

Case No. 21-1038

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

NEURELIS, INC.,
Appellant,

v.

AQUESTIVE THERAPEUTICS, INC.,
Appellee.

Appeal from a decision of the United States Patent and Trademark Office,
Patent Trial and Appeal Board in IPR2019-00451

APPELLANT NEURELIS INC.'S OPENING BRIEF

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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.

28. The method of claim 1, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25%(w/v) dodecyl maltoside, q.s. dehydrated ethanol.

30. The method of claim 1, wherein the solution consists of diazepam from 5 to 15% (w/v), dodecyl maltoside from about 0.01 to 1% (w/v) , vitamin E from 45 to 65% (w/v), ethanol from 10 to 25% (w/v) and benzyl alcohol from 5 to 15% (w/v).

31. The method of claim 1, wherein the solution consists of diazepam from 5 to 15% (w/v), dodecyl maltoside from 0.01 to 1% (w/v), vitamin E from 45 to 65% (w/v), ethanol from 10 to 25% (w/v)and benzyl alcohol from 5 to 15% (w/v).

32. The method of claim 1, wherein the solution consists of diazepam from 9 to 11% (w/v), dodecyl maltoside from 0.1 to 0.5% (w/v), vitamin E from 50 to 60% (w/v), ethanol from 15 to 22.5% (w/v) and benzyl alcohol from 7.5 to 12.5% (w/v).

33. The method of claim 1, wherein the solution consists of diazepam 10% (w/v), dodecyl maltoside from 0.15 to 0.3% (w/v), vitamin E from 50 to 60% (w/v), ethanol from 17 to 20% (w/v) and benzyl alcohol from 10 to 12% (w/v).

(underlining added)

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel for Appellant Neurelis, Inc. certifies that:

1. The full name of every entity represented by me is: Neurelis, Inc.
2. The full names of all real parties in interest for the entity, if that entity is not the real party in interest, 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 are: Lee Johnson, Alina Litoshyk, and Nathaniel Leachman.
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.

Dated: February 2, 2021

/s/Jeffrey Guise
Jeffrey Guise
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STATEMENT OF RELATED CASES

No other appeal in or from the same *inter partes* review was 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

The Patent Trial and Appeal Board (“Board”) had jurisdiction to enter a final written decision under 35 U.S.C. §318(a). 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).

STATEMENT OF THE ISSUES

1. Did the Board prejudicially err in applying the wrong written-description standards to deny claims 1-36 of appellant Neurelis, Inc.’s U.S. Patent No. 9,763,876 (the “’876 patent”) priority benefit to U.S. Provisional Patent Application Serial No. 61/040,558 (the “’558 provisional application”)?
2. Did the Board prejudicially err in misconstruing ’876 patent claims 26-28 and 30-33 as requiring generic “alkyl glycoside” rather than the claimed “dodecyl maltoside”, and then denying these claims priority to the ’558 provisional application, which discloses dodecyl maltoside as claimed?
3. Did the Board prejudicially err in holding all ’876 patent claims obvious?

INTRODUCTION

The Board prejudicially erred in holding claims 1-36 unpatentable for at least three reasons. First, the Board held the original priority document—the ’558 provisional application—lacked written description for the ’876 patent claims’ “alkyl glycoside” limitation. By repeatedly misapplying incorporation-by-reference law, the Board failed to recognize express possession of listed alkyl glycosides in the specification. Moreover, the Board improperly required a preference for “alkyl glycosides” rather than simple possession. Second, the Board overlooked the “dodecyl maltoside” limitations in dependent claims 26-28 and 30-33, which have

literal support in the '558 provisional application, as Neurelis pointed out. Third, all claims were held obvious over at least one reference that was not prior art (but for the Board's errors deciding priority) and that—even if prior art—do not support an obviousness conclusion. These prejudicial errors warrant reversing the Board's judgment against Neurelis. A remand would not cure these defects, because the record does not support the grounds on which Aquestive Therapeutics, Inc. ("Aquestive") petitioned; hence, Neurelis respectfully requests reversal of the Board's decision.

STATEMENT OF THE CASE

A. Technical Background

The '876 patent discloses nasally administering benzodiazepine drugs. Benzodiazepine drugs can be used to treat epilepsy, one of the most common serious neurological disorders, affecting nearly 1% of Americans. Appx10914-10915. Epilepsy can create challenges for education, employment, social interaction, driving, and independent living. *Id.* Immediate cessation of epileptic seizures, which fast-acting medication provides, is essential to treating this potentially life-threatening condition. *Id.* Without treatment, morbidity and mortality increase significantly. *Id.*

Treating epilepsy with benzodiazepine formulations intravenously was known by 2008, but medical professionals had to inject these products, greatly

limiting their use for epileptic patients outside a hospital or clinic setting.

Appx10915-10916. A rectal gel (Diasat®) was also available, but again its use was limited to specific situations, and not conducive to administration in public. *Id.* Diasat® was approved in 1997 and remained the only FDA-approved benzodiazepine product on the market in 2008 (the time of invention) that non-medical professionals could use to treat epileptic seizures. Appx10918-10919. Indeed, it was the only such product until the FDA approved NAYZILAM® in 2019 and Neurelis's nasal product early in 2020. Appx656, Appx10931. Hence, an enormous unmet need existed when Neurelis filed the '558 provisional application describing intranasal benzodiazepine formulations, as Dr. Daniel Wermeling, Aquestive's replacement expert, reported before this litigation began. Appx00656-00659, Appx10639.

The '876 patent claims all relate to methods of treating a patient by nasally administering a benzodiazepine solution. Claim 1 is the sole independent claim and recites (indenting added):

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.

The definition for the pharmaceutical solution uses the closed phrase “consisting of” to limit the scope of both claim 1 and its dependent claims. Dependent claim 27 recites that “the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and *dodecyl maltoside*” (emphasis added). Dependent claims 26, 28, and 30-33 also recite dodecyl maltoside. Dodecyl maltoside is an alkyl glycoside (*see, e.g.,* ’876 patent, col. 17, lines 5-8 and col. 35, lines 59-63).

While benzodiazepine drugs are effective for immediate cessation of epileptic seizures, administering therapeutically efficacious doses other than intravenously or rectally proved daunting. Appx10915-10916. Indeed, Aquestive still does not have an approved benzodiazepine product. Before 2008, administering benzodiazepines in a clinically-sufficient dose to rescue a seizing patient was known to be challenging because benzodiazepines have low solubility in aqueous solutions. Appx10916-10918. Insolubility thwarted efforts to deliver a sufficient dose and to avoid precipitate formation, which would irritate the nasal cavity and reduce uptake of the benzodiazepine. Appx473-474, Appx10928-10929. Furthermore, non-aqueous solvents such as benzyl alcohol were known irritants and could further exacerbate irritation to the nasal cavity. Appx49-50, Appx501-502, Appx10947-10949.

The art at the time of invention was unpredictable. Indeed, Dr. Sveinbjörn Gizurarson, a successful inventor in nasal formulations and the expert witness for Neurelis, expressed surprise that Neurelis was able to create a successful product in 2008. Appx10962-10963. Neurelis achieved its claimed breakthrough by combining miscible solvents and biological detergents to maintain a benzodiazepine in solution until the patient needed it, yet still provide a solution tolerable to the sensitive nasal membranes. Benzodiazepines are so important for treating epilepsy that the FDA gave Neurelis orphan drug designation for its intranasal diazepam product (VALTOCO®) in 2015 for the treatment of acute repetitive seizures and, with its approval early last year, VALTOCO satisfies epileptics' long-felt need for an alternative to either rectal diazepam or medical-professional administration. Appx508-512, Appx10909-10910, Appx10962-10964.

B. Neurelis' Priority Claim

The '876 patent claims priority under 35 U.S.C. §119 to the '558 provisional application, filed on March 28, 2008. Only this priority claim is contested. The contested disclosure—alkyl glycosides generally and dodecyl maltoside specifically—in the '558 provisional application is incorporated by reference. After discussing the importance of absorption enhancers to the invention, the '558 provisional application discloses:

In some embodiments, enhancing agents that are appropriate include . . . surface active agents (*especially non-ionic materials*) . . . and *biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference)*. * * * Suitable concentrations are up to 20% w/v.

Appx7814 (emphasis added). The six expressly incorporated SIGMA pages identify four classes of suitable biological detergents: anionic, cationic, zwitterionic, and nonionic. Appx10705-10710. Most of the nonionic options listed on page 316 are alkyl glycosides, specifically including n-dodecyl β -D-maltoside. Appx10705. Seven alkyl glycosides are listed on the first page and three more alkyl glycosides are listed in greater detail on pages 319-320. Appx10708-10710. The listed alkyl glycosides are (underlining added):

n-Decyl β -D-glucopyranoside,

n-Dodecyl β -D-glucopyranoside,

n-Dodecyl β -D-maltoside,

n-Heptyl β -D-glucopyranoside,

n-Octyl β -D-glucopyranoside,

n-Octyl α -D-glucopyranoside,

n-Nonyl β -D-glucopyranoside,

n-Heptyl β -D-thio-glucoside,

n-Hexyl β -D-glucopyranoside, and

Octyl β -D-thiogluconoside.

