is supported by an adequate written description is a question of fact, which this Court reviews for substantial evidence. *Bamberg v. Dalvey*, 815 F.3d 793, 797 (Fed. Cir. 2016). For a patent claim to be entitled to priority to the filing date of an earlier application, that application must comply with the written description requirement of 35 U.S.C. § 112. *Bradford Co. v. Conteyor N. Am., Inc.*, 603 F.3d 1262, 1269 (Fed. Cir. 2010). This requirement is satisfied if the applicant “convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate[s] that by disclosure in the specification of the patent.” *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (quoting *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008)).

Obviousness is a question of law based on underlying factual findings that are reviewed only for substantial evidence. *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1379 (Fed. Cir. 2017). Whether a person of ordinary skill would have been motivated to combine the prior art is also a factual question reviewed for substantial evidence. *Intercontinental Great Brands LLC v. Kellogg N. Am. Co.*, 869 F.3d 1336, 1343 (Fed. Cir. 2017).

Whether secondary considerations support a finding of nonobviousness is a factual question. *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015). There is no long-felt need if prior art products were effective for the purpose of the claimed invention. *See B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996) (discounting long-felt need because invention “was similar to the teachings” of prior art).

“[T]he PTAB is permitted to weigh expert testimony and other record evidence and, in so doing, rely on certain portions of an expert’s declaration while disregarding others.” *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1041 (Fed. Cir. 2016); *see, e.g., In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) (“[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations. . . .”) (citations omitted). In fact, when the PTAB evaluates the credibility of witness testimony, those credibility determinations are “virtually unreviewable” unless the testimony is “inherently improbable or discredited by undisputed evidence or physical fact.” *Curtis v. Dept. of Treasury*, 97 Fed. Appx. 296, 296-97 (Fed. Cir. 2004) (quoting *Hambsch v. Dep’t of Treasury*, 796 F.2d 430, 436 (Fed. Cir. 1986) and *Dittmore-Freimuth Corp. v. United States*, 390 F.2d 664, 685 (1985)).

B. The ‘558 Provisional Fails To Provide Adequate Written Description Support -- The ‘876 Patent Claims Are Not Entitled To The Benefit Of The Provisional’s Filing Date And Gwozdz And Cartt’784 Are Prior Art Under 35 U.S.C. § 102(e)(1)

The ‘558 provisional must satisfy the written description requirement of Section 112 before the ‘876 patent claims are entitled to the benefit of the provisional’s filing date. *New Railhead*, 298 F.3d at 1294. However, there is no reason to presume that the ‘876 patent is entitled to the benefit of the ‘558 provisional’s filing date. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305 (Fed. Cir. 2008). Consequently, “care must be taken to ensure” the ‘558 provisional adequately provides written description support for the “alkyl glycosides” limitations recited in each of the challenged claims of the ‘876 patent. *Dynamic Drinkware*, 800 F.3d at 1380 (citing MPEP § 211.05(I)(A) (2014)).

Paragraphs 150-152 of the ‘558 provisional broadly disclose numerous acceptable “enhancers.” Appx7814. Disclosed in these three paragraphs are about 150 biological detergents listed in the SIGMA catalog. Appx 10705-10710; see Appx7814 (¶152). However, nothing in the ‘558 provisional would have indicated to a POSA that Neurelis then possessed what it now claims. Appx10575-10576 (¶¶176-177). As Dr. Wermeling opined:

A POSA reading the ‘558 Provisional would understand it as generically specifying enhancers by their different mechanisms: mucolytic agents, degradative enzyme inhibitors, and compounds which increase permeability of the mucosal cell membranes. The POSA would then understand that the remaining descriptions in ¶¶ 150-152 are directed to “compounds which increase permeability of the mucosal cell membranes.” The POSA would understand that there are at least fifteen further classes of enhancing agents listed: lysophospholipids, acyl carnitines, chelating agents, surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and fatty acid salts, tyloxapol, biological detergents listed in the SIGMA Catalog 1998 pp. 316-321, enamines, malonates, salicylates, bile salts and bile analogues and fusidates. The classes include unspecified and unidentified candidates.

Appx10574 (¶172) (emphasis supplied); *see* Appx10574-10576 (¶¶173-177).

Neurelis argues that the mere existence of 12 alkyl glycosides in the SIGMA catalog provides adequate written description. However, Neurelis fails to address that a POSA would have had to go through the host of acceptable enhancers described in paragraphs 150-152, and then the 150 biological detergents listed in the 6 pages of the incorporated SIGMA catalog, to reach the 12 listed alkyl glycosides.

Moreover, the ‘558 provisional’s “forest” of enhancers fails to provide sufficient blaze marks to identify the alkyl glycoside “trees” in sufficient detail so as to enable the POSA to clearly conclude the inventors possessed alkyl glycosides as “the” enhancer for the claimed invention.

Neurelis states that the definition of its pharmaceutical solution uses the closed phrase “consisting of” in connection with alkyl glycosides, and thus confines its claimed invention to alkyl glycosides. Blue Br. 14. Neurelis is correct, but that makes its burden of production of evidence of written description even more difficult. With the claims so limited, a POSA reading the ‘558 provisional would have had to understand that the inventors were excluding all of paragraphs 150-152’s “absorption enhancers”, including the listed preferred lysophospholipids and acyl carnitines (§151), and excluding all but 12 of the 150 biological detergents incorporated by reference. However, nothing in the ‘558 provisional provides guidance to the POSA that all these enhancers, including those characterized as preferred, should be excluded, and that only the alkyl glycosides should be included. Appx7814; Appx10572-10576 (§§171-177). *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (“prior application itself must describe an invention . . . in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought”); see *Purdue Pharma L.P. v. Iancu*, 767 Fed. Appx. 918, 924 (Fed. Cir. 2018).

