

Padagis US LLC v. Neurelis, Inc.

IPR2025-00464 ('546 Patent) • IPR2025-00465 ('414 Patent) • IPR2025-00466 ('786 Patent)
Petitioner's Oral Hearing Demonstratives • June 16, 2026

Consolidated PTAB Oral Hearing

Grounds and Claims at Issue

Reference(s)	Basis	Claims Challenged
Gwozdz (EX1009) Meezan (EX1010)	35 U.S.C. § 103(a)	'546 patent: claims 17, 22 '414 patent: claims 1-18 '786 patent: claims 1-25
Gwozdz (EX1009) Meezan (EX1010) Cartt (EX1065)	35 U.S.C. § 103(a)	'786 patent: claims 20-21
Gwozdz (EX1009) Meezan (EX1010) USP 23/NF 18 (EX1066)	35 U.S.C. § 103(a)	'786 patent: claims 26-27

Pet. (-00464) at 1, 5; Pet. (-00465) at 6; Pet. (-00466) at 6.

Live '546 claims

Neurelis disclaimed all '546 claims except claims 17 and 22.

POR (-00464) at 4.

Petitioner's Technical Expert: Maureen Donovan, Ph.D.



Maureen Donovan, Ph.D.

Professor, Department of Pharmaceutical Sciences and
Experimental Therapeutics
University of Iowa College of Pharmacy

- Ph.D. in Pharmaceutics
- More than 40 years of education and experience in pharmaceutics and pharmaceutical science
- Extensive teaching and research experience in formulation, solubility, drug absorption, and nasal drug delivery
- More than 40 peer-reviewed publications on mechanisms of nasal absorption and nasal drug delivery
- EX1062 – Original Declarations in Support of Petitions (CV attached)
- EX1078 – Reply Declarations

Same Patent Family, Same Prior Art, Same Core Obviousness Dispute

AQUESTIVE THERAPEUTICS, INC.,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

IPR2019-00451
Patent 9,763,876 B2

FWD issued by the
Board in the '451
IPR on August 6,
2020

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

VI. ORDER

In consideration of the foregoing, it is hereby:

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

United States Court of Appeals for the Federal Circuit

NEURELIS, INC.,
Appellant

v.

AQUESTIVE THERAPEUTICS, INC.,
Appellee

2021-1038

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

Federal Circuit
affirms finding
of obviousness
on October 7,
2021

THIS CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

PER CURIAM (MOORE, *Chief Judge*, NEWMAN and
REYNA, *Circuit Judges*).

AFFIRMED. See Fed. Cir. R. 36.

Pet. (-00466) at 7; Ex. 1068, p.2

Pet. (-00466) at 1; Ex. 1040 at 68-69

Topics of Discussion

- **Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art**
- **Contested Issues:**
 - **Collateral Estoppel**
 - **Priority Date and Gwozdz Status as Prior Art**
 - **No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”**
 - **Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside**
 - **Motivation to Combine and Reasonable Expectation of Success**
 - **Cartt Status as Prior Art (Ground 2 in the -00466 IPR)**
 - **USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)**
- **Motions to Strike and Exclude Evidence**

Known Problems with Diazepam Formulations and Solubility



(12) **United States Patent**
Cartt et al.

(10) **Patent No.:** US 11,793,786 B2
(45) **Date of Patent:** *Oct. 24, 2023

(54) **ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

(71) Applicant: **Neurelis, Inc.**, San Diego, CA (US)

(72) Inventors: **Steve Cartt**, Hillsborough, CA (US); **David Medeiros**, Sparks, NV (US); **Garry Thomas Crowell**, San Diego, CA (US); **Andrew Lenkey**, Brensville, NY (US); **Mark Winchick**, San Diego, CA (US); **David F. Hale**, San Diego, CA (US); **Edward T. Maggio**, San Diego, CA (US)

(73) Assignee: **Neurelis, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 101 days. This patent is subject to a terminal disclaimer.

(21) Appl. No.: 17/228,514

(22) Filed: Apr. 12, 2021

(65) **Prior Publication Data**
US 2022/002227 A1 Mar. 3, 2022

Related U.S. Application Data

(63) Continuation of application No. 15/955,397, filed on Apr. 17, 2018, now abandoned, which is a continuation of application No. 12/413,439, filed on Mar. 27, 2009, now abandoned.

(69) Provisional application No. 61/040,558, filed on Mar. 28, 2008.

(51) **Int. Cl.**
A61K 31/555 (2006.01)
A61K 9/00 (2006.01)
A61K 31/551 (2006.01)

(52) **U.S. Cl.**
CPC — **A61K 31/555** (2013.01); **A61K 9/00** (2013.01); **A61K 31/551** (2013.01)
CN — **H555F** (2013.01)
JP — (Continued)

(58) **Field of Classification Search**
CPC — **A61K 9/0043**; **A61K 9/008**; **A61K 31/555**; **A61K 31/5513**
See application file for complete search history.

(56) **References Cited**
U.S. PATENT DOCUMENTS
3,102,116 A 8/1963 Chase
3,109,843 A 11/1963 Reader et al.
3,138,415 A 6/1964 Reader et al.
3,243,427 A 3/1966 Reader et al.
3,286,240 A 1/1967 Bell
3,299,053 A 1/1967 Archer et al.
3,340,253 A 6/1967 Reader et al.
3,371,085 A 2/1968 Reader et al.
3,374,225 A 3/1968 Reader et al.
3,547,828 A 12/1970 Mansfield et al.