Appx478-479. These non-ionic detergents would have been instantly recognizable as alkyl glycosides to a person of ordinary skill in the art (“POSA”), as the testimony of both Neurelis’s Dr. Gizurarson and Aquestive’s Dr. Peppas confirmed. *See* Appx10935-10938, Appx10884-10885. A POSA who followed the explicit direction to look at the biological detergents of the incorporated material would have had no doubt that the inventors possessed an invention including the use of alkyl glycosides, specifically including dodecyl maltoside. Appx10908-10909, Appx10912-10913, Appx10935-10938; *see also* Appx10834-10835.

C. The Inter Partes Review

Aquestive Therapeutics, Inc. (“Aquestive”) filed the IPR leading to this appeal, alleging all of the ’876 patent claims were obvious over either the combination of WO2009/120933 (“Gwozdz”) and US2006/0046962 (“Meezan”), or the combination of Gwozdz, Meezan, and US2008/0279784 (“Cartt”). Appx210. All three references in the IPR—Gwozdz, Meezan, and Cartt—were cited during prosecution. Appx71-73. The lead inventors on both Gwozdz and Cartt are also named inventors on the ’876 patent. Gwozdz and Cartt are noted as cited references in the ’876 patent, but were not applied during prosecution. The examiner considered Meezan during the examination of parent applications. Appx214.

To assert Gwozdz as prior art, Aquestive had to strip Neurelis of its priority claim to the '558 provisional application, arguing that Neurelis should only receive benefit of a later application. Appx223-225, Appx486-489. Neither Aquestive nor its expert, Dr. Peppas, addressed the disclosure incorporated from the SIGMA catalog when the IPR petition was filed. Instead, Aquestive asserted that “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.” Appx225. Aquestive provided no alternative theory for unpatentability if Neurelis received benefit of its claimed priority.

In fact, the '558 provisional application recommends use of a biological detergent—preferably a non-ionic surfactant—and explicitly incorporates into its disclosure pages 316-321 of the 1988 SIGMA catalog, which listed alkyl glycosides, including dodecyl maltoside, as non-ionic surfactants. Appx478-480, Appx10932-10938. These alkyl glycosides were well known in 2008 and would have been instantly identifiable to a POSA. Appx10932-10938. Yet Aquestive failed to even acknowledge or file pages 316-321 of the 1988 SIGMA catalog as an exhibit, much less explain why the catalog’s explicit disclosure of several alkyl glycosides, including dodecyl maltoside, fell short of providing sufficient written description for the claims. Appx486-489. When the incorporation by reference of

the 1988 SIGMA catalog is properly considered, the '558 provisional application has express support for alkyl glycosides, including dodecyl maltoside.

In its Preliminary Response (“Preliminary Response”), Neurelis explained that Aquestive’s petition failed to address the '558 provisional application’s disclosure of alkyl glycosides generally and of dodecyl maltoside specifically once the incorporated SIGMA catalog pages were considered. Appx341-344, Appx643-646. The Preliminary Response explained this failure is critical because this incorporation provided the disclosure Aquestive said was missing—i.e., Aquestive had failed to meet its burden to demonstrate Gwozdz is even eligible as prior art. Appx344. Without Gwozdz as prior art, the IPR could not have been instituted. Appx342. Presciently, the Preliminary Response concluded with the caution from *Allsteel Inc. v. DIRT T Envtl. Sols. Ltd.* (IPR2015-01690) that the “Board cannot supply arguments for petitioner.” Appx344.

Nevertheless, the Board instituted review on a new and legally wrong theory. The Board acknowledged the '558 provisional application’s incorporation of the SIGMA catalog but explained, “our Rules do not permit the incorporation by reference of essential material from non-patent publications. See 37 C.F.R. §1.57 (d); see also 37 C.F.R. §1.57(h).” Appx357. The Board found the “‘alkyl glycoside’ limitation appears to be essential material” and therefore “reliance on the disclosure of the SIGMA catalog for adequate support ... is improper.”

Appx358. In a footnote, the Board stated “[s]ince all of the remaining claims of the ’876 patent depend, directly or indirectly, from Claim 1, they also require the presence of ‘an alkyl glycoside’.” Appx356.

Neurelis requested rehearing noting that rather than rely on Aquestive’s theory of unpatentability, the Board *sua sponte* raised an inapplicable formality objection. Appx406-407; *cf.* 35 U.S.C. §312(a)(3) (requiring petitioner to identify the challenge with particularity).

Neither the petition nor the decision even suggests that a person of ordinary skill in the art would have failed to understand the provisional specification ***(including the specifically and precisely incorporated biological detergents from six pages of the commercially-available 1988 SIGMA catalog, EX2006)*** or appreciate from the specification what the inventors had invented.

Appx408 (emphasis added). Neurelis also explained the long-standing official agency interpretation of 37 CFR §1.57 (“Rule 57”) is that it only applies to ***non***provisional applications ***during*** prosecution, rather than to a provisional application or a granted patent (which are not undergoing examination). Appx410-414.

The Board denied relief on rehearing, instead altering the block quote above to omit the emphasized parenthetical requirement to consider the SIGMA catalog and held that the thus-altered misquotation was not true because both the petition and decision addressed written description. Appx457. Based on this distortion of the request for rehearing, the Board held it did not need to reach any other

arguments in the request, including the incorrect application of Rule 57 at the heart of the Board's decision. Appx460. Neurelis requested consideration by the Board's Precedential Opinion Panel, but the request was denied without explanation. In its patent-owner response, Neurelis further addressed the misapplication of Rule 57, ensuring that it was preserved for appeal. Appx489-491.

Aquestive filed a Reply with a declaration from a new expert, Dr. Wermeling ("Wermeling declaration").¹ Appx552. Aquestive argued Rule 57 applies to provisional applications. Appx560. Neither Aquestive's reply nor the Wermeling declaration addressed the explicit disclosure of dodecyl maltoside in the SIGMA catalog. In a surreply, Neurelis pointed out that Aquestive had employed new arguments and evidence never suggested in its petition to address the SIGMA catalog's disclosure, thus denying Neurelis its opportunity to produce a response with supporting evidence. Appx638-643, Appx661-662. Board practice did not permit Neurelis to respond to Dr. Wermeling's new theories with its own expert evidence. Neurelis also pointed out that neither of Aquestive's experts denies that the SIGMA catalog is incorporated into the '558 provisional application and discloses alkyl glycosides. Appx647. In fact, once he considered the pages of

¹ For its reply, Aquestive replaced its original expert, Professor Peppas, after his cross examination in which he agreed with Neurelis on key issues, as discussed more below.

the SIGMA catalog as identified in the '558 provisional, Aquestive's Dr. Peppas agreed with Neurelis's Dr. Gizurarson that the SIGMA catalog was incorporated by reference and that it disclosed alkyl glycosides. Appx479-480, Appx487-488, Appx646-647, Appx801.

The Board issued a final written decision holding all '876 patent claims unpatentable over Gwozdz and Meezan, and over Gwozdz, Meezan, and Cartt. Appx68-69. The Board's Final Written Decision credited the testimony of Drs. Peppas (Aquestive's first expert witness) and Wermeling (Aquestive's new expert) in their determination that one of ordinary skill in the art would have had a reasonable likelihood of success in combining the disclosures of Gwozdz and Meezan to achieve the claimed invention. Appx37-51. However, while the Board relied on both experts in the Decision, the Board did not address the contrary evidence provided by Dr. Peppas during deposition, including (in addition to agreement that the incorporated SIGMA catalog disclosed alkyl glycosides) whether water was present in the claimed formulations and whether solutions include particulates. Appx649-651, Appx655-656.

Regarding the Board's shift from its incorporation-by-reference analysis at institution, the Decision stated that "we do not need to decide the Rule 57 issue because, even assuming the material in the SIGMA catalog was properly incorporated by reference, we find that this disclosure is not sufficient to provide

written description support for the ‘alkyl glycoside’ limitation in the claims.”

Appx19. Yet the decision never explained why the separately-argued dependent claims that expressly recite dodecyl maltoside were not supported by its express disclosure on the first page of the catalog, leaving the unavoidable inference that either the Board did not read these dependent claims or it did not actually consider the catalog to be incorporated.

SUMMARY OF THE ARGUMENT

The IPR from which this appeal is taken started with fatal deficiencies in the petition, particularly on the priority question. The ’558 provisional application expressly incorporated biological detergents specifically identified on pages from a SIGMA catalog for use as enhancers. Those pages expressly disclose alkyl glycosides, including dodecyl maltoside. Incorporation means that disclosure was part of the ’558 provisional application. Yet the Board improperly rejected this incorporation in its institution decision, then created new and flawed requirements for written description in its final written decision. At institution, the Board wrongly held that the catalog could not be incorporated. In the final decision, the Board assumed the incorporation was proper, but then required blaze marks to incorporate the disclosure that had already been incorporated. Although the Board applied the wrong standard to the incorporated materials, even under that standard, the ’558 provisional application nevertheless provided guidance that would

necessarily lead a POSA to the catalog's alkyl glycosides. The Board erred by requiring guidance that would lead *only* to the alkyl glycosides.

Because Neurelis is entitled to priority to the '558 provisional application, the Gwozdz reference is not prior art. Since Gwozdz is required for both grounds used in the Final Written Decision, the obviousness conclusion is fatally deficient. No remand is needed because the record cannot support any other result.

The Board's error in the institution decision regarding the propriety of incorporation also created a serious due-process violation. Aquestive did not address the incorporated material until its reply, at which point Neurelis could not respond with evidence. Prior to Neurelis filing its patent owner's response (its last occasion to provide new evidence), neither Aquestive nor the Board provided Neurelis with notice of Aquestive's theory regarding the incorporated material. If this Court reverses, this violation is moot; but in the event of a remand, due process requires Neurelis be provided with an opportunity to respond with evidence and argument.