On appeal, Neurelis presses several unpersuasive arguments in an effort to demonstrate that the PTAB erred in finding that the ‘558 provisional fails to provide adequate written description support. First, Neurelis, referring to Rule 57,

contends the Board did not actually consider the SIGMA catalog to be incorporated into the '558 provisional. Blue Br. 21-23. Second, Neurelis contends that the Board required a “preference for alkyl glycosides and dodecyl maltoside” before alkyl glycosides could be incorporated into the '558 provisional, and that the '558 provisional provided the required direction and “blaze marks.” Blue Br. 26-31. Lastly, ignoring the parties’ respective burdens, Neurelis claims it was blindsided and prejudiced by Aquestive’s written description argument. Blue Br. 31-34.

Each of these arguments is unavailing and cannot overcome the substantial evidence demonstrating that the '558 provisional fails to provide sufficient written description support for the alkyl glycoside and dodecyl maltoside limitations.

1. The PTAB considered the SIGMA catalog as being incorporated into the '558 provisional.

Notwithstanding Neurelis’ arguments to the contrary (Blue Br. 19-21, 25), the Board could not have been clearer that, in reaching its Decision, it was considering the entirety of SIGMA catalog along with all its 150 biological detergents and 12 alkyl glycosides as being incorporated into 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

Appx19.

⁷ [W]e 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.

Appx19, n.7.⁶

Neurelis’ additional argument that the PTAB “instituted trial based on a misapplication of Rule 57” so as to improperly exclude the SIGMA catalog is legally irrelevant and factually wrong. *See* Blue Br. 21-23. Equally wrong is Neurelis’ argument that the Board did not consider all the biological detergents listed in the six pages of the SIGMA catalog as being incorporated. Blue Br. 25, n.4.

While the Board said in the Decision to Institute that Rule 57 restricted the incorporation of the SIGMA catalog, the Board, in denying Neurelis’ request for rehearing of the Decision to Institute, clarified that application of Rule 57 was not

⁶ The disingenuous nature of Neurelis’ arguments that the PTAB failed to consider the biological detergents of the SIGMA catalog as being incorporated into the ‘558 provisional is further highlighted by Neurelis’ contrary assertion that the PTAB “improperly treat[ed] the **incorporated** biological detergents as a laundry list.” Blue Br. 29 (emphasis added).

necessary for the institution of this proceeding. Appx460 (“Given [Neurelis’] failure to satisfy its burden of production to show that all of the ’876 patent claims are supported throughout the priority chain, we need not address [Neurelis] additional arguments regarding the application of 37 C.F.R. § 1.57 at this time.”). In this regard, appeal of PTAB proceedings does not include review of the institution decision. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2141 (2016); *see* 35 U.S.C § 314(d). Consequently, this Court can quickly dispose of Neurelis’ arguments regarding the PTAB’s purported (and demonstrably incorrect) reliance on Rule 57.

2. The PTAB did not require a “preference for alkyl glycosides” and correctly concluded that the ’558 provisional provided no direction or “blaze marks” and failed to provide adequate written description

Neurelis criticizes the PTAB’s Decision, contending that the Board purportedly required that the ’558 provisional disclose a “preference” for alkyl glycosides before those particular “enhancers” could be considered incorporated. Blue Br. 23-26. To support this argument, Neurelis crops the paragraph below and presents only the following italicized excerpts from the PTAB’s Decision, while omitting excerpts appearing in bold:

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

Appx19-20.

Based on its incomplete reference to the Board’s Decision, and relying on nothing more than attorney argument, Neurelis posits the PTAB imposed “an improperly high standard for written description (requiring a preference for some compounds for incorporation),” maintaining “the Board appears to require direction to incorporate **only** the twelve alkyl glycosides”. Blue Br. 24-25 (emphasis in original). Neurelis’ “preference” argument fails on several levels.

As an initial matter, when the two italicized sentences Neurelis extracts from the PTAB’s Decision, are read in context with the omitted excerpts appearing in

bold, the suspect nature of Neurelis’ “preference” argument is exposed. Contrary to Neurelis’ assertion, the Board was not requiring direction to incorporate the twelve alkyl glycosides as Neurelis alleges (Blue Br. 26-27, 29); rather, the Board was employing the correct analysis to conclude there was inadequate written description support because of an absence of sufficient “blaze marks” directing a POSA to the alkyl glycoside “trees” in the “forest” of the ‘558 provisional’s enhancers. Appx19-20; see *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996).

Nevertheless, Neurelis insists that the ‘558 provisional did provide “two important blaze marks in ¶152”: “a preference for non-ionic materials” and “an incorporation of SIGMA catalog pages on biological detergents in which most of the non-ionic biological detergents are alkyl glycosides.” Blue Br. 30.⁷

Notably, Dr. Wermeling provided substantial testimony that a POSA would not have recognized from reading the ‘558 provisional that the named inventors were in possession of “alkyl glycosides” as recited in the claims of the ‘876 patent. See, e.g., Appx10574-10576 (¶¶171-177); see *Waldemar Link, GmbH & Co. v.*

⁷ Most “non-ionic” biological detergents were not alkyl glycosides. Of the 150 biological detergents listed in the SIGMA catalog, 100 are considered non-ionic. Out of those 100 non-ionic materials, Dr. Wermeling testified that only 12 are alkyl glycosides. Appx10574-10576 (¶¶175-176); see Appx20, n.8.