FOREIGN PATENT DOCUMENTS
1310574 A 7/2001
030777 A1 11/1999 (Continued)

OTHER PUBLICATIONS
US 5,849,884 A, 12/1998, Wacziarg et al. (withdrawn) (Continued)

Primary Examiner — Adam C. Milligan
(74) **Attorney, Agent, or Firm** — DE A Piper LLP (US)

(57) **ABSTRACT**
The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for oral administration, methods for producing and for using such compositions.

27 Claims, No Drawings

Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.

Pet. (-00466) at 28; Ex. 1001 at 1:44-49; Ex. 1062 ¶101.

The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount may be metabolized. Thus, it may require large doses to achieve therapeutic plasma levels. Furthermore, due to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally.

Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles.

Pet. (-00466) at 28; Ex. 1001 at 1:50-67; Ex. 1062 ¶101.

Suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient's intimate acquaintances and the patient's professional medical caretakers.

Pet. (-00466) at 28; Ex. 1001 at 2:1-6; Ex. 1062 ¶101.

Diazepam Was Already Being Administered Intranasally

EMS Manual

2.5.3 Seizure Disorders

This protocol should be used when the patient has witnessed continuous convulsions (generalized tonic-clonic seizure or Grand Mal) or repeating episodes without regaining consciousness or sufficient respiratory decompensation. Consider underlying etiology, such as: hypoglycemia, drug overdose, head injury, or fever. Other types of seizures include: absence (Petit Mal), simple partial (focal motor and Jacksonian), complex partial (Psychomotor or Temporal Lobe), atonic (drop attacks), and myoclonic. When the patient is continuously showing signs of these other types of seizures, Medical Supportive Care should be initiated and the paramedic should contact medical control for further direction.

Supportive Care

- ◆ Medical Supportive Care 2.1.3.

ALS Level I

- ◆ If Eclamptic female, administer Magnesium Sulfate 4 gm IV (mixed in 50 ml of D5W given over 5–10 minutes) (see Adult Protocol 2.7.4 - Eclampsia/ Preeclampsia) (d).
- ◆ Administer one of the following benzodiazepines:
 - Diazepam (Valium®) 5mg IV. If unable to start IV, administer Diazepam 5 mg intranasal or 10 mg per rectum. May repeat PRN up to 20 mg maximum dose (a)(b).

or

Pet. (-00466) at 35-36; Ex. 1019 at 54; Ex. 1062 ¶69-70.

Dr. Donovan

70. As illustrated above, the EMS reference discloses that 5 mg doses of diazepam could be administered intranasally in emergent seizure patients requiring treatment with benzodiazepines, by utilizing the MAD device noted above.

Pet. (-00466) at 19; Ex. 1062 at ¶70.

PDR

VALIUM®

[val 'ee-um]

brand of diazepam
INJECTION

The following text is complete prescribing information based on official labeling in effect June 1999.

DESCRIPTION

Each mL contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

Diazepam is a benzodiazepine derivative developed through original Roche research. Chemically, diazepam is 7-chloro-1,

Pet. (-00466) at 38 ; Ex. 1017 at 2676; Ex. 1062 ¶69-70.

Gwozdz Addresses the Known Problems in the Art

Gwozdz

Pharmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents. By therapeutic agents

Pet. (-00466) at 28; Ex. 1009 at 7:29-34; Ex. 1062 at ¶¶102-103

Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so

Pet. (-00466) at 28; Ex. 1009 at 9:19-22; Ex. 1062 at ¶103

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 October 2009 (01.10.2009)

(10) International Publication Number
WO 2009/120933 A2

(51) International Patent Classification:
A61K 9/00 (2006.01)

(21) International Application Number:
PCT/US2009/038518

(22) International Filing Date:
27 March 2009 (27.03.2009)

(25) Filing Language:
English

(26) Publication Language:
English

(30) Priority Data:
61/040,281 28 March 2008 (28.03.2008) US

(71) Applicant (for all designated States except US): PARTICULAR SCIENCES, INC. (US); 3894 Courtney Street, Suite 180, Bethlehem, PA 18017 (US)

(72) Inventors and
(73) Inventors/Applicants (for US only): GWOZDZ, Garry, Thomas (US); 329 South Main Street, Nazareth, PA 18064 (US); LOXLEY, Andrew (GB); 128 Market Street, 4th, Philadelphia, PA 19106 (US); MITCHELL, Mark (US); 80 Three Mile Harbor Drive, East Hampton, NY 11937 (US)

(74) Agent: LICATA, Jane, Manney; Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ 08053 (US)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TD, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, SG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BI, CF, CG, CI, CM, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published
without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: PHARMACEUTICAL SOLUTIONS AND METHOD FOR SOLUBILIZING THERAPEUTIC AGENTS

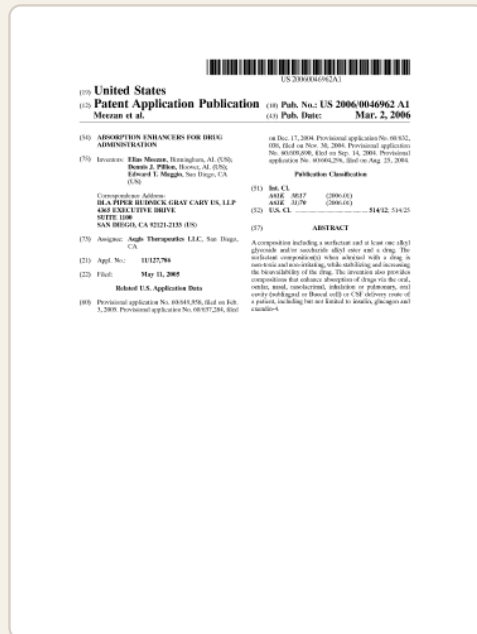
(57) Abstract: Pharmaceutical solutions containing hydrophobic or lipophilic therapeutic agents and methods for producing the same are provided. Pharmaceutical solutions of the invention are produced by dissolving the therapeutic agent in one or more tocopherols or tocotrienols and one or more alcohols or glycols. These solutions are used to produce pharmaceutical compositions.