Even with the Board improperly shifting the burden on priority to Neurelis without an adequate opportunity to respond to Aquestive's new expert evidence with its reply, the Board's holding on priority is not supported by substantial evidence because the Board failed to consider contrary evidence. As a matter of law, the SIGMA pages are part of the '558 provisional application disclosure,

which means that everything on those pages was disclosed. Neurelis's Dr. Gizurarson and Aquestive's first expert, Dr. Peppas, agreed that the SIGMA pages are expressly incorporated and would have been understood to disclose alkyl glycosides, including dodecyl maltoside. In sum, ample contrary evidence that the Board disregarded proves that '558 provisional application (when properly considered with the incorporated content) reasonably conveyed possession of alkyl glycosides (among other compounds) as enhancers for the invention.

For dependent claims 26-28 and 30-33, the priority decision is even more flawed because the SIGMA catalog pages expressly recite dodecyl maltoside. Neurelis pointed this out in its response, but the Board did not even address these claims other than to acknowledge that they recite dodecyl maltoside. The Board appears to have construed the claims to all require "an alkyl glycoside", which the Board determined was not supported. The Board never addressed whether the SIGMA catalog sufficiently supported those dependent claims requiring the more specific dodecyl maltoside.

Even assuming the intervening art is eligible prior art, the Board's Decision finding the claims of the '876 patent unpatentable as obvious should be reversed, at least because a POSA would have lacked motivation to combine the asserted references and a reasonable expectation of success in doing so. The teachings in the references are incompatible and the difficulties in solubilizing benzodiazepines

were well-known. Moreover, the Board disregarded strong evidence of long-felt need and failure of others based on a legally flawed nexus determination. As such, a POSA would not have found the claims of the '876 patent to have been obvious.

ARGUMENT

A. Legal Standards

Obviousness is a question of law based on underlying fact determinations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). While subsidiary fact questions are subject to substantial-evidence review, such review must take into account evidence that both supports and detracts from the decision. *ATI Techs. ULC v. Iancu*, 920 F.3d 1362, 1368 (Fed. Cir. 2019) (“[S]ubstantial evidence’ review involves examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency’s decision.” (quoting *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000))). A factfinder “cannot, through a credibility determination, ignore the wealth of evidence, especially as in this case where the expert did not even address it.” *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1324 (Fed. Cir. 2017). Moreover, whether the agency applied the correct standard to the facts is a question of law reviewed *de novo*. *Shea v. Willkie*, 926 F.3d 1362, 1368 (Fed. Cir. 2019). Claim construction and eligibility as prior art are questions of law reviewed *de novo*. *Riverwood Int’l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1352 (Fed. Cir. 2003). Critically for the dependent claims, the

phrase ***consisting of*** creates a very strong presumption that that claim element is “closed”, i.e., excludes any ingredients not specified in the claim. *Shire Development, LLC v. Watson Pharmaceuticals, Inc.*, 848 F.3d 981, 984 (Fed. Cir. 2017).

Determination of priority is a question of law reviewed *de novo*, based on subsidiary fact findings. *Bayer AG v. Schein Pharms., Inc.*, 301 F.3d 1306, 1312 (Fed. Cir. 2002). Written description is a question of fact. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). However, written description is highly case specific and no bright-line rules govern; for example, the number of species needed to define a genus is case specific. *Id.* at 1351-52. Hence, application of written-description standards to the facts of a given case is reviewed for legal error. *In re Global IP Holdings LLC*, 927 F.3d 1373, 1377 (Fed. Cir. 2019). In proceedings before the United States Patent and Trademark Office, the challenger has the initial burden of production to show a lack of priority. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996) (vacating for failure to consider contrary expert testimony on written description); *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Allowing the challenger to ignore the relevant portions of the priority disclosure is indistinguishable from an improper burden shift.

“Incorporation by reference provides a method for integrating material from various documents into a host document ... by citing such material in a manner that

makes clear that the material is effectively part of the host document as if it were explicitly contained therein.” *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). The standard has long been that a host document incorporates material by reference if it identifies with detailed particularity what specific material it incorporates and clearly indicates where that material is found in the various documents. *See Harari v. Lee*, 656 F.3d 1331, 1334 (Fed. Cir. 2011). “Whether and to what extent an application incorporates material by reference is a question of law reviewed *de novo*.” *Harari v. Lee*, 656 F.3d at 1334 (citing *Harari v. Hollmer*, 602 F.3d 1348, 1351 (Fed. Cir. 2010)). In making such a determination, the question is whether a skilled artisan would understand the host document to describe with sufficient particularity the material to be incorporated. *See id.*; *Husky Injection Molding v. Athena Automation Ltd.*, 838 F.3d 1236, 1248 (Fed. Cir. 2016).

The Board’s reliance on a new theory—never argued by any party—in resolving a dispositive issue is reviewed *de novo*. *See In re Stepan Co.*, 660 F.3d 1341, 1343-44 (Fed. Cir. 2011); *see also In re NuVasive, Inc.*, 842 F.3d 1376, 1384 (Fed. Cir. 2016) (vacating the Board’s obviousness determinations where the Board neither expressly adopted the petitioner’s arguments regarding motivation to combine nor provided reasoned explanations for crediting the arguments). Where an agency departs from established precedent without a reasoned explanation, its

decision will be vacated as arbitrary and capricious. *Fred Beverages Inc. v. Fred's Capital Mgmt. Co.*, 605 F.3d 963, 967 (Fed. Cir. 2010) (reversing TTAB decision).

**B. The Board Erred in Denying Neurelis its Claimed Priority Date;
Thus Erroneously Concluding Gwozdz Was Prior Art**

The '876 patent claims priority to the '558 provisional application, filed on March 28, 2008. Appx71. Gwozdz also claims priority to a provisional application filed on March 28, 2008. Appx8018. Gwozdz was not *before* the '558 provisional application. Thus, Gwozdz cannot be prior art *unless* the '876 patent is stripped of its priority to the '558 provisional application.

The Board stripped the '876 patent claim of its priority date by failing to consider the incorporated material as actually incorporated and only thus finding inadequate support for “the ‘alkyl glycoside’ limitation.” Appx23. This misapplication of the law was error because, under *Husky*, the incorporated material including all of the identified, subcategorized compounds in the SIGMA catalog pages was indeed part of the '558 provisional application disclosure. The question is not whether the listed alkyl glycosides were preferred, as the Board required: the listed alkyl glycosides are literally part of the '558 disclosure by virtue of their incorporation by reference.

To find otherwise, the Board employed a shifting array of strategies—none based in the petition—to disregard the expressly incorporated disclosure in the

'558 provisional application. *Cf. SAS Institute Inc. v. Iancu*, 584 U.S. ___, 138 S. Ct. 1348, 1355 (2018) (“in an inter partes review the petitioner is master of its complaint”). Indeed, the petition did not address the incorporated material or even provide the incorporated document (the SIGMA catalog) as an exhibit. In the institution decision, the Board denied the material was incorporated despite the USPTO’s own longstanding interpretation of its rule to the contrary. Aquestive neither advanced this theory in its petition nor defended it in its reply, probably because the theory is indefensible.

In the Final Written Decision, the Board said it would assume the incorporation was proper, but stated that the specification did not point to a preference for alkyl glycosides. Again, petitioner never made this legally-baseless argument in the petition or reply. The Board’s new theory inverts proper written-description analysis, superimposing a preference test rather than looking at what a POSA would have understood from the expressly incorporated alternatives. *Ariad*, 598 F.3d at 1351 (explaining “the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.”). The Board had it backwards, when the specification—with the incorporated material properly considered as part of the disclosure—expressly discloses a dozen alkyl glycosides as among the enhancers considered to be part of the invention, the

question cannot be whether those alkyl glycosides were actually disclosed. *Husky*, 838 F.3d at 1248.

The '558 provisional application supports every claim of the '876 patent because a POSA would have appreciated that the inventors possessed alkyl glycosides as enhancers simply from reading the specification *including the incorporated catalog*. The Board erred in refusing to recognize the disclosure of alkyl glycosides in the '558 provisional application (by virtue of its incorporation by reference of the SIGMA catalog) generally, and the disclosure of dodecyl maltoside specifically. Without this error, the '876 patent is entitled to its priority date, and Gwozdz is not prior art.²

1. The '558 provisional application properly incorporated the SIGMA catalog by reference

As this Court's predecessor explained, "our primary concern is whether the description requirement has been complied with, not the mode selected for compliance." *In re Edwards*, 568 F.2d 1349, 1352 (CCPA 1978); *accord*

² Although Neurelis simplifies consideration of the priority question to dispositive analysis of the only primary reference asserted (i.e., Gwozdz), Cartt is likewise not prior art based on Aquestive's position. Specifically, Cartt was only asserted by Aquestive as prior art under 35 U.S.C. § 102(e)(1) based on its May 7, 2008, formal filing date of U.S. Patent Application Serial No. 12/116,842, and its November 13, 2008 publication date. Thus, based on Aquestive's position, Cartt is likewise not prior art if the '876 patent is entitled to its priority date.