Osteonics Corp., 32 F.3d 556, 558 (Fed. Cir. 1994) (a POSA reading the original specification must “immediately discern the limitation at issue in the parent”). Dr. Wermeling’s testimony stands unrebutted.⁸ *See infra*, at 48-49.

Additionally, Neurelis’ “preference for non-ionic materials” argument, mischaracterizes the ‘558 provisional’s disclosure. *See* Appx7814. Importantly, of the various enhancers disclosed and described in paragraphs 150-152 only two are identified as “preferred” - lysophospholipids and acyl carnitines. Appx7814 (¶151); Appx10574-575 (¶¶173, 175). Paragraph 152 also describes “surface active agents (especially non-ionic materials).” Contrary to Neurelis’ suggestion, the phrase “non-ionic material” modifies the disclosed “surface active agents,” not the biological detergents listed in the SIGMA catalog. Blue Br. 5-6, 8, 26-30.

Tellingly, both Dr. Wermeling and Dr. Gizurarson testified that nothing in ¶152 associates the non-ionic surface active agents with the biological detergents listed in the SIGMA catalog. Appx10574-10575 (¶175 & n.5); Appx10352-10353 (51:18-52:9). Moreover, as Dr. Wermeling testified, paragraphs 150-152 teach both ionic and non-ionic enhancers, the ‘558 provisional does not provide guidance to a POSA to exclude, *inter alia*, the SIGMA catalog’s “anionic” or “cationic”

⁸ Disingenuously, Neurelis proclaims that Dr. Peppas “agreed” that a POSA would have recognized “that the inventors had possession of the claimed subject matter.” Blue Br. 29. Not surprisingly, Neurelis fails to point to any testimony by Dr. Peppas to support its baseless proposition.

biological detergents, and certainly does not direct a POSA to consider only “non-ionic” materials.⁹ Appx10574-10575 (¶175).

Neurelis stresses that when assessing written description, the disclosure must be considered “as a whole”. Blue Br. 26-27, 31. Yet, with the exception of the biological detergents listed in the SIGMA catalog, Neurelis and its expert disregard the entirety of the ‘558 provisional’s disclosure of acceptable enhancers in paragraphs 150-152 in proposing the ‘558 provisional provides adequate written description support. *See, e.g.*, Appx10932-10933 (¶ 68); *see Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1346 (Fed. Cir. 2000) (compliance with the written description requirement requires that the original application considered “as a whole” must convey to the POSA the invention claimed). Consequently, Dr. Gizurarson’s flawed written description opinion fails to start with the entire “forest of enhancers” disclosed and described in paragraphs 150-152, but rather, first cuts down all enhancers not listed in the SIGMA catalog, and impermissibly picks alkyl glycosides and specifically the dodecyl maltoside subspecies from that remaining forest to opine “here is the [‘876 patent] invention.” *See, e.g.*, Appx10932-10938

⁹ Neurelis’ assertion that the PTAB required “blaze marks” to alkyl glycosides before those compounds could be considered incorporated, *see, e.g.*, Blue Br. 26-27, 29, is simply incorrect and a misrepresentation of the PTAB’s Decision. *See supra*, at 40-42.

(¶¶ 68-75); Appx10345-10358; *see Purdue Pharma*, 230 F.3d at 1326-27; *Fujikawa*, 93 F.3d at 1571.

In contrast, in opining there was insufficient written description support, Aquestive’s expert considered the entirety of the ‘558 provisional’s enhancer disclosures, *i.e.*, paragraphs 150-152. *See, e.g.*, Appx10576 (¶177).

Moreover, by maintaining that a POSA would have culled the non-ionic materials from the list of biological detergents identified in the SIGMA catalog, *e.g.*, Blue Br. 5-8, 26-29, Neurelis improperly conflates the obviousness and written description requirements. *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (“[A] description that merely renders the invention obvious does not satisfy” the written description requirement.); *see Lockwood*, 107 F.3d at 1572 (“It is not sufficient for purposes of the written description requirement of Section 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.”).

Neurelis’ constant refrain that Drs. Gizurarson and Peppas observed that the SIGMA catalog discloses alkyl glycosides, including dodecyl maltoside, is of no consequence. *See* Blue Br. 11-12, 15, 29, 32. Further, “failure to explicitly discuss every issue or every piece of evidence does not alone establish that the tribunal did not consider it.” *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1328 (Fed.

Cir. 2017). Thus, Neurelis’ naked admonishment of the PTAB for allegedly not “account[ing]” for and for “overlook[ing]” Dr. Peppas’ comments regarding the incorporation of the SIGMA catalog and the catalog’s disclosure of alkyl glycosides is unavailing. Blue Br. 11-12, 15, 30-31, 39, 56.

Neurelis’ arguments to the contrary are insufficient to displace the fact that substantial evidence supports the Board’s finding that “the ‘558 provisional does not provide adequate written description support for the ‘alkyl glycoside’ limitation.” Appx23.

3. Neurelis was not prejudiced by Aquestive’s actual notice of the lack of written description and Neurelis was provided with ample opportunity to provided support for its written description claim

Neurelis’ claim that it was blindsided by Aquestive’s written description argument and its feigned cry of prejudice and lack of due process strains credulity and, as discussed below, reflects a fundamental misunderstanding of the parties’ respective burdens. Blue Br. 14, 31-34, 56.

Aquestive clearly stated that it was the failure to provide written description for alkyl glycosides and dodecyl maltoside in the ‘558 provisional that vitiated any priority claim:

[T]he presence of any **alkyl glycosides** (either generally or particularly) – regardless of amount – was **not disclosed, described**, or enabled by ‘558 Provisional.