WO 2009/120933 A2

EX1009

Meezan Adds to the Teachings of Gwozdz

Meezan



EX1010

[0004] The present invention is based, in part, on the development of a therapeutic composition containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug. In particular, the drug enhancing agents of the invention contain a non-toxic surfactant consisting of at least an alkyl glycoside and/or

low molecular weight heparin and inhibitory RNA), methods of administering and using the compositions e.g. via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or cerebral spinal fluid (CSF) delivery route, and methods of ameliorating a disease state in a subject by administration of such compositions

Pet. (-00466) at 29; Ex. 1010 at ¶0004; Ex. 1062 at ¶104

A Motivation Existed to Combine Gwozdz and Meezan with a Reasonable Expectation of Success – and the Board Agreed

'451 FWD

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

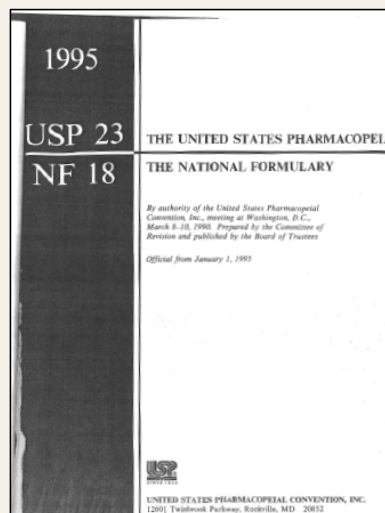
Pet. (-00466) at 27; Ex. 1040 at 54.

Cartt and USP Provide Disclosures for Dependent Claim Limitations

 US 2008/0279784 A1	
(10) United States	(10) Pub. No.: US 2008/0279784 A1
(12) Patent Application Publication	(12) Pub. Date: Nov. 13, 2008
(54) NASAL ADMINISTRATION OF BENZODIAZEPINES (75) Inventors: Steve Cartt, Union City, CA (US); David Medendorp, South San Francisco, CA (US) Correspondence Address: WILSON HOSNEN GOODRICH & RONATI, 650 PAGE MILL ROAD, PALO ALTO, CA 94304-1095 (US) (70) Assignee: QUESTOR PHARMACEUTICALS, INC., Union City, CA (US) (21) Appl. No.: 12/115,862 (22) Filed: May 7, 2008	
(60) Provisional application No. 60/916,550, filed on May 7, 2007. (51) Int. Cl. A61K 9/12 (2006.01); A61K 31/551 (2006.01); A61P 25/00 (2006.01); A61K 31/557 (2006.01) (52) U.S. Cl. 424/03; 514/221; 514/220; 514/219 (57) ABSTRACT: Particulate formulations of benzodiazepines, such as diazepam, are used for nasal administration of diazepam drugs to patients. Multidose particulate formulations of benzodiazepines and methods for their use, e.g. by nasal administration for the treatment of seizures, are also provided.	

[0063] Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process dis-

Pet. (-00466) at 64; Ex. 1065 at ¶0063; Ex. 1062 at ¶251.



Official Monographs / Vitamin 1631

Vitamin E

» Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following: *d*- or *dl*-alpha tocopherol ($C_{29}H_{50}O_2$); *d*- or *dl*-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); *d*- or *dl*-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$). It contains not less than 96.0 percent and not more than 102.0 percent of $C_{29}H_{50}O_2$, $C_{31}H_{52}O_3$, or $C_{33}H_{54}O_5$, respectively.

Pet. (-00466) at 64; Ex. 1066 at 1631; Ex. 1062 at ¶251.

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - ***Collateral Estoppel***
 - Priority Date and Gwozdz Status as Prior Art
 - No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”
 - Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside
 - Motivation to Combine and Reasonable Expectation of Success
 - Cartt Status as Prior Art (Ground 2 in the -00466 IPR)
 - USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)
- Motions to Strike and Exclude Evidence

Collateral Estoppel

Petitioner Arguments:

- (1) Collateral estoppel applies to the finding of obviousness in the '546 patent IPR (-00464), because “dodecyl maltoside” was recited in the claims of the previous '876 patent, and was argued in the '451 patent IPR; and
Pet. (-00464) at 6-7; Reply (-00464) at 2-5.
- (2) Collateral estoppel applies to the finding of obviousness in the '414 and '786 patent IPRs (-00465 and -00466, respectively), because the claimed requirement of “n-dodecyl- β -D-maltoside” does not present a materially different question of patentability over the previous “dodecyl maltoside” limitation
Pet. (-00466) at 6-7; Reply (-00466) at 2-6; Pet. (-00465) at 6-7; Reply (-00465) at 2-6.

The Claims of the '546, '414, and '786 Patents Do Not Materially Alter the Invalidity Issues Decided for the '876 Patent

Padagis.