MPEP 608.01(p)(I)(B) (explaining the statutes do not restrict incorporation so the rule only applies to an application under examination). Although Rule 57 restricts the manner of incorporation, the plain language of the rule makes clear that it applies *during* examination of non-provisional applications, not to priority (foreign and provisional applications) applications, which are not examined. For example, Rule 57(h) (emphasis added) provides:

An incorporation of material by reference that does not comply with paragraphs (c), (d), or (e) of this section is not effective to incorporate such material **unless corrected within any time period set by the Office**, but in no case later than **the close of prosecution** as defined by §1.114(b), or **abandonment of the application**, whichever occurs earlier.

The '558 provisional application was never examined, was not the subject of this IPR, and the Office certainly never set a period for it to be corrected. If there were any doubt about the proper interpretation, both official USPTO guidance and a past Board decision confirm this reading. The USPTO has long interpreted its own rule on incorporation by reference (Rule 57) to permit incorporation of non-patent documents in 35 U.S.C. §119 priority documents. Under the subheading **“Review of Applications Which Are Relied on To Establish an Earlier Effective Filing Date”**, the Manual of Patent Examining Procedure instructs examiners that:

The limitations on the material which may be incorporated by reference in U.S. patent applications which are to issue as U.S. patents *do not apply to applications relied on only to establish an earlier*

effective filing date under 35 U.S.C. 119 or 35 U.S.C. 120. Neither 35 U.S.C. 119(a) nor 35 U.S.C. 120 places any restrictions or limitations as to how the claimed invention must be disclosed in the earlier application to comply with 35 U.S.C. 112(a). Accordingly, ***an application is entitled to rely upon the filing date of an earlier application***, even if the earlier application itself incorporates essential material by reference to another document. *See Ex parte Maziere*, 27 USPQ2d 1705, 1706-07 (Bd. Pat. App. & Inter. 1993).

MPEP §608.01(p)(I)(B) (emphasis added).

Maziere overturned a rejection based on applying Rule 57 to a parent application rather than asking whether the parent-application disclosure with the incorporated material was sufficient. 27 USPQ2d at 1706-07. Here the Board instituted trial based on a misapplication of Rule 57, arbitrarily and capriciously changing the rule’s meaning without notice or explanation. *Fred Beverages*, 605 F.3d at 967 (unexplained change in practice was arbitrary).³

2. The Board erroneously required a *preference* for alkyl glycosides, rather than simple possession

The Decision states “[w]e do not find that the ’558 provisional application’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. The Board also

³ A *sua sponte* agency decision contrary to its own long-established practice and without notice or explanation is the type of “shenanigan” *Cuozzo Speed Techs., LLC v. Lee* explained would be held arbitrary and capricious on review. 579 U.S. ___, 136 S. Ct. 2131, 2142 (2016).

stated, “[t]here is nothing in the disclosure of the ’558 provisional application that directs one of skill in the art to the relatively small number of alkyl glycosides disclosed in the SIGMA catalog.” *Id.* These findings expose the flawed legal standard the Board applied.

The ’558 provisional application incorporated ***all*** of the biological detergents as they were presented and subcategorized on the six catalog pages; hence, the provisional application reasonably showed possession of ***all*** of the 150 biological detergents, specifically including the dozen listed alkyl glycosides categorized as non-ionic biological detergents. However, the Board appears to require direction to incorporate ***only*** the twelve alkyl glycosides before it will find them described at all. Appx19.

Under long-standing practice, an incorporation by reference “make[s] one document become a part of another document by referring to the former in the latter in such a manner that it is apparent that the cited document is part of the referencing document as if it were fully set out therein.” *In re Lund*, 376 F.2d 982, 989 (CCPA 1967); *Husky*, 838 F.3d at 1248. If the Board had properly treated all of the SIGMA pages and the subcategories of detergents those pages disclose as incorporated into the ’558 provisional application, the question of whether anything “directs one of skill in the art to the relatively small number of alkyl glycosides disclosed in the SIGMA catalog”, Appx19, would have been moot

because they were already expressly incorporated.⁴ Appx7814 (incorporating the catalog pages). Contrary to the Board’s analysis, nothing requires the disclosed invention be the only, or even the preferred, embodiment. *In re Brower*, 433 F.2d 813, 817 (CCPA1970).

The question was not whether a POSA would have known to incorporate those twelve alkyl glycosides—the ’558 provisional application gave express guidance to do so—but whether in this context those twelve species were sufficient to be recognized by a POSA as a genus. *Ariad*, 598 F.3d at 1352 (precedent “has always expressly permitted the disclosure of structural features common to the members of the genus”). The Board never addressed the correct question, apparently because it did not actually treat the pages of the SIGMA catalog and the subcategories of detergents (including the twelve alkyl glycoside species) as already incorporated. Consequently, the Board required Neurelis to meet an improperly high standard for written description (requiring a preference for some catalog compounds for incorporation) rather than the proper standard (whether actually disclosing subcategories of biological detergents including twelve

⁴ The Board says that, for purposes of the decision, it assumes the incorporation is proper. Appx19 n.7. Yet the Board’s requirement for guidance to pick and choose from the incorporated materials before incorporating anything is inconsistent with the very idea of incorporation by reference. Whatever it said, the Board was plainly not treating the SIGMA pages, including their subcategorization of the listed detergents, as incorporated in their entirety.

different alkyl glycosides was sufficient to demonstrate possession of alkyl glycosides as enhancers in the invention).

3. The '558 provisional application provided explicit blaze marks to the alkyl glycosides in the SIGMA catalog

The Board also required “blaze marks” to the alkyl glycosides before they would be considered incorporated. Appx19-20 (“[N]othing in the '558 provisional application’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.”); see also n.8 (“[T]his list would still include over 100 compounds with no guidance in choosing the alkyl glycosides over other non-ionic compounds.”). As discussed in the previous section, this reflects the wrong standard by calling for a preference and the wrong question because the listed alkyl glycosides were already incorporated and subcategorized. Nevertheless, the '558 provisional application blazed a reasonably sufficient trail to the alkyl glycosides in the SIGMA catalog pages.

The disclosure must “reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad*, 598 F.3d at 1351. In assessing written description, the disclosure must be considered “as a whole”. *Edwards*, 568 F.2d at 1354. The '558 provisional

application considered as a whole—necessarily including the incorporated and subcategorized compounds, including alkyl glycosides—satisfies the written description requirement. The very paragraph that incorporates the SIGMA catalog pages, expresses a preference for “non-ionic materials”. Appx7814. A POSA would have looked to the non-ionic detergents list, which is one of the “four major detergent categories” listed within the Biological Detergents at page 316 of the SIGMA catalog. Appx10705. As shown below, among the detergents on page 316 of the SIGMA catalog appearing under the category “Non-Ionic,” most are an alkyl glycoside (n-Decyl β -D-glucopyranoside, n-Dodecyl β -D-glucopyranoside, n-Dodecyl β -D-maltoside, n-Heptyl β -D-glucopyranoside, n-Octyl β -D-glucopyranoside, n-Octyl α -D-glucopyranoside, and n-Nonyl β -D-glucopyranoside). Appx10935-10936.

BIOLOGICAL DETERGENTS

Sigma offers a wide range of detergents useful to the biochemist for the solubilization of proteins and membrane components. This section is organized into the four major detergent categories:

Anionic

Cationic

Zwitterionic (Amphoteric)

Nonionic (Polar)

Included below is a table of Critical Micelle Concentration (CMC) values and molecular weights for selected detergents. Detergents with high CMC values are generally easy to remove by dilution; detergents with low CMC values are advantageous for separations on the basis of molecular weight. As a general rule, detergents should be used at their critical micelle concentration* at a detergent-to-protein weight ratio of approximately ten.*

Ref.: 1. Womack, M.D., et al., *Biochim. Biophys. Acta*, **733**, 210 (1983).
2. Matson, R.S. and Goheen, S.C., *LC-GC*, **4(7)**, 624 (1986).

BIOLOGICAL DETERGENT	CMC (mM)	AGGREGATION NUMBER	MOLECULAR WEIGHT
Anionic			
Caprylic Acid, Sodium Salt	351	—	166.2
Cholic Acid, Sodium Salt	14	2-4	430.6
1-Decanesulfonic Acid, Sodium Salt	32.6	—	244.3
Deoxycholic Acid, Sodium Salt	5	4-10	414.6
Glycocholic Acid, Sodium Salt	13	—	487.6
Glycodeoxycholic Acid, Sodium Salt	2	—	471.6
Lauryl Sulfate, Sodium Salt	8-27	62	288.5
Taurocholic Acid, Sodium Salt	10-15	4	537.7
Taurodeoxycholic Acid, Sodium Salt	2-6	5	521.7
Cationic			
Cetylpyridinium Chloride	0.90	—	274.0
Dodecyltrimethylammonium Bromide	14	—	308.4
Hexadecyltrimethylammonium Bromide	0.026	169	364.5
Tetradecyltrimethylammonium Bromide	0.28	—	336.4
Zwitterionic			
CHAPS	8	10	614.9
CHAPSO	8	11	630.9
Non-Ionic			
n-Decyl β -D-glucopyranoside	2.2	—	320.4
Digitonin	—	6	1229.3
n-Dodecyl β -D-glucopyranoside	0.19	—	348.5
n-Dodecyl β -D-maltoside	0.16	—	348.5
n-Heptyl β -D-glucopyranoside	70 (est.)	—	278.4
n-Octyl β -D-glucopyranoside	25	27	292.4
n-Octyl α -D-glucopyranoside	10	—	292.4
Nonidet P-40	0.29	—	602.8
n-Nonyl β -D-glucopyranoside	6.5	—	306.4
Triton X-100	0.24	140	624.9

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Reading the preference for non-ionic detergents—a major category of biological detergent in the incorporated materials with alkyl glycosides prominently featured—would have been ample to show possession of alkyl

glycosides as being among the penetration enhancers the inventors intended for the invention. Appx478-480, Appx10932-10938. Yet the Board incongruously stated that it found no blaze marks to restrict the incorporation to just non-ionic detergents, improperly treating the incorporated biological detergents as a laundry list of 150 uncategorized compounds that a POSA would not select as part of the invention without even more guidance. Appx19-20 text & n.8. Again, this is the wrong question: the Board seeks blaze marks for what to incorporate rather than what was part of the invention. The blaze mark for incorporation could not be clearer—it is all of “biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference).” [EX1008, ¶152]—no selection is required. The blaze-marks test has no bearing on incorporation because the POSA was not required to pick and choose what incorporated disclosure is relevant; rather, all of the incorporated disclosure was relevant and the POSA only needed to see that alkyl glycosides were part of the incorporated disclosure.