Rather, **the first disclosure, description, and enablement for the presence of an alkyl glycoside in general (or dodecyl maltoside in particular) – in any amount – was no earlier than ‘439 application’s March 27, 2009 filing date. . . . [The] ‘558 Provisional’s generic disclosure of “surface active agents (especially non-ionic materials)” (‘558 Provisional, [152], Exhibit 1008, p. 0031) does not disclose, describe, and/or enable alkyl glycosides in general (or dodecyl maltoside in particular).**

Appx225 (emphasis supplied); *see* Appx9164 (¶68) (“the ‘558 Provisional does not mention, disclose, or provide written support for alkyl glycosides (or any particular species thereof, e.g., dodecyl maltoside.”); Appx223-224; Appx9142-9144 (¶29); Appx9162-9165 (¶¶64-67, 69-70).

That statement more than satisfied Aquestive’s initial burden, and contrary to Neurelis’ protestations, no more was required. *See, e.g.*, Appx354-358; Appx457-460; Appx13-23; *Dynamic Drinkware*, 800 F.3d at 1379-80 (while petitioner always has the ultimate burden of persuasion to prove unpatentability, once petitioner goes forward with evidence of prior art, patent owner must demonstrate entitlement to the priority date when the patent owner relies on that priority date to overcome an anticipation or obviousness argument); *see Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327-28 (Fed. Cir. 2008). Tellingly, Neurelis neglects to even cite or distinguish *Dynamic Drinkware*.

Neurelis’ complaint that Aquestive did not expressly discuss the SIGMA catalog in its Petition in connection with the absence of adequate written

description for alkyl glycosides is of no moment. *See* Blue Br. 20, 31-32.

Aquestive was required to produce evidence of Gwozdz' and Cartt'784's entitlement to their respective filing dates, which it did, and provide evidence and notice of the '876 patent's lack of priority, which it also did. Appx225; Appx9162-9165 (¶¶64-67, 69-70); Appx9164 (¶68) ("the '558 Provisional does not mention, disclose, or provide written support for alkyl glycosides (or any particular species thereof, e.g., dodecyl maltoside.)"). The burden of production then shifted to Neurelis to produce evidence that Gwozdz and Cartt'784 are not prior art because the claims of the '876 patent are entitled to the '558 provisional's filing date. Because Neurelis failed to meet its burden, the burden shifting ended. *Dynamic Drinkware*, 800 F.3d at 1379.

Curiously, Neurelis complains that it was deprived of the opportunity to present evidence that could possibly rebut the substantial evidence proffered by Dr. Wermeling addressing the absence of sufficient written description support. Blue Br. 33. However, Neurelis had ample opportunity to marshal evidence to meet its burden of production in its: preliminary response; response; request for rehearing; expert's declaration; depositions of Aquestive's experts; sur-reply; and at trial.

Notably, Neurelis does not even reference, much less refute, the substantial evidence proffered by Aquestive's expert, Dr. Wermeling, demonstrating that the '558 provisional fails to convey to a POSA that the inventors were in possession of

the invention recited in the ‘876 patent. *See, e.g.*, Appx10572-10576 (¶¶171-177).¹⁰ In fact, during his deposition, Neurelis consciously chose to remain silent and refrained from asking Dr. Wermeling a single question about his opinion that the ‘558 provisional failed to provide sufficient written description support for the alkyl glycoside and dodecyl maltoside claim limitations.

That may explain why, on appeal, Neurelis does not challenge the substance of Dr. Wermeling’s “written description” opinion, but rather its timing, alleging his testimony constitutes “new evidence” that Neurelis did not have an opportunity to refute. *See, e.g.*, Blue Br. 11, 14, 33. However, the PTAB correctly found that Dr. Wermeling’s testimony constituted proper rebuttal evidence. *See* Appx16-17; Appx21-33; Appx66; *see Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1380 (Fed. Cir. 2017) (“petitioner in a *inter partes* review proceeding may introduce new evidence after the petition stage if the evidence is a legitimate reply to evidence introduced by patent owner”); *Idemitsu Kosan*, 870 F.3d at 1381 (“To the extent [Patent Owner] suggests that the Board could not reach a counterargument because it was not preemptively addressed by the petition or institution decision, [Patent Owner] is plainly mistaken.”).

¹⁰ In denying Neurelis’ motion to exclude, the PTAB found that “Dr. Wermeling’s opinions [in paragraphs 171-177] 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” were “properly supported.” Appx68.

Finally, Neurelis attempts to change the focus from whether the SIGMA catalog's incorporation by reference into the '558 provisional provides adequate written description support to what was actually incorporated by reference from the SIGMA catalog. *See* Blue Br. 28-31. This is a red herring as demonstrated by Neurelis' reliance on *Husky Injection Molding Sys. v. Athena Automation Ltd.*, 838 F.3d 1236 (Fed. Cir. 2016). *Husky* discussed the parts of a document that were incorporated by reference, which is irrelevant to this appeal. *Id.* at 1248. It is beyond dispute that the PTAB considered all six pages of the SIGMA catalog incorporated into the '558 provisional. *See, e.g.*, Appx19, n.7; *supra*, at 25-26, 38-40.

C. The PTAB did not construe claims to eliminate dependent claim limitations for “dodecyl maltoside”

Neurelis argues that the PTAB construed dependent claims 27-28 and 30-33 as excluding “dodecyl maltoside”. Blue Br. 34-40. Neurelis' argument lacks merit as the PTAB stated that claims 27-28 and 30-33 each depend from claim 1 and expressly require dodecyl maltoside. Appx33-35.