Claims 1, 4, 7, 26, and 27 of 9,763,876 Found Unpatentable in IPR 2019-00451	Claims 1, 17, and 22 of 8,895,546	Claim 1 of 11,241,414	Claim 1 of 11,793,786
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. 4. The method of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. 7. The method of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. 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.	1. A pharmaceutical solution for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside. 17. The solution of claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside. 22. The solution of claim 16, wherein the alkyl glycoside is dodecyl maltoside	1. A pharmaceutical solution for nasal administration consisting of: diazepam or a pharmaceutically acceptable salt thereof; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w); ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and n-dodecyl beta-D-maltoside.	1. A pharmaceutical solution for nasal administration consisting of: a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof; one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w); one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and n-dodecyl beta-D-maltoside

The '876 Patent Includes Claims Reciting “Dodecyl Maltoside”

'451 FWD

Claim 26 depends from claim 25 and specifies that the alkyl glycoside is dodecyl maltoside. *Id.* at 64:54–55. Petitioner presents evidence that

Reply (-00466) at 3; Ex. 1040 at 33.

'876 Patent Claim 26

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

Reply (-00466) at 2-3; Ex. 1003 at cl. 26 (-00464); Ex. 1069 at cl. 26 (-00465, -00466).

“Meezan '962 teaches that 0.25% is a preferred amount of alkyl glycoside,” “dodecyl maltoside is a specifically preferred alkyl glycoside,” and “0.25% dodecyl maltoside is also specifically disclosed.” *Id.* (citing Ex. 1011 ¶¶ 56, 61, 150, 151, 158, 167, Table I, Fig. 1; Ex. 1041 ¶¶ 365–367).

Reply (-00466) at 3; EX1040 at 34.

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

Reply (-00466) at 3; Ex. 1040 at 37.

Patent Owner's Federal Circuit Briefs Establish that Dodecyl Maltoside was Litigated

Padagis.

Neurelis Federal Circuit Opening Brief – Statement of Issues

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?

Reply (-00466) at 3-4; Ex. 1081 at 1.

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

Reply (-00466) at 4-5; Ex. 1081 at 40.

Neurelis Federal Circuit Reply Brief

a. *Neurelis Argued Dodecyl Maltoside Below*

Aquestive accuses Neurelis of a new argument on appeal about the dependent claims being further narrowed to dodecyl maltoside. Aquestive Br. 51 (“Neurelis’ argument is too little, too late.”). Neurelis’ opening brief, however, points to express argument in its Patent Owner Response before the Board connecting these dependent claims to the express disclosure of dodecyl maltoside in the incorporated material. Neurelis Br. 35; Appx487 n.7. Like the Board below, Aquestive simply ignores this argument rather than addressing it.

Reply (-00466) at 4; Ex. 1082 at 7.

Identity of Claim Language is Not Required for Collateral Estoppel

Ohio Willow Wood Co. v. Alps South, LLC, 735 F.3d 1333, 1342 (Fed. Cir. 2013)

“Our precedent does not limit collateral estoppel to patent claims that are identical. Rather, it is the identity of the issues that were litigated that determines whether collateral estoppel should apply. See *Bourns, Inc. v. U.S.*, 210 Ct.Cl. 642, 537 F.2d 486, 491 (1976); *Westwood Chem., Inc. v. U.S.*, 207 Ct.Cl. 791, 525 F.2d, 1367, 1372 (1975). If the differences between the unadjudicated patent claims and adjudicated patent claims do not materially alter the question of invalidity, collateral estoppel applies. *Bourns*, 537 F.2d at 493.”

Reply (-00466) at 5.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Soverain Software LLC v. Victoria's Secret Direct Brand Mgmt., LLC, 778 F.3d 1311, 1319 (Fed. Cir. 2015)

“In *Ohio Willow Wood*, we applied issue preclusion to invalidate a claim where a different claim in another patent had previously been invalidated because “the[] patents use[d] slightly different language to describe substantially the same invention.” *Id.* We also found that a difference in claim scope was not fatal to the application of estoppel. *Id.* at 1343. The previously-invalidated claim contained a limitation requiring only polymeric gel, whereas the unadjudicated claim required, more specifically, block copolymer gel. *Id.* We held that, because the patentee failed to explain how the additional limitation would change an invalidity analysis, the patentee had not met its burden in opposing summary judgment. *Id.* The additional limitation here—transmitting a hypertext statement over the Internet, rather than over a generic network—does not materially alter the question of the validity of claim 39.”

Reply (-00466) at 5.

The Claims of the '546, '414, and '786 Patents Do Not Materially Alter the Invalidity Issues Decided for the '876 Patent

Padagis.

Claims 1, 4, 7, 26, and 27 of 9,763,876 Found Unpatentable in IPR 2019-00451	Claims 1, 17, and 22 of 8,895,546	Claim 1 of 11,241,414	Claim 1 of 11,793,786
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. 4. The method of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. 7. The method of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. 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.	1. A pharmaceutical solution for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside. 17. The solution of claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside. 22. The solution of claim 16, wherein the alkyl glycoside is dodecyl maltoside	1. A pharmaceutical solution for nasal administration consisting of: diazepam or a pharmaceutically acceptable salt thereof; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w); ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and n-dodecyl beta-D-maltoside.	1. A pharmaceutical solution for nasal administration consisting of: a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof; one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w); one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and n-dodecyl beta-D-maltoside

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - Collateral Estoppel
 - ***Priority Date and Gwozdz Status as Prior Art***
 - No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”
 - Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside
 - Motivation to Combine and Reasonable Expectation of Success
 - Cartt Status as Prior Art (Ground 2 in the -00466 IPR)
 - USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)
- Motions to Strike and Exclude Evidence

The '558 Provisional Identifies at Least 15 Different Classes of “Enhancers” with Little/No Guidance for the Compounds in Each Class

Padagis.