Moreover, as Dr. Gizurarson explained (and Dr. Peppas agreed), a POSA would have readily appreciated from the incorporated pages of the SIGMA catalog that the inventors had possession of the claimed subject matter, including alkyl glycosides. Appx10932-10938. A POSA would have immediately apprehended the presence of *alkyl glycosides*, including n-Dodecyl β -D-maltoside, from the pages of the SIGMA catalog. *See* Appx10935-10936. Indeed, out of the approximately 150

different compounds on the cited pages, nearly 10% are part of the POSA-recognized class of “alkyl glycosides.” Appx802, Appx10935. Furthermore, a POSA looking at the first incorporated page of the catalog (p. 316) would see a table listing 25 “selected detergents,” of which seven (including n-**Dodecyl** β -D-**maltoside**) are alkyl glycosides. Appx10705.

Thus, to the extent blaze marks are required, the ’558 provisional application provided 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. As Dr. Gizurarson put it: “As such a POSA would have known and recognized from the incorporation by reference that the ’558 Provisional Application highlighted alkyl glycosides, and that the inventors were in possession of alkyl glycosides as a key part of the claimed inventive concept.” Appx10938. In sum, clear blaze marks pointed the way to alkyl glycosides among other acceptable enhancers for the invention.

Nothing in the case law requires blaze marks to “restrict” the disclosure to a single preferred embodiment. *Brower*, 433 F.2d at 817. The Board simply created and applied the wrong standard for the first time in its decision to reach the wrong result. Applying this wrong standard requiring the priority document show a preference for alkyl glycosides, rather than simply sufficient possession led the Board to ignore contrary evidence by Aquestive’s expert Dr. Peppas where he

acknowledged that the incorporated pages disclosed alkyl glycosides. Appx10884-10885; *Cf. Alton*, 76 F.3d at 1175-76 (vacating for failure to consider contrary expert testimony on written description).

4. Aquestive's references are not prior art

Neurelis is entitled to its priority date for an invention including an alkyl glycoside; hence, Gwozdz is not available as prior art. Gwozdz is the primary reference for all of the grounds the Board used to find claims 1-36 unpatentable. Appx69. Because Gwozdz is not prior art, the unpatentability decision fails and the obviousness conclusions in the Final Written Decision must be reversed.

5. The delayed presentation of the issue was prejudicial

The disclosure must be considered “as a whole” to determine whether the written-description requirement has been satisfied. *Edwards*, 568 F.2d at 1354. Yet Aquestive's first expert, Dr. Peppas, conceded that he had not even considered the incorporated subject matter in his original analysis of written descriptive support (*see* Appx646, Appx10881-10885) and, once he had considered it, he understood that pages 316-321 of SIGMA catalog “does disclose alkyl glycosides” Appx10884-10885. Because the “whole” disclosure was not even considered in the petition (as Neurelis repeatedly pointed out), Aquestive did not put on its substantive case until its reply, for which it retained a new expert.

Aquestive has the ultimate burden of proof on patentability. 35 U.S.C. §316(e). Before the USPTO, the challenger also has the initial burden of production to show the priority disclosure was not sufficient. *Alton*, 76 F.3d at 1175 (“If . . . the specification contains a description of the claimed invention, albeit not in *ipsis verbis* (in the identical words), then the examiner or Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.”). Aquestive cannot carry its initial burden of production by simply closing its eyes (and its expert’s) to expressly incorporated disclosure. The Board’s insistence that Aquestive could simply allege a problem eliminated Aquestive’s initial burden entirely and left Neurelis without notice regarding what Aquestive’s substantive case would be. Nor did Aquestive provide supplemental information prior to Neurelis’s filing its response to allow Neurelis to respond with evidence. Critically, at the time of Neurelis’s response, ***the original expert for each party agreed*** the incorporated disclosure in the SIGMA catalog would convey to a POSA that the inventors possessed “alkyl glycosides” among the disclosed biological detergents, especially among the non-ionic biological detergents, categorized in the incorporated SIGMA catalog pages. Appx479-480, Appx487-488, Appx646-647, Appx801. The Board repeatedly found Dr. Peppas credible (Appx39, Appx41, Appx59), but failed to account for his concession on written description for alkyl glycoside. *Alton*,

76 F.3d at 1175. That Dr. Peppas held contrary views to Aquestive’s reply theory on the adequacy of the incorporated materials speaks volumes—not only on the merits—but also on how much of a departure Aquestive’s reply and reply evidence was from the theory Aquestive provided in its petition.

Aquestive first provided a substantive argument on the incorporated materials in its reply, using a new expert, Dr. Wermeling, who provided a new theory. At that stage, Neurelis could no longer file responsive evidence (other than the transcript and exhibits from Dr. Wermeling’s cross examination). Consol. Trial Practice Guide 73 (2019) (“The sur-reply may not be accompanied by new evidence other than deposition transcripts of the cross-examination of any reply witness.”), *now codified at* 37 CFR §42.23(b). Thus, the improper initial burden shift prejudicially continued to deny Neurelis of due-process basics like notice and the opportunity to respond with evidence. 5 U.S.C. §554; *Arthrex, Inc. v. Smith & Nephew, Inc.*, 935 F.3d 1319, 1328 (Fed. Cir. 2019) (discussing cases where “the Board departed markedly from the evidence and theories presented by the petition or institution decision, creating unfair surprise”), *quoted in M & K Holdings, Inc. v. Samsung Electronics Co., Ltd.*, No. 20-1160, slip op. 12-13 (Fed. Cir. Feb. 1, 2021) (vacating unpatentability for affected claim).

As explained above, the Board held the evidence already of record showed a POSA would not have known what to incorporate, which is the wrong question

because the incorporated materials were already incorporated. The record provides ample uncontroverted evidence that alkyl glycosides were an intended option for the invention, so no remand is necessary: outright reversal on the present record is appropriate. Nonetheless, if this Court holds that a remand is required, Neurelis should be permitted to submit a response with evidence to remedy the due-process violation that resulted from the improper burden shift.

C. The Board Erroneously Construed Claims 26-28 and 30-33, Denying Priority Despite Explicit Disclosure, to Treat Gwozdz as Prior Art

Claim 1 defines the invention in terms of use of a solution *consisting of* a set of ingredients, including an alkyl glycoside. The phrase “consisting of” limits the claims to the listed ingredients. Dependent claims 26-28 and 30-33 all depend from claim 1 and further define the invention as follows (emphasis added):

26. The method of claim **25**, wherein the solution contains about 0.01% to 1% (w/w) of *dodecyl maltoside*.

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

28. The method of claim **1**, wherein the solution *consists of* about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25%(w/v) *dodecyl maltoside*, q.s. dehydrated ethanol.

30. The method of claim **1**, wherein the solution *consists of* diazepam from 5 to 15% (w/v), *dodecyl maltoside* from about 0.01 to 1% (w/v) , vitamin E from 45 to 65% (w/v), ethanol from 10 to 25% (w/v) and benzyl alcohol from 5 to 15% (w/v).

31. The method of claim 1, wherein the solution *consists of* diazepam from 5 to 15% (w/v), **dodecyl maltoside** from 0.01 to 1% (w/v), vitamin E from 45 to 65% (w/v), ethanol from 10 to 25% (w/v) and benzyl alcohol from 5 to 15% (w/v).

32. The method of claim 1, wherein the solution *consists of* diazepam from 9 to 11% (w/v), **dodecyl maltoside** from 0.1 to 0.5% (w/v), vitamin E from 50 to 60% (w/v), ethanol from 15 to 22.5% (w/v) and benzyl alcohol from 7.5 to 12.5% (w/v).

33. The method of claim 1, wherein the solution *consists of* diazepam 10% (w/v), **dodecyl maltoside** from 0.15 to 0.3% (w/v), vitamin E from 50 to 60% (w/v), ethanol from 17 to 20% (w/v) and benzyl alcohol from 10 to 12% (w/v).