1. Neurelis waived any argument that the listing of dodecyl maltoside in the SIGMA catalog provides adequate written description support

Neurelis maintains that the mere appearance of “dodecyl maltoside” in the SIGMA catalog provides sufficient written description support for dependent claims 26-28 and 30-33. *See* Blue Br. 13-15, 34-36, 38-40, 56-57. Neurelis’ argument is too little, too late.

Written description, a question of fact, is assessed on a claim-by-claim basis. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1556, 1567 (Fed. Cir. 1991) (“*separately* analyze whether the ‘written description’ requirement has been met as to the subject matter of *each* claim”) (italics in original). However, Neurelis failed to present evidence that there was sufficient written description support for dependent claims 26-28 and 30-33. Appx27. In fact, at Oral Hearing, Neurelis candidly conceded:

Regarding Your Honor’s questions regarding whether we laid out in our papers the provisional support for each and every limitation of the claim, **its not explicitly here.**

Appx829 (59:7-9, emphasis supplied); *see* Appx803 (33:8-17). Having failed to present any argument to the Board regarding written description support for the dodecyl maltoside limitation recited in claims 26-27 and 30-33, Neurelis is not entitled to proffer that argument for the first time on appeal. *See, e.g., Novartis*, 853 F.3d at 1329 (“a party waives an argument that it ‘failed to present to the

Board’ because it deprives the court of ‘the benefit of the Board’s informed judgment’”) (quoting *In re Watts*, 354 F.3d 1362, 1367-68 (Fed. Cir. 2004)); *In re Baxter, Int’l, Inc.*, 678 F.3d 1357, 1362 (Fed. Cir. 2012) (“Absent exceptional circumstances . . . we generally do not consider arguments that the applicant failed to present to the Board.”) (internal citations omitted).

Neurelis conceded that it did not present separate arguments as to the validity of dependent claims 2-36. Appx829 (59:7-9); see Appx27 (Neurelis “does not present separate arguments for any of the dependent claims.”). On appeal, the only dependent claims discussed by Neurelis are dependent claims 26-28 and 30-33. Blue Br. 34-40. However, Neurelis’ arguments regarding those claims have not only been waived, they lack merit. *See supra*, at 10-17. Additionally, because Neurelis has failed to separately argue the validity of the remaining dependent claims and has failed to refute the substantial evidence underlying the PTAB’s obviousness conclusion, Neurelis has waived any argument that dependent claims 2-36 are nonobvious. *See, e.g., NuVasive*, 842 F.3d at 1380 (“a party waives an argument that it ‘failed to present to the [PTAB]’ because it deprives the court of ‘the benefit of the [PTAB]’s informed judgment’”) (citation omitted).

2. The PTAB did not ignore the dodecyl maltoside limitation recited in claims 27-28 and 30-33

Neurelis also maintains that the PTAB's acknowledgement that all claims require "an alkyl glycoside" means that the Board failed to take into account dependent claims 27-28 and 30-33's "dodecyl maltoside" limitation. Blue Br. 34-38. Neurelis' reliance on the PTAB's statement that "the '558 provisional does not provide adequate support for the 'alkyl glycoside' limitation" (Appx14) fails to provide any legitimate support for Neurelis' argument or refute the Board's express acknowledgement that claims 27-28 and 30-33 recite "dodecyl maltoside". See Appx33-35.

Additionally, the Board recognized that the SIGMA catalog's listing of alkyl glycosides included "dodecyl maltoside". See, e.g., Appx15. Thus, when the Board held that the incorporation of the SIGMA catalog (including its listing of alkyl glycosides) was insufficient for written description, it was necessarily including the lack of written description for "dodecyl maltoside." Moreover, the Board expressly refers to all 150 biological detergents and the 12 alkyl glycosides.

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.

Appx19.

Neurelis continues its attempts to bolster its arguments by infusing a non-existent claim construction to nullify the PTAB's decision. *See* Blue Br. 38-40. Notwithstanding that the Board concluded that no terms of the '876 patent require express claim construction. Appx13; Appx60.

D. Gwozdz, Meezan'962 And Cartt'784 Disclose All The Limitations Of All The Claims Of The '876 Patent And A POSA Would Have Been Motivated To Combine The References

Dr. Peppas provided comprehensive testimony as to the application of Gwozdz, Meezan'962 and Cartt'784 to each claim of the '876 patent. Appx9285-9313 (¶¶363-455). Neurelis does not dispute that Gwozdz, Meezan'962 and Cartt'784 disclose each limitation of all 36 claims of the '876 patent. *See, e.g., supra*, at 10-15 (discussion of the teachings of Gwozdz, Meezan'962 and Cartt'784). Additionally, as to the overlapping ranges of the prior art disclosures with the '876 patent claim ranges, the burden was on Neurelis to provide evidence of criticality and associated unexpected results – it did not. *See E.I. du Pont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006, 1008 (Fed. Cir. 2018).

In an effort to refute Dr. Peppas' testimony, Neurelis presents a hodgepodge of arguments as to why purportedly a POSA would have lacked a motivation to combine the teachings of these references or have a reasonable expectation of success. Blue Br. 41-51.

At a fundamental level, common sense supports the substantial evidence proffered by Aquestive expert's testimony that a POSA, considering improvements to intranasal drug administration to enhance bioavailability for example, would have considered these references, would have considered combining their teachings and due to their overlapping teachings would have possessed a reasonable expectation of success. *See generally* Appx9255-9256 (¶¶257-263); Appx9285-9313 (¶¶363-455); Appx10567-10571 (¶¶157-170).