'558 Provisional

[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.

Pet. (-00466) at 15-16; Reply (-00466) at 8-9; Ex. 1008 at ¶¶150-52; Ex. 1062 at ¶¶46-53.

Dr. Donovan Original Declaration

permeability of the mucosal cell membranes.” A POSA understood that there are at least fifteen further classes of chemical enhancing agents listed: lysophospholipids, acyl camitines, 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 (Ex. 1026), enamines, malonates, salicylates, bile salts and bile analogues and fusidates. The '558 Provisional provides no guidance or recitation of specific compounds within each of these fifteen classes of compounds. The '558 Provisional discloses a vast number of potential compounds in paragraph [152], without any direction as to which compound classes are preferred, or any guidance for choosing specific compounds over others.

Pet. (-00466) at 15; Reply (-00466) at 15; Ex. 1062 at ¶49.

A POSA Would Have No Reason to Select “Dodecyl Maltoside” or “n-Dodecyl-β-D-Maltoside” from the 150+ Biological Detergents

Padagis.

Dr. Donovan Original Declaration

51. Moreover, given the overall discussion of enhancing agents in ¶¶ [150]-[152] of the '588 Provisional, it is my opinion that the '588 Provisional application does not identify with detail and particularity that it is incorporating the alkyl glycosides referred to in the Sigma Catalog. A POSA looking at the more than 150 ionic and non-ionic compounds listed in the Sigma Catalog would have no reason to select alkyl glycoside(s) over other compounds disclosed in the Sigma Catalog. Additionally, it would require the POSA to conduct undue experimentation to determine whether any of the alkyl glycosides are useful or preferred over any of the other biological detergent candidates. The '588 Provisional does not provide a POSA with any direction or sufficient disclosure to select alkyl glycosides, in particular n-dodecyl beta-D-maltoside as claimed in the '786 Patent claims.

Pet. (-00466) at 16; Reply (-00466) at 9 at 9; Ex. 1062 at ¶51.

Dr. Donovan Original Declaration:

52. Again, from reading the '588 Provisional (including paragraphs [150]-[152]) and the Sigma Catalog, it is my opinion that the inventors did not have any particular enhancing agent in mind as part of their invention (other than paragraph [151]'s preference for lysophospholipids and acyl carnitine alternatives). It is my further opinion that a POSA would have understood the '588 Provisional application as not disclosing alkyl glycosides, let alone n-dodecyl beta-D-maltoside.

Pet. (-00466) at 15; Reply (-00466) at 10 at 9; Ex. 1062 at ¶52.

Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282-83 (Fed. Cir. 2000).

“To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. See *In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement “clearly identifying the subject matter which is incorporated and where it is to be found”).

Reply (-00466) at 8.

Neurelis Accounted for this Lack of Support by Reciting “Alkyl Glycosides” and “Dodecyl...β-D-Maltoside” in the Subsequent Non-Provisional Filing

Padagis.

'558 Provisional:

[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.

[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.

'439 Application:

Additional Excipients

[0136] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is at least one alkyl glycoside. In some embodiments, the alkyl glycoside is trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments,

[0137] The term “penetration 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.

[0139] 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.

Pet. (-00466) at 15-16; Reply (-00466) at 8-9; Ex. 1008 at ¶¶150-52; Ex. 1062 at ¶¶46-53.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Reply (-00466) at 9; Ex. 1039 at ¶0136.

Laundry List Disclosures Are Not Sufficient – The Specification Must Provide Blaze Marks

Padagis.

Regents of the Univ. of Minn. v. Gilead Sciences, Inc., 61 F.4th at 1350 (Fed. Cir. 2023)

“Clearly, however, just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a “laundry list” disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not ‘reasonably lead’ those skilled in the art to any particular species.”

Reply (-00466) at 10; *Regents of the Univ. of Minn. v. Gilead Sciences, Inc.*, 61 F.4th 1350, 1357 (Fed. Cir. 2023).

“These blaze marks must be clear because ‘it is easy to bypass a tree in the forest, even one that lies close to the trail.’”

Reply (-00466) at 10; *Regents of the Univ. of Minn. v. Gilead Sciences, Inc.*, 61 F.4th 1350, 1358 (Fed. Cir. 2023).

The '558 Provisional Does Not Provide Sufficient Blaze Marks

Dr. Donovan Original Declaration:

50. Additionally, paragraph [152] of the '558 Provisional makes reference to the "Sigma Catalog, 1988, pp. 316-321," which includes well over 100 biological detergents on the cited pages of the catalog, of which only a very small percentage (i.e., only about a dozen) are alkyl glycosides. Sigma Catalog, Ex. 1026. Paragraph [152] of the '558 Provisional includes both ionic and non-ionic compounds (there are many charged, polar molecules listed in addition to non-ionic molecules to choose from)¹. Therefore, in my opinion, the '588 Provisional application does not identify with any specificity that the biological detergents in the Sigma Catalog should be non-ionic or ionic, or that alkyl glycosides are in any way preferred.