Because claim 1 is closed to the inclusion of ingredients other than those listed, the dependent claims must further limit those ingredients. Therefore, the dodecyl maltoside recited in the dependent claims cannot be a new ingredient; rather, it necessarily limits the claim 1's alkyl glycoside to the recited dodecyl maltoside. *Shire*, 848 F.3d at 984. In addition to the "consisting of" transitional phrase in independent claim 1, each of dependent claims 27, 28, and 30-33 recites a solution "consisting of" the recited components where dodecyl maltoside is the only alkyl glycoside. Neurelis noted that these claims were limited to dodecyl maltoside specifically. Appx487, n7. ("specifically identifying dodecyl maltoside (claimed in claims 26-28 and 30-33) as disclosed within the catalog entry"). Indeed, the Board acknowledged that claims 26-28 and 30-33 further require dodecyl maltoside. Appx33-35. The Board, however, failed to connect this understanding to the Neurelis priority claim, despite Neurelis identifying the

connection in its response. Appx487, n7. Instead, the Board improperly construed these claims together with the other '876 patent claims as merely calling for “an alkyl glycoside.” Appx14, n.6 (“Since all of the remaining claims of the '876 patent depend, directly or indirectly, from Claim 1, they also require the presence of ‘an alkyl glycoside.’”).

The Board’s construction is erroneous because it ignores the express further limitation of alkyl glycoside in these dependent claims to the recited dodecyl maltoside. This error is prejudicial because the '558 provisional application provides express support for dodecyl maltoside. Once claims 26-28 and 30-33 are properly construed, the Board’s unexplained conclusion that these dependent claims lack priority to the '558 provisional application is wholly unsupported and must be reversed. As a matter of law, the incorporated SIGMA catalog pages are literally part of the '558 provisional application’s specification. *Husky*, 838 F.3d at 1248. In addition to disclosing alkyl glycosides generally, the incorporated SIGMA catalog pages specifically disclose dodecyl maltoside twice, thereby literally providing written description for the feature which is allegedly missing from the '558 provisional application, as Aquestive’s first expert Dr. Peppas testified. Appx10884-10885. Neither Aquestive’s petition, the institution decision, Aquestive’s reply, nor the Final Written Decision can or do provide any basis for

holding dependent claims 26-28 and 30-33 were not supported in the '558 provisional application.

1. The Board's claim construction ignores the literal claim language and the disclosure of the '876 patent

Claims 26-28 and 30-33 all recite "dodecyl maltoside." Appx111-112.

However, the Board gave this limitation no weight in its Decision; instead, the Board simply held "[c]laim 1 requires 'an alkyl glycoside'. . . . **Since all of the remaining claims of the '876 patent, depend, directly or indirectly, from Claim 1, they also require the presence of 'an alkyl glycoside.'**" Appx14. Yet the plain language of claim 26-28 and 30-33 makes clear that they require dodecyl maltoside specifically rather than just any alkyl glycoside. The Board's construction fails to account for the *further limitation* in dependent claims 26-28 and 30-33 that the alkyl glycoside is specifically dodecyl maltoside. 35 U.S.C. §112(d) (dependent claims incorporate limitations and further limit).

Claims 27-28 and 30-33 all require that the solution used in carrying out the claimed method "consists of" amongst other things "dodecyl maltoside" with no possibility of the inclusion of a different additional alkyl glycoside. The closed nature of claims 27-28 and 30-33 means that these dependent claims' dodecyl maltoside *is* claim 1's alkyl glycoside. The Board's conclusion that these dependent claims of the '876 patent are not supported by the disclosure of the '558

provisional application is not explained, but it appears the Board misconstrued these claims to require an alkyl glycoside generally rather than dodecyl maltoside specifically, and thus swept these claims in with its holding for claim 1.

Claim 26 depends from claim 25, which depends from claim 24, which depends from claim 1. While claims 1, 24, and 25 specify an alkyl glycoside, claim 26 further narrows claim 25 to “wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside”, which is the same range claim 25 specifies for its alkyl glycoside. The ’876 patent specification identifies dodecyl maltoside as an example of an alkyl glycoside. Appx81. Thus, the dodecyl maltoside of claim 26 necessarily is the alkyl glycoside of claim 25. Hence, claim 26 cannot be construed, as the Board apparently did, to call for an alkyl glycoside generally; rather, it requires dodecyl maltoside specifically.

The Board’s construction of claims 26-28 and 30-33 was wrong and, under *de novo* review, should be reversed. Dependent claims 26-28 and 30-33 require the recited dodecyl maltoside specifically and, thus, an analysis based solely on alkyl glycoside generally is prejudicial error.

2. An accurate construction of dependent claims 26-28 and 30-33 justifies priority to the provisional filing date

The Board’s construction of claims 26-28 and 30-33 highly prejudiced Neurelis, resulting in denial of priority to the ’558 provisional application and

qualification of Gwozdz as prior art. Proper construction of claims 26-28 and 30-33 limits the claims to a dodecyl maltoside embodiment. Because the '558 provisional application expressly discloses dodecyl maltoside as an enhancer, these claims are entitled to the effective filing date of the '558 provisional application.

The error traces to Aquestive's petition which contends that the '558 provisional application's "generic disclosure of 'surface active agents (especially non-ionic materials)' . . . does not disclose, describe, and/or enable alkyl glycosides in general (or dodecyl maltoside in particular)." Appx225. Yet Aquestive did not address the SIGMA catalog at all, much less explain how the '558 provisional application including the incorporated catalog pages fails to disclose dodecyl maltoside. Appx10705, Appx10708 (*see, e.g.*, pp. 316, 319 ("n-Dodecyl- β -D-Maltoside")). Indeed, Aquestive did not even submit the SIGMA catalog into the record and Aquestive's first expert, Dr. Peppas, did not consider it in forming his opinions. Appx646, Appx10881-10885. Aquestive never addressed, much less challenged, the support for dodecyl maltoside in the SIGMA catalog. When asked during cross examination, Dr. Peppas agreed that the SIGMA catalog includes alkyl glycosides, specifically identifying dodecyl maltoside as disclosed within the incorporated catalog pages. Appx10857-10858. Consequently, no evidence (much less substantial evidence) supports a determination that claims 26-28 and 30-33 when properly construed lack support in the '558 provisional

application with the incorporated catalog pages. Properly construed, claims 26-28 and 30-33 unquestionably recite dodecyl maltoside specifically rather than alkyl glycoside generically.

3. Gwozdz is not prior art to dependent claims 26-28 and 30-33

Gwozdz are not available as prior art for at least claims 26-28 and 30-33, because Neurelis is entitled to the '558 provisional application's priority date for dodecyl maltoside. Without Gwozdz as prior art, both of the unpatentability grounds in the Decision fail. Accordingly, the obviousness conclusions for claims 26-28 and 30-33 should be reversed. A remand would be pointless because neither Aquestive nor the Board made a record to support any other conclusion on priority or on obviousness once proper priority is considered.

D. The Board Erred by Holding the Claims Obvious

Even assuming *arguendo* that Neurelis is not entitled to priority to the '558 provisional application filing date, the Board still erred in holding that the claims were obvious in view of the combinations of Gwozdz and Meezan (Ground 1) or of Gwozdz, Meezan, and Cartt (Ground 2). A POSA would have lacked motivation to combine the references and a reasonable expectation of success in doing so to meet the limitations of the '876 patent claims. Further, the claimed invention

fulfills a long-felt need in the art which others tried and failed to meet. As such, the Decision's holding the claims of the '876 patent obvious must be reversed.

1. Grounds for The Board's Unpatentability Decision and the Relied Upon Prior Art

In its Decision, the Board held the claims of the '876 patent were unpatentable based on the following Grounds using Gwozdz as the primary reference. Appx210, Appx5.

Ground	Claims Challenged	35 U.S.C.	Reference/Basis
1	1-16 and 24-36	§103	Gwozdz and Meezan
2	17-23	§103	Gwozdz, Meezan, and Cartt

Gwozdz is directed to a pharmaceutical solution to assist in solubilizing therapeutic agents such as, e.g., diazepam. Gwozdz accomplishes this without using an alkyl glycoside, as it does not disclose or suggest use of alkyl glycosides in its solutions. Appx238-239, Appx246, Appx9228.

Aquestive relied on Meezan for its disclosure of alkyl glycosides as an example of an absorption enhancer for use with intranasal solutions and, specifically, as *surfactants* to solubilize compounds in *aqueous* intranasal formulations. Appx10939-10940, Appx10871. However, Meezan does not apply to non-aqueous solutions, such as those Gwozdz disclosed or the '876 patent

claimed, nor does Meezan disclose benzodiazepines. Appx111-112, Appx10951-10955, Appx242, Appx9238.

Cartt discloses particulate formulations of benzodiazepines (Appx239, Appx9247-9248) and was cited by Aquestive for disclosing dosing regimens of particle formulations of benzodiazepines. Appx239. As Aquestive recognized, neither Gwozdz nor Meezan disclose particulate formulations (instead disclosing solutions). Appx239.

The Board agreed with the Grounds of unpatentability proposed by Aquestive.

2. A POSA lacked a motivation to combine the references

To invalidate a patent on obviousness grounds, the Board must “identify a reason that would have prompted a [POSA] in the relevant field to combine the elements” as the new invention does. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018) (“An obviousness determination requires finding that a [POSA] would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so.”) (citation omitted). The Board erred in holding the claims of the ’876 patent obvious because a POSA would have lacked (1) motivation to modify Gwozdz in the manner disclosed by the ’876 patent claims; and (2) motivation to combine the non-aqueous solutions of

Gwozdz with the aqueous solutions of Meezan or the particulate formulations of Cartt. Indeed, one of the striking features of the Final Written Decision is its confidence in a POSA's ability to modify the references despite internal indications it would not likely succeed; yet the Board considered the same POSA to be incapable of recognizing expressly recited alkyl glycosides as a common type within the non-ionic surfactants in the incorporated SIGMA catalog pages.

a. No motivation to modify Gwozdz; no expectation of success

Gwozdz pertains to “[p]harmaceutical solutions containing hydrophobic or lipophilic therapeutic agents and methods for producing same.” Appx8018. Gwozdz discusses solubilizing therapeutic agents, such as diazepam, and accomplishes this without using an alkyl glycoside. Appx8025-8026. Indeed, Gwozdz does not disclose the use of alkyl glycosides in any of its solutions. Appx238-239, Appx246, Appx9228. Rather than provide motivation to modify its disclosed formulations, Gwozdz instead teaches a different approach to solubilizing hydrophobic/lipophilic therapeutic agents.