Importantly, evaluating the testimony of the parties' respective experts, the PTAB credited the testimony of Aquestive's experts Drs. Peppas and Wermeling with respect to both the POSA's motivation to combine (Appx39-41, Appx46-47, Appx58-59) and a POSA's reasonable expectation of success (Appx49-50). A POSA would for instance be motivated to look at and combine the references because, *e.g.*, Gwozdz, Meezan'962 and Cartt'784 each teach methods of optimizing, *inter alia*, bioavailability. *See* Appx10496 (¶42); *see supra*, at 11-15. Gwozdz does this by increasing the solubility of the benzodiazepine to increase bioavailability. Appx8025 (7:3-8); Appx9229 (¶194); Appx9237 (¶219); Appx9300 (¶424); Appx10561-10562 (¶146). Meezan'962 does this by adding a mucosal absorption enhancer to the drug delivery system to increase bioavailability. Appx25; Appx7950 (¶4); Appx9239 (¶¶223-224); Appx10562 (¶15); Appx10564-10565 (¶¶149-150). Cartt'784 does this through the use of

absorption enhancers to increase bioavailability. Appx55; Appx8060 (¶124). *See supra*, at 13-15.

Nevertheless, in its attempt to attack the substantial evidence demonstrating motivation and a reasonable expectation of success, Neurelis argues that (i) Gwozdz was satisfied with its ability to increase bioavailability which left no room for optimization;¹¹ (ii) Meezan'962 would not work in a non-aqueous environment such as Gwozdz and that Meezan'962 did not expressly disclose benzodiazepines or provide information sufficient for a POSA to use Meezan'962's alkyl glycosides with Gwozdz' solution;¹² and (iii) that Cartt'784 dealt with particulates instead of solutions and would not work with Meezan'962 or Gwozdz. Blue Br. 41-51. Each of Neurelis' assertions were rejected in view of the substantial evidence presented by Aquestive. *See, e.g.*, Appx38-51.

Neurelis argues that Meezan'962 primarily relates to water-soluble compounds and thus, a POSA would not have found Meezan'962 relevant to poorly water-soluble drugs such as benzodiazepines. Blue Br. 56. But midazolam, a benzodiazepine, is water-soluble. Appx10570 (¶167).

¹¹ This is a strange statement to make, as Gwozdz, the inventor was not satisfied, since he appears, as a co-inventor, on the '876 patent. Appx71.

¹² Meezan'962's disclosure encompasses benzodiazepines. Appx9238 (¶222); Appx45.

Moreover, a POSA would have been motivated to look at multiple ways of optimizing intranasal delivery of drugs, “even in situations of already high bioavailability”. Appx10563 (¶146, n.4); *see* Appx45. Moreover, a POSA would not have been deterred from making changes to Gwozdz’ formula such as adding benzyl alcohol, which Neurelis’ claims might reduce solubility and risk drug precipitation. *See* Blue Br. 44. Dr. Wermeling testified that a POSA would have recognized that adding benzyl alcohol to a tocopherol+ethanol co-solvent system – as suggested by Gwozdz – would have resulted in a ternary co-solvent system with its potential benefits. Appx10558 (¶139); Appx40-42. As to any concerns about precipitation, Dr. Wermeling noted that administration in more than one nostril would allow for the use of a lower concentration of drug, thereby avoiding precipitation. Appx10555 (¶¶130-132); *see* Appx43-44.

Neurelis’ suggestion that Meezan’962 teachings are inapplicable to non-aqueous solutions or benzodiazepines is wrong. Blue Br. 41-42. Meezan’962 expressly discloses using alkyl glycosides in aqueous and 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 **nonaqueous 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**,....

Appx7955-7956 (¶74) (emphasis supplied); *see* Appx46-47.

Additionally, Dr. Wermeling opined that a POSA would indeed use alkyl glycosides with non-aqueous solutions. Appx10568-10569 (¶¶161-165). In fact, Neurelis' expert Dr. Gizurason was unaware of any evidence that alkyl glycosides could not be used in non-aqueous solutions or that alkyl glycosides could not be used with benzodiazepines. Appx10386 (85:2-6); Appx10395 (94:9-18). Weighing the evidence presented, the PTAB noted that “[g]iven [Meezan‘962’s] 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.’” Appx46-47; *see* Appx10566 (¶152).

In an effort to refute the substantial evidence supporting a conclusion of obviousness, Neurelis contends that one of Dr. Wermeling’s patents teaches away from the use of benzyl alcohol in nasal solutions. Blue Br. 50. However, Dr. Wermeling testified that the patent Neurelis points to was directed to the use of lorazepam as a sedative and to treat conditions of anxiety, not life-threatening situations and nowhere does his patent refer to, *e.g.*, epileptic seizures or other life-threatening situations. Thus, Dr. Wermeling’s patent’s statement regarding benzyl alcohol is inapplicable to life-threatening situations. Appx10591-10592 (¶¶209-

211); *see In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (a reference does not teach away if it does not “criticize, discredit, or otherwise discourage the solution claimed” in the patent). Moreover, Neurelis’ expert conceded that one of his own patents disclosed the use of benzyl alcohol for intranasal applications. Appx10376 (75:11-21); *see* Appx9826 (¶4) (“in the case of acute health threatening indications, a relative high local irritation to the mucosa may be acceptable.”); *see* Appx39-40. The prior art Florida EMS protocol called for the intranasal use of Diazepam (Valium®) IV which is a solution containing benzyl alcohol. Appx9779; Appx9587; *see supra*, at 16-17.