Pet. (-00466) at 15; Reply (-00466) at 10; Ex. 1062 at ¶150.

Dr. Donovan Original Declaration:

alkyl glycosides referred to in the Sigma Catalog. A POSA looking at the more than 150 ionic and non-ionic compounds listed in the Sigma Catalog would have no reason to select alkyl glycoside(s) over other compounds disclosed in the Sigma Catalog. Additionally, it would require the POSA to conduct undue experimentation to determine whether any of the alkyl glycosides are useful or preferred over any of the other biological detergent candidates. The '588 Provisional does not provide a POSA with any direction or sufficient disclosure to select alkyl glycosides, in particular n-dodecyl beta-D-maltoside as claimed in the '786 Patent claims.

Pet. (-00466) at 15; Reply (-00466) at 9-10; Ex. 1062 at ¶151.

The Board Previously Found Insufficient Blaze Marks in the '558 Provisional

Padagis.

'451 FWD:

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

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - Collateral Estoppel
 - Priority Date and Gwozdz Status as Prior Art
 - ***No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”***
 - Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside
 - Motivation to Combine and Reasonable Expectation of Success
 - Cartt Status as Prior Art (Ground 2 in the -00466 IPR)
 - USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)
- Motions to Strike and Exclude Evidence

Petitioner Has Withdrawn its Claim Construction Briefing - There is No Inconsistency

Claim Construction Stipulation

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC., <i>Plaintiff,</i>	C.A. No. 24-562 (MN)
v.	(LEAD CASE)
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD., <i>Defendants.</i>	
NEURELIS, INC., <i>Plaintiff,</i>	C.A. No. 25-821 (MN)
v.	
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD., LUPIN INC., LUPIN LTD., AND LUPIN PHARMACEUTICALS, INC., <i>Defendants.</i>	
NEURELIS, INC., <i>Plaintiff,</i>	C.A. No. 25-1228 (MN)
v.	
PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD., <i>Defendants.</i>	

**DEFENDANTS' PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL
PHARMACEUTICALS LTD. STIPULATION REGARDING CLAIM CONSTRUCTION**

Withdrawal of Claim Construction Position

WHEREAS, on September 17, 2025, the PTAB granted institution of Padagis's petitions for *inter partes* review of the Asserted Patents. See IPR2025-00464 at Paper 13; IPR2025-00465 at Paper 13; IPR2025-00466 at Paper 13. In its institution decisions, the PTAB noted that Padagis "suggests the transitional phrase 'consisting of' means the claimed pharmaceutical solutions include only those components recited in the claims . . . [s]uch interpretation tracks the conventional meaning of the 'consisting of' transitional phrase in claim drafting." See IPR2025-00464 at Paper 13 at 7, n. 5; IPR2025-00465 at Paper 13 at 9, n. 7; IPR2025-00466 at Paper 13 at 10, n. 9.

Reply (-00466) at 6; Ex. 1083 at 2.

1. Padagis withdraws the claim construction positions it raised in the parties' joint claim construction brief with respect to the Asserted Patents, including both the proposed construction and indefiniteness position and the supporting Declaration of Maureen Donovan, Ph.D. See C.A. No. 24-562 at D.I. 83 and 84 (Exhibit 30).
2. Padagis agrees to adopt Neurelis's proposed construction with respect to the disputed claim term (i.e., "no construction necessary; the scope of 'consisting of' is established by law"), which is consistent with the construction proposed by Padagis in its petitions for *inter partes* review of the Asserted Patents. See C.A. No. 24-562, D.I. 83 at 20; see also IPR2025-00464 at Paper 13 at 7, n. 5; IPR2025-00465 at Paper 13 at 9, n. 7; IPR2025-00466 at Paper 13 at 10, n. 9.

Reply (-00466) at 6; Ex. 1083 at 3.

Ex. 1083 at 1.

Petitioner and Dr. Donovan Applied the Plain Meaning of "Consisting Of" to the Prior Art

Padagis.

Petitions

Finally, as noted by Dr. Donovan, “Gwozdz and Meezan render obvious a pharmaceutical solution for nasal administration “consisting of” (i.e., containing only) the claimed benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and an alkyl glycoside.” EX1062, ¶131.

Pet. (-00466) at 36.

'451 FWD

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

Reply (-00466) at 17; Ex. 1040 at 12-13.

Dr. Donovan Original Declaration

131. In addition, Counsel has explained to me that the “consisting of” language in the claim preamble requires that the claimed solution includes only those components explicitly recited in the claim. For the reasons noted below, it is my opinion that Gwozdz and Meezan render obvious a pharmaceutical solution for nasal administration “consisting of” (i.e., containing only) the claimed benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and n-dodecyl beta-D-maltoside.

Pet. (-00466) at 36; Ex. 1062 at ¶131 (-00466); Ex. 1078 ¶33.

Institution Decisions

⁹ In Petitioner’s obviousness analysis, Petitioner suggests the transitional phrase “consisting of” means the claimed pharmaceutical solutions include only those components recited in the claims. See, e.g., Pet. 36 (noting “consisting of” means “containing only”). Such interpretation tracks the conventional meaning of the “consisting of” transitional phrase in claim drafting. See *AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001) (“[C]losed transition phrases such as ‘consisting of’ are understood to exclude any elements, steps, or ingredients not specified in the claim.”). It is also consistent with the ’786 patent’s definition of the “consisting of” phrase. Ex. 1001, 15:34–36 (“As used herein, the term ‘consisting of’ . . . indicate[s] that the claimed invention includes only those elements set forth in the claim.”).