Gwozdz's approach to solubilizing therapeutic agents focused on the use of tocopherol and an alcohol, and provided no motivation to modify its formulations with additional excipients. Appx9229. In one example, Gwozdz combined diazepam with tocopherol and ethanol and identified that “at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95%

tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.” Appx8025. A POSA, knowing that Gwozdz’s solubility level for diazepam is close to the clinical dose needed for therapeutic effect (10 mg), would have understood increasing the amount of tocopherol and decreasing the amount of ethanol increases the solubility of diazepam, and approaches its saturation concentration (which risks causing precipitation in the humid nasal cavity). Appx10944. Further, a POSA would have understood from Gwozdz that adding less tocopherol (such as 70% instead of 95%) reduces the solubility of diazepam (8% versus 9%, in the above example), risking the patient receiving a less than therapeutic amount of diazepam. Appx10943-10945. Hence, a POSA would have had no motivation to modify the formulation any further (let alone adding any additional excipient such as the claimed benzyl alcohol or alkyl glycoside); instead, a POSA would have doubted success because making the modification would require decreasing the amount of either or both of the tocopherol and ethanol, in turn decreasing the solubility of diazepam. Appx10941-10945. Neither Aquestive nor the Board demonstrated why a POSA would have been motivated to risk reducing drug solubility by removing or reducing a co-solvent taught by Gwozdz as necessary for maximizing the solubility of diazepam. *Id.* As such, a POSA would not have been motivated to modify the formulations of Gwozdz.

b. No motivation to combine Gwozdz with Meezan

Additionally, a POSA would have lacked motivation to combine Gwozdz with Meezan. Meezan discloses using alkyl glycosides as surfactants to solubilize compounds in aqueous intranasal formulations. Appx10939-10940, Appx10871. For example, Meezan tests the effect of adding alkyl glycoside to MIACALCIN®, a calcitonin-salmon nasal spray containing sodium chloride, benzalkonium chloride, nitrogen, hydrochloric acid, and ***purified water***. Appx9583-9584, Appx7962-7966. Indeed, Meezan discloses alkyl glycosides as a stabilizer only in aqueous formulations and does not exemplify a non-aqueous embodiment. Appx10871, Appx7962-7966. Dr. Gizurarson explained that by excluding water, the '876 patent claims “create[d] a milieu not conducive for a surfactant to function” since surfactants require water to “align themselves at the air- or oil-interface; without water, surfactants would have lacked the substrate needed to orient itself and function as a surface-active/tension-reducing agent.” Appx10955. Even Dr. Peppas testified that he had no understanding of how Meezan’s formulations would function in the absence of water. Appx652, Appx10872-10873. Meezan does not apply to non-aqueous solutions, such as those Gwozdz disclosed or the '876 patent claimed. Appx111-112, Appx10951-10955. Further, Meezan does not disclose benzodiazepines. Appx242, Appx9238.

Instead, Meezan is concerned with increasing absorption and decreasing adverse effects of water-soluble therapeutic drugs through non-intravenous routes of administration and increasing stability of its peptide and protein formulations by adding surfactants (including alkyl glycosides). Appx10952, Appx7950. The therapeutic drugs disclosed in Meezan do not include benzodiazepines, and instead primarily relate to water-soluble compounds, including the “anti-seizure agents” topiramate and zonisamide. Appx10952-10953. Accordingly, a POSA would not have found Meezan relevant to poorly water-soluble drugs such as benzodiazepines.

Additionally, a POSA would have doubted the utility of modifying the non-aqueous formulations of Gwozdz to include an alkyl glycoside because Meezan disclosed the use of such surfactants in an aqueous setting. Appx10953-10954, Appx7962-7966. Indeed, Aquestive’s expert Dr. Peppas testified that he did not know how Meezan’s alkyl glycosides would function in the absence of water (as and claimed in the ’876 patent). Appx10872, Appx10955. Dr. Peppas testified that a POSA would need information outside of either the Gwozdz or Meezan disclosure in order to determine how the alkyl glycosides of Meezan would function, including, *e.g.*, “[s]olubility of the glycoside in other solvents, [] other carrier . . . [p]robably a number of other parameters; pH, pH sensitivity, concentrations” etc. Appx10872. As such, a POSA would have lacked motivation

to combine Gwozdz with Meezan in a manner that rendered independent claim 1 of the '876 patent obvious. In ruling otherwise, the Board did not address contrary evidence from Aquestive's Dr. Peppas that water was *not* present in the claimed formulations. Appx649-651, Appx655-656.

c. No motivation to combine with Cartt

Furthermore, a POSA would have lacked motivation to combine Cartt with Gwozdz or Meezan. Cartt discloses particulate formulations of benzodiazepines. Appx239, Appx9247-9248. As Aquestive recognized, neither Gwozdz nor Meezan disclose particulate formulations (instead disclosing solutions). Appx239. Aquestive's expert Dr. Peppas acknowledged the lack of motivation to combine such disparate teachings, stating "[s]olutions and particulates don't go together." Appx10876. In ruling otherwise, the Board did not address this contrary evidence from Dr. Peppas. Appx649-651, Appx655-656.

Indeed, Gwozdz actually distinguished its non-aqueous lipophilic and hydrophobic formulations from the particulate formulations of Cartt, stating "[a]dvantageously, the resulting pharmaceutical solution is not an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions." Appx8022-8023, Appx10958-10959. A POSA reading the Gwozdz disclosure would have appreciated that Gwozdz taught it was a superior

alternative to Cartt, and thus would have lacked motivation to combine Gwozdz with Cartt.

Further, while Aquestive relied on Cartt as providing motivation to combine ethanol and benzyl alcohol as claimed in the '876 patent, a POSA would have been lost in the large list of available solvents disclosed in Cartt. Appx10959-10960. Aquestive's Dr. Peppas acknowledged as much, indicating Cartt provides "too many combinations" of solvents and otherwise does not specifically call out ethanol and benzyl alcohol as a preferred combination of solvents. Appx10959-10960, Appx10878-10879. This contrasts with the Board's conclusion that "one of ordinary skill would have looked to Cartt '784's disclosure when seeking dosing regimens for the compositions disclosed in Gwozdz and Meezan '962"; yet this same person of ordinary skill apparently would not have been able to recognize the alkyl glycosides disclosed in the '558 provisional application despite the blaze marks pointing to the predominantly alkyl glycoside non-ionic detergents incorporated from the SIGMA catalog. Appx59.

For all of these reasons, a POSA would have lacked motivation to combine the asserted prior art references as laid out in the Board's decision, and thus the claims cannot be deemed obvious under either Grounds 1 or 2.

3. A POSA lacked a reasonable expectation of success

Further, one of ordinary skill in the art would have lacked a reasonable expectation of success in modifying the intranasal formulations of Gwozdz. For example, one of ordinary skill in the art would have appreciated that alkyl glycosides were known nonionic surfactants and would also have been aware that nonionic surfactants reduced microbial activity of ethanol and/or benzyl alcohol. Appx9213, Appx8328. A POSA would have recognized that especially when dealing with multidose intranasal use, the inactivation of microbial activity could have consequences in the successful approval of an intranasal formulation. Appx10946-10947. As such, one of ordinary skill in the art would have been less likely to look to a nonionic surfactant to combine with a formulation, such as Gwozdz, that already included ethanol and benzyl alcohol. *Id.*. The Board credited Dr. Wermeling's testimony stating "a POSA would not expect that the very small amounts of nonionic surfactants being used would be sufficient to inactivate the antimicrobial properties of high concentrations of ethanol and/or benzyl alcohol", but this is undercut by the language in claim 25 reciting ethanol and benzyl alcohol in as little an amount as 10%, and up to 1% of an alkyl glycoside. Appx49, Appx111. A POSA would thus have lacked a reasonable expectation of success with such a combination.

Additionally, one of ordinary skill in the art would have lacked a reasonable expectation of success in modifying the Gwozdz formulation to include benzyl alcohol. This is because benzyl alcohol was known to accelerate the autoxidation of fats, such as the tocopherols or tocotrienols present in the Gwozdz formulation. Appx8334. Accordingly, a POSA would have recognized that modifying Gwozdz's formulation to include benzyl alcohol would negate the anti-oxidation properties of the tocopherols and, as a result, degrade the tocopherols such that undesirable by-products could be introduced into the formulation. Appx10945-10946.

Additionally, a POSA as of 2008 was well aware that solvents, including benzyl alcohol, were known irritants to the nasal cavity. Appx9179-9180, Appx10947-10948. Yet Aquestive's expert Dr. Peppas relies on a formulation containing benzyl alcohol (Valium® diazepam injection) as an example of solvents used for administration of diazepam. Appx9180. However, a POSA would have understood that because of the presence of benzyl alcohol (used as a preservative in pharmaceutical formulations), injectable compositions containing benzyl alcohol could not be used in intranasal formulations. Indeed, lorazepam (a benzodiazepine) injectable composition specifically indicated that it "was not acceptable for intranasal spray administration because benzyl alcohol is irritating to the mucosa." Appx11025.