Neurelis also argues that the alleged anti-microbial effect of tocopherols on alcohols, purported impact of benzyl alcohol on the autooxidation of fats and hence tocopherols, would also militate against combining the references. Blue Br. 49-50. However Dr. Wermeling rebutted these arguments testifying that (1) any anti-microbial effect was irrelevant as packaging was aseptic and the small amounts of alkyl glycosides would have no impact (Appx10567 (¶¶155-156)), and (2) a POSA would not be concerned about auto-oxidation because oxygen is absent in single-use products and there is no evidence that tocopherols would auto-oxidize in the presence of benzyl alcohol. Appx10557 (¶134, n.2); *see* Appx49-50.

Neurelis further asserts that a POSA would not have been motivated to combine Cartt’784 with Gwozdz or Meezan’962. Neurelis’ rationale - a POSA

would be hesitant to combine the Cartt‘784’s particulate formulations with the Meezan‘962’s disclosure of alkyl glycosides in solution – disregards the fact that all involve the nasal administration of drugs and discuss increasing bioavailability. Blue Br. 47. Nevertheless, Cartt‘784 teaches that its disclosures are applicable to solutions. Appx9251 (¶¶247-248); *see* Appx57-59. Moreover, a POSA looking at Cartt‘784’s and Meezan‘962’s overlapping teachings of using alkyl glycosides would thus have had an additional reason to consider combining these references. Cartt‘784 teaches the very same alkyl glycosides for use in its nasal sprays (including nasal spray solutions) that Meezan‘962 teaches for use in its nasal spray solutions. *LG Elecs., Inc. v. Conversant Wireless Licensing S.A.R.L.*, 759 Fed. Appx. 917, 925 (Fed. Cir. 2019) (“The fact that the references are directed to the same field of art helps to support the Board's finding that a person of ordinary skill in the art would be motivated to combine their teachings . . .”).

Interestingly, Cartt‘784 also describes in language almost verbatim to that found in the ‘558 provisional, the same three paragraphs from the ‘558 provisional, and in verbatim references the “biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference)”. *Compare* Appx7814 (¶¶150-152) *with* Appx8060 (¶¶124-126). This is the same SIGMA catalog that Neurelis urges provides adequate written description for “alkyl glycosides” as recited in claims 1-36. But Cartt‘784 goes further than mere

incorporation of a list of about 150 biological detergents and expressly identifies alkyl glycosides, including n-dodecyl β -D-maltoside (“dodecyl maltoside”). See Appx8131-8132 (¶¶128-129); *see also* Appx8049-8050 (¶¶47-48); Appx9251-9252 (¶¶250-252).

To further its argument that Cartt‘784 is inapplicable to the other references, Neurelis resorts to taking the testimony of Dr. Peppas out of context. Blue Br. 47. Dr. Peppas’ statement that “solutions and particulates don’t go together” was to the effect that a solution, by definition, does not contain particulates and not that the disclosures of both cannot be combined. Appx10876 (11:13-17). Dr. Peppas made this clear during his deposition when testifying that the dosing regimens of Cartt‘784 for particulate formulations would be applicable to a solution formulation of benzodiazepines. Appx10877 (146:3-16).

Moreover, a POSA would have had a reasonable expectation of success in experimenting with different amounts of components as Neurelis never demonstrated criticality or unexpected results for the different amounts of components claimed.¹³ Appx9155-9162 (¶¶49-62); Appx10577-10583 (¶¶178-

¹³ For example, Neurelis has not demonstrated any criticality in the combined amounts of benzyl alcohol and ethanol recited in claims 1-7, 11-14, 16-27, 29, and 34-36 or the separate ranges for benzyl alcohol and ethanol (or dehydrated ethanol) recited in claims 8, 9, 10, 15, 28, and 30-33. Appx10577-10579 (¶¶178-182); Appx10586-10590 (¶¶195-207); Appx9160 (¶¶56-57).

189); Appx10586-10590 (¶¶195-207). Based on the evidence proffered, the PTAB found there was no criticality or unexpected results as to the amounts of tocopherols (Appx26, Appx32) and ethanol and benzyl alcohol (Appx26-27, Appx29-30, Appx32). Thus, a POSA would have easily been able to experiment with different amounts and types of tocopherols, alcohols, benzodiazepines, and alkyl glycosides with a reasonable expectation of success in increasing bioavailability. Appx9285-9287 (¶¶363-364, 368); see Appx47-50.

E. Neurelis Failed To Demonstrate Any Nexus Or That There Was Any Long-Felt Need

Neurelis contends that its VALTOCO® product satisfied an alleged long-felt need for the claimed invention. Blue Br. 52-53. However, the PTAB observed that Neurelis' expert does not "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." Appx53.

In fact, before the Board, Neurelis did not even allege or proffer any evidence of the requisite "nexus" between the VALTOCO® formulation and the claims. See *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir.

2019) (“to be accorded substantial weight in the obviousness analysis, the evidence of secondary considerations must have a ‘nexus’ to the claims, *i.e.*, there must be ‘a legally and factually sufficient connection’ between the evidence and the patented invention”).

As found by the Board, Neurelis only offered a broad-brushed analysis by simply asserting that VALTOCO® “is representative of the ’876 patent claims” and “met [the] long-felt but unmet need”. Appx52-53. In fact, Neurelis offered no description of the VALTOCO® formulation or a comparison of that formulation to the claims of the ’876 patent. *Id.* Moreover, Neurelis’ expert Dr. Gizurarson testified that he does not know the VALTOCO®’s formulation, Appx10319-10320 (18:3-19:20) and could not say that VALTOCO® satisfies a long felt-need, Appx10322 (21:16-20); *see* Appx53. To this day, the exact VALTOCO® formulation is not of record.