Paper 13 (-00466) at 10 n.9; Reply (-00466) at 6.

Gwozdz Discloses the Claimed "Ethanol"

Gwozdz

Examples of alcohol(s) for use in the present invention include, but are not limited to **ethanol**, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof. Examples of glycols for use in the present invention include, but are not limited to ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, and any isomers thereof, and any combinations thereof. In one embodiment of the present invention the alcohol is ethanol (ethyl alcohol). Preferred is use of an ethanol that is biocompatible in the sense that it is not toxic and does not cause any physiological or pharmacological effects. In this regard, the ethanol is desirably 180 to 200 proof ethanol, *i.e.*, in the range of 90-100% ethanol. Advantageously, diluting a tocopherol or

Pet. (-00466) at 46-47; Ex. 1009 at 6:16-19.

'451 FWD

Claim 1 also recites "ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w)." Ex. 1001, 63:33-34. Petitioner and Dr. Peppas present evidence that **Gwozdz teaches the use of ethanol, benzyl alcohol, and combinations thereof¹⁰ wherein "[t]he alcohol (or combinations of alcohols) may be present in amounts of about 1-70%" and "[e]thanol may be present in amounts of 1-40% or 10-30%."** Pet. 40, 68 (citing Ex. 1014, 4:19-21, 7:10-11, 7:20-24). Therefore, the range of

Reply (-00464) at 17; Ex. 1040 at 26-27.

'451 FWD

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

Reply (-00464) at 17; Ex. 1040 at 27.

Even Neurelis' Misguided "Zero Impurity" Requirement for Ethanol is Disclosed by Gwozdz

Padagis.

Gwozdz

Examples of alcohol(s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof. Examples of glycols for use in the present invention include, but are not limited to ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, and any isomers thereof, and any combinations thereof. In one embodiment of the present invention the alcohol is ethanol (ethyl alcohol). Preferred is use of an ethanol that is biocompatible in the sense that it is not toxic and does not cause any physiological or pharmacological effects. In this regard, the ethanol is desirably 180 to 200 proof ethanol, i.e., in the range of 90-100% ethanol. Advantageously, diluting a tocopherol or

Reply (-00464) at 17; Ex. 1009 at 6:28-29.

Gwozdz Does Not Require the Inclusion of Water in its Formulations

Gwozdz

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, e.g., saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

Reply (-00466) at 22; Ex. 1009 at 10:6-8.

Gwozdz

Formulations suitable for parenteral administration can be aqueous or non-aqueous injection solutions, which are generally isotonic with the blood of the intended recipient.

Reply (-00466) at 22; Ex. 1009 at 11:17-19.

Meezan Does Not Require Water in its Formulations – It Discloses Use of Alkyl Glycosides in Non-Aqueous Carriers and the Board Agreed

Padagis.

Dr. Donovan Original Declaration

113. Meezan also discloses using alkyl glycosides in non-aqueous systems:

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

Meezan, Ex. 1010, ¶ 74.

Reply (-00466) at 21; Ex. 1062 at ¶113.

’451 FWD

172; Ex. 2011, 141:8–11, 141:14–18). Patent Owner asserts that Petitioner fails to discuss how alkyl glycosides function in a non-aqueous environment and Meezan ’962 “discloses alkyl glycosides as a stabilizer *only* in aqueous formulations.” PO Sur-Reply 15 (citing Ex. 2011, 140:20–23).

Reply (-00466) at 24; Ex. 1040 at 45.

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

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

Reply (-00466) at 24; Ex. 1040 at 45.

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - Collateral Estoppel
 - Priority Date and Gwozdz Status as Prior Art
 - No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”
 - ***Meezan Discloses and Renders Obvious n-Dodecyl- β -D-maltoside***
 - Motivation to Combine and Reasonable Expectation of Success
 - Cartt Status as Prior Art (Ground 2 in the -00466 IPR)
 - USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)
- Motions to Strike and Exclude Evidence

Meezan Discloses “Dodecyl-β-D-Maltoside” Which Was Understood to Refer to “n-Dodecyl-β-D-Maltoside”

Padagis.

Meezan:

was maintained for up to two hours. Insulin administered ocularly with 0.5% dodecyl-β-D-maltoside (see Table I) or 0.5% decyl-β-D-maltoside (see Table III) results in a prompt and sustained fall in blood glucose levels which are maintained in the normoglycemic (80-120 mg/dl) or near-normoglycemic (120-160 mg/dl) range for the two hour duration of the experiment. Hence, at least two alkylmaltosides

Reply (-00466) at 5; Ex. 1010 ¶[0156]; Ex. 1078 ¶¶43, 48.

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

Time (min)	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Blood Glucose Concentrations (mg/dl)				
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

Reply (-00466) at 5; Ex. 1010 ¶[0156]; Ex. 1078 ¶48.

Dr. Donovan Original Declaration

151. Therefore, based on Meezan’s teaching of 0.25% alkyl glycoside, including dodecyl maltoside, and the fact that the amount and identity of the alkyl glycoside is not critical (and is, in fact, predictable), a POSA would routinely select n-dodecyl beta-D-maltoside to add to Gwozdz’s solution.³

Pet. (-00466) at 41; Reply (-00466) at 15; Ex. 1062, ¶151.