Further, as discussed above, a POSA would have lacked a reasonable expectation of success in modifying the formulation of Gwozdz to include an additional excipient such as the claimed benzyl alcohol or alkyl glycoside because doing so would potentially decrease the solubility of diazepam. As such, one of ordinary skill in the art would not have had a reasonable expectation of success in modifying the intranasal formulations of Gwozdz.

For at least the foregoing reasons, the claims would not have been obvious in view of the combinations of Gwozdz and Meezan or Gwozdz, Meezan, and Cartt. As such, the Board's Decision holding the claims of the '876 patent unpatentable for obviousness must be reversed.

4. Long-felt need and the failure of others confirms the nonobviousness of the '876 patent claims; and the Board's dismissal of that evidence was legal error

The Board also erred in its examination of the objective indicia of non-obviousness achieved by the claimed invention. The existence of a long-felt but unsolved need that is met by the claimed invention is useful in establishing non-obviousness. *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017), citing *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081-83 (Fed. Cir. 2012) (“[W]here ... the obviousness determination turns on whether ... a particular formulation of [a drug] would be [a] successful ... [or] effective treatment[,] objective indicia of ... longfelt

need [is] particularly telling.”). Neurelis presented evidence of the failure of others to develop the benzodiazepine formulation of the ’876 patent and long-felt but unmet need to do so that still existed as of 2008. Appx508-511, Appx10909-10910, Appx10961-10963. The Board improperly dismissed this evidence as affording “very little weight in our obviousness analysis” for allegedly lacking a nexus with the VALTOCO formulation. Appx52-53. The Board, at best, improperly failed to consider the totality of the evidence of objective evidence of non-obviousness, and at worst, fell into “the understandable but improper trap of constructing a selective version of the facts relating to the objective considerations so as to confirm its hunch that the asserted claims were obvious.”

Cyclobenzaprine, 676 F.3d at 1075-77; Appx508.

Researchers have explored benzodiazepines for the treatment of epilepsy since at least the 1980s, but it was not until 2019 that an intranasal benzodiazepine formulation became FDA-approved (both midazolam in Dr. Gizurason’s Nayzilam® and diazepam in Valtoco® were approved in 2019 and 2020, respectively). Appx656-657, Appx509-510. Indeed, despite its therapeutic promise in stopping and preventing seizures in patients, as of 2008 (the filing date of the ’558 provisional) benzodiazepine formulations had only been approved and commercially developed for treating seizures via intravenous and rectal routes of administration. Appx509, Appx10918-10920.

This long-felt need was explicitly articulated in a 2009 paper by Aquestive's replacement expert, Dr. Wermeling. Appx656-657. In his paper, Dr. Wermeling (as the sole author) wrote, "there remains *a significant unmet need* to serve the pharmacotherapeutic requirements of epilepsy patients through commercial development and marketing of intranasal antiepileptic products." Appx10639 (emphasis added), Appx657. Dr. Wermeling doubled down in that same paper, stating that "[t]he literature demonstrates *an unmet medical need exists to provide well-designed nasally delivered benzodiazepines for the treatment [of] seizures.*" Appx10645 (emphasis added), Appx657. Yet the Board dismissed this evidence, stating instead that "[p]etitioner has presented persuasive evidence that benzodiazepines were delivered intranasally prior to 2009" and "these paragraphs discuss prior art references that describe intranasal delivery of benzodiazepines for the treatment of seizures prior to 2009, upon which we find Dr. Wermeling qualified to opine." Appx53-54, Appx67. However, the Dr. Wermeling statements on which the Board relied were made 10 years after the relevant date and were prepared for use in this adversarial proceeding; as such, they are entirely insufficient to overcome his statements made when he lacked such litigation-driven motivation during the relevant time period in a peer-reviewed journal. *See Velander v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003) (expert's litigation-driven testimony entitled to less weight than the expert's pre-litigation writings);

Appx657. For at least these reasons, the Board erred in failing to acknowledge the objective evidence of non-obviousness in the form of long-felt need.

The Board further failed to address abundant evidence showing the failure of others. A 1989 study on diazepam and lorazepam concluded that the intranasal route of administration “may be of limited utility for benzodiazepines in the treatment of status epilepticus where rapid onset of effect is essential.”

Appx10727, Appx10961, Appx510. Other researchers had similar difficulties with the benzodiazepine clonazepam. Appx510, Appx10961, Appx10729. Neurelis’s expert, Dr. Gizurason, who has worked in the field of intranasal therapeutics, including benzodiazepines, for over 30 years indicated that developing intranasal benzodiazepine formulations has not been a straightforward task, and that he “was surprised to see that Neurelis had succeeded in formulating diazepam into an intranasal formulation by 2008.” Appx10916-10918, Appx10932, Appx10962-10963, Appx474-475. This is partly due to benzodiazepine’s poor water solubility characteristics, which had thwarted previous efforts to treat epilepsy with intranasal benzodiazepines. Appx10916-10920, Appx473. Indeed, even Dr. Wermeling acknowledged in 2009 that “the benzodiazepines, do not have sufficient water solubility to formulate a nasal product.” Appx10641.

The record below demonstrates long-felt need and a failure of others to arrive at a method of treating a patient intranasally with a benzodiazepine drug, as

claimed in the '876 patent. The Board erred in failing to address this evidence, which demonstrated the nonobviousness of the claims. *ATI Techs.*, 920 F.3d at 1368 (requiring consideration of contrary evidence).⁵

REMEDY

This IPR could never have been instituted or tried without the mistakes made by the panel below. *Cuozzo Speed Technologies, LLC v. Lee*, 579 U.S. ___, 136 S. Ct. 2131, 2142 (2016) (“Such ‘shenanigans’ may be properly reviewable in the context of §319 and under the Administrative Procedure Act, which enables reviewing courts to ‘set aside agency action’ that is ‘contrary to constitutional right,’ ‘in excess of statutory jurisdiction,’ or ‘arbitrary [and] capricious.’”). First, the panel permitted Aquestive to ignore the most relevant disclosure in the '558 provisional application without explanation, effectively shifting the initial burden to prove priority to Neurelis without a facial showing from Aquestive. Second, the panel *sua sponte* provided its own legally-erroneous reason for ignoring the disclosure, inverting the established agency interpretation of its own rule without notice or explanation. Third, when these errors were challenged on rehearing, the

⁵ The Board asserts that at oral argument Neurelis backed away from claiming nexus for VALTOCO to the claims. Appx53. In fact, the cited portion of the transcript only states that *commercial success* is not argued, which is not surprising or inconsistent given the product had just been approved.

panel misquoted the rehearing request to hold that the main contested issue had been conceded.

The mistakes continued during the trial, when the panel permitted Aquestive to provide evidence on the incorporated material for the first time in its reply, when Neurelis could no longer respond with its own evidence. The panel also overlooked the consistent testimony of Aquestive's Dr. Peppas and Neurelis's Dr. Gizurarson supporting priority, favoring instead the belated and inconsistent testimony of Dr. Wermeling. In the final written decision, the panel ignored briefed differences in the dependent claims and, again, *sua sponte* provided a new and legally-erroneous written-description standard requiring an express preference in the disclosure. The lack of notice, *sua sponte* use of incorrect standards and interpretation, and disregard for contrary argument and evidence violates Neurelis's right to due process, violates statutory requirements for threshold determinations and placement of burdens, and is arbitrary and capricious. *Cuozzo*, 579 U.S. ___, 136 S. Ct. at 2142 ("shenanigans" reviewable).

A reversal is appropriate in this case. When the entirety of the disclosure is considered under the proper standard, there can be no question that alkyl glycosides, specifically including dodecyl maltoside, were expressly disclosed in the '558 provisional application as enhancers—even if other enhancers were also disclosed. Nor is there a genuine issue of whether a POSA would have recognized

the dozen expressly disclosed alkyl glycosides as a distinct class of non-ionic detergents, as two of the three experts testified they would have. Hence, the '558 provisional application provides express support for using alkyl glycosides, specifically including dodecyl maltoside, as enhancers. Neither the panel below nor Aquestive have produced evidence to the contrary. When the proper priority is considered, the key Aquestive reference Gwozd is plainly not prior art, leaving no obviousness ground to adjudicate. A remand would thus serve no useful purpose, but would cause additional delay and risk additional mistakes.

If this Court deems a remand for some portion of the case unavoidable, Neurelis respectfully requests the Court to provide clear guidance on the scope and nature of the remand. Based on the course of the IPR below, Neurelis has a well-justified concern that if the case is remanded to the same panel further mistakes will ensue. At a minimum, if the Board may rely on the belated evidence in Aquestive's reply, Neurelis should be permitted to provide its own responsive evidence.

CONCLUSION

For the reasons stated above, the Court should reverse. A remand cannot remedy these prejudicial error because the record did not support Aquestive without them. If the Court nevertheless deems a remand necessary, Neurelis requests the order require the Board to decide based on arguments the parties

actually made, and that Neurelis be permitted an opportunity to present evidence responding to Aquestive's reply.

Date: February 2, 2021

Respectfully submitted,

/s/Jeffrey Guise

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