Neurelis’ argument that because its diazepam product VALTOCO® received approval “for the treatment of acute repetitive seizures . . . VALTOCO [therefore] satisfies epileptics’ long-felt need for an alternative to either rectal diazepam or medical professional administration,” misses the mark. Blue Br. 5; *see* Blue Br. 52-55. The ’876 patent claims are not limited to the treatment of epileptic seizures but recite the treatment of any disorder. Each claim of the ’876 patent recites a method of treating “a disorder” treatable with benzodiazepines.

See, e.g., Appx111 (63:26-27). Because none of the claims are restricted to treating seizures, and most claims of the ‘876 patent are not limited to diazepam, Neurelis has not - and cannot - demonstrate that the requisite nexus exists between its epileptic seizure VALTOCO® product and the claims of the ‘876 patent. *See BTG Int’l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1076 (Fed. Cir. 2019) (“The Asserted Claims only require an effective treatment for prostate cancer. As such, because the use of abiraterone and prednisone to treat prostate cancer was well-known and did not provide unexpectedly superior results, and because other treatments for prostate cancer were available, the evidence presented here does not establish that there was a specific unsolved, long-felt need for the treatment.”).

Neurelis also contends that there was arguably a long-felt need because the FDA had yet to approve such a product. Blue Br. 3, 5, 52. However, Neurelis’ contention is factually deficient, especially since there are many prior art disclosures of intranasal benzodiazepine products. *See supra*, at 15-17. *AstraZeneca LP v. Breath Ltd.*, 603 Fed. Appx. 999, 1002-1003 (Fed. Cir. 2015) (affirming district court’s finding that the unmet need for a nebulized budesonide product was met by other products even though they did not receive FDA approval).

Neurelis never discussed why there was a long-felt need for an expensive FDA approved drug, when inexpensive alternatives already existed. As

Aquestive's expert, Dr. Wermeling testified, existing off-label use of benzodiazepines (diazepam, lorazepam) administered intranasally, *e.g.*, using MAD nasal kits, was relatively inexpensive when compared to the consumer cost of FDA approved products such as the midazolam nasal spray Nayzilam™ as well as the cost of receiving approval. Tellingly, price and other market factors were not considered by Neurelis or its expert regarding any long-felt need. Appx10510-10511 (¶¶66-67).

Neurelis' contentions of long-felt need are further refuted by numerous prior art disclosures of nasally administered benzodiazepines to treat, *inter alia*, seizures. Appx53-54; *see* Appx10522-10527 (¶¶82–88); *see also* Appx10144-10149; Appx10214-10259. One prior art method for the intranasal administration of benzodiazepines included spraying off-the-shelf IV preparations of benzodiazepines into the nose through use of a mucosal atomization device. Appx10260-10266; *see supra*, at 15-17. Examples of this prior art method included: (1) the intranasal administration of a lorazepam IV solution, drawn into a syringe attached to a MAD device, which was then squirted into a nostril (Appx10253; Appx10524 (¶87)), and (2) the intranasal administration of Diazepam (Valium®), or Lorazepam (Ativan®) or Midazolam (Versed®) (all intravenous) and specifically directing that the dose for intranasal be the same as the dose for IV. Appx9779; *see, e.g.*, Appx9720; Appx10525 (¶88). In fact, Dr.

Wermeling confirmed the use of a MAD device with IV solutions of a benzodiazepine. Dr. Wermeling testified that he administered benzodiazepine IV solutions intranasally using MAD devices according to University of Kentucky protocols that were similar to 2005 Florida EMS protocols. Appx11301-11302 (114:21-115:10); see Appx10523-10524 (¶¶86, 88); see also *supra*, at 16-17.

By taking a statement out of context, Neurelis also contends that Dr. Wermeling indicated in an article that there was a long-felt need for nasally delivered benzodiazepines. Blue Br. 53. Contrary to Neurelis' contention, Dr. Wermeling's article describes how existing, effective methods for intranasal administration of benzodiazepines could be optimized, not replaced. Appx10641-10642. Further, Dr. Wermeling testified that there were existing options for intranasal delivery, that "they worked", and that his long-felt need reference was always to "optimize from something that was also known to work". Appx11315-11316 (128:17-129:8).

In sum, Neurelis' arguments that a long-felt need existed for the subject matter recited in the claims of the '876 patent are insufficient to overcome the strong showing of primary considerations that render the claims of the '876 patent obvious. See, e.g., *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

CONCLUSION

Contrary to Neurelis' contentions, the record reflects that the PTAB carefully considered each argument advanced by Neurelis and gave appropriate weight to the evidence of record and the credibility of the parties' respective experts. The record also reflects that the PTAB clearly and rightly found that Aquestive had proven that the '558 provisional fails to provide adequate written description support, such that the claims of the '876 patent was not entitled to the benefit of the '558 provisional's filing date, that the claims of the '876 patent are obvious and that there was no nexus between the claims of the '876 patent, Neurelis' VALTOCO® product and any alleged long-felt need. The PTAB's factual underpinnings for its written description and obviousness findings were amply supported by substantial evidence. Aquestive respectfully requests that the Court affirm the findings of the PTAB's holding that claims 1-36 of the '876 patent are obvious pursuant to 35 U.S.C. § 103(a).

Date: March 31, 2021

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

The foregoing brief complies with the relevant type-volume limitation of the Federal Rules of Appellate Procedure and Federal Circuit Rules because the filing has been prepared using a proportionally-spaced typeface, namely Microsoft Word 365 in 14-point Times New Roman, and includes 13,927 words, excluding any items listed as exempted under Fed. R. App. P. 5(c), Fed. R. App. P. 21(d), Fed. R. App. P. 27(d)(2), Fed. R. App. P. 32(f), or Fed. Cir. R. 32(b)(2).

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