Dr. Donovan Reply Declaration

48. Relatedly, as noted in my opening declaration, a POSA would have understood the shortened name “dodecyl maltoside” to refer to n-dodecyl-β-D-maltoside. See, e.g., Ex. 1062 (Donovan Op. Decl.) at ¶¶147-152. The above corrected Meezan specification underscores that point. Indeed, Meezan discloses that “DDM” and “dodecyl maltoside” are shorthand for “n-dodecyl-β-D-maltoside.” For example, Meezan discloses an example in which “0.5% dodecyl-β-D-maltoside” was included in an ocular formulation and test results were reported in “Table I.” Ex. 1010 (Meezan) at ¶ [0156]. But in Table I, Meezan simply lists “dodecyl maltoside” despite making it clear that Table I was discussing “dodecyl-β-D-maltoside.” *Id.* at ¶ [0158], Table I.

Reply (-00466) at 15; Ex. 1078, ¶48.

“n-” Prefix Is Unnecessary to Denote a Straight-Chain Alkane

Dr. Donovan Reply Declaration:

15. I disagree with Dr. Brown that the “n-” prefix is necessary in the context of chemical nomenclature to understand when an alkane is a straight-chain isomer as opposed to a branched isomer. Indeed, the Streitwieser textbook that Dr. Brown relies on to support his opinions discusses *n*-alkanes as a general class of straight-chain alkanes (as opposed to branched alkanes), but does not state or recommend that straight-chain alkanes must or should always be named with the “n-” prefix. See, e.g., Ex. 2051 (Streitwieser) at 9. For example, Streitwieser explains that “[t]he normal alkanes are named according to the number of carbon atoms in the chain (Table 3.2),” but does not state that the “n-” prefix should be used. *Id.* Indeed, Table 3.2 of Streitwieser identifies the normal alkanes by their “name” *without* using the “n-” prefix:

Reply (-00466) at 13; Ex. 1078, ¶15.

Streitwieser:

TABLE 3.2

<i>n</i>	Name	Formula
1	methane	CH ₄
2	ethane	CH ₃ CH ₃
3	propane	CH ₃ CH ₂ CH ₃
4	butane	CH ₃ CH ₂ CH ₂ CH ₃
5	pentane	CH ₃ (CH ₂) ₃ CH ₃
6	hexane	CH ₃ (CH ₂) ₄ CH ₃
7	heptane	CH ₃ (CH ₂) ₅ CH ₃
8	octane	CH ₃ (CH ₂) ₆ CH ₃
9	nonane	CH ₃ (CH ₂) ₇ CH ₃
10	decane	CH ₃ (CH ₂) ₈ CH ₃
11	undecane	CH ₃ (CH ₂) ₉ CH ₃
12	dodecane	CH ₃ (CH ₂) ₁₀ CH ₃
13	tridecane	CH ₃ (CH ₂) ₁₁ CH ₃
14	tetradecane	CH ₃ (CH ₂) ₁₂ CH ₃
15	pentadecane	CH ₃ (CH ₂) ₁₃ CH ₃
20	eicosane	CH ₃ (CH ₂) ₁₈ CH ₃
21	heneicosane	CH ₃ (CH ₂) ₁₉ CH ₃
22	docosane	CH ₃ (CH ₂) ₂₀ CH ₃
30	triacontane	CH ₃ (CH ₂) ₂₈ CH ₃
40	tetracontane	CH ₃ (CH ₂) ₃₈ CH ₃

Reply (-00466) at 13; Ex. 2051 at 9-10; Ex. 1078 ¶15.

Only Branched Alkyl Chains Require Prefixes

Dr. Donovan Reply Declaration:

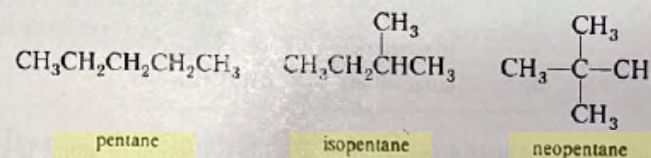
16. As described in Streitwieser,, a POSA would understand that “pentane” (i.e., named without the “n-” prefix) refers to the straight-chain isomer having the number of carbon atoms indicated by “penta-” (meaning “five” in Greek). Indeed, Streitwieser does just that when it discusses the three isomers of pentane:

Id. at 11. It is the *branched* alkanes that are appended with an appropriate prefix to specify *which* branched structure is being identified (e.g., “iso” and “neo” are added as prefixes to denote specific branched structures of a five-carbon alkane). When presented with the manner in which Streitwieser refers to pentane at his deposition, Dr. Brown suggested that it could be a typographical error given that Streitwieser also refers to “*n*-butane” two paragraphs above. Ex. 1077 (Brown Dep. Tr.) at 111:15-24. But, what this shows a POSA is that there is no requirement to use the “n-” prefix when referencing an alkane that is a straight-chain isomer, which is consistent with Table 3.2 and the remainder of the discussion in Streitwieser.

Reply (-00466) at 13; Ex. 1078 at ¶16.

Streitwieser:

There are three C_5H_{12} isomers.



Reply (-00466) at 13; Ex. 2051 at 11; Ex. 1078 at ¶16.

Only Branched Alkyl Chains Need Prefixes – IUPAC Nomenclature Governs

Dr. Donovan Reply Declaration:

goes on to explain that the “method of systematic nomenclature” used to name organic compounds has long-been determined by the International Union of Pure and Applied Chemistry (“IUPAC”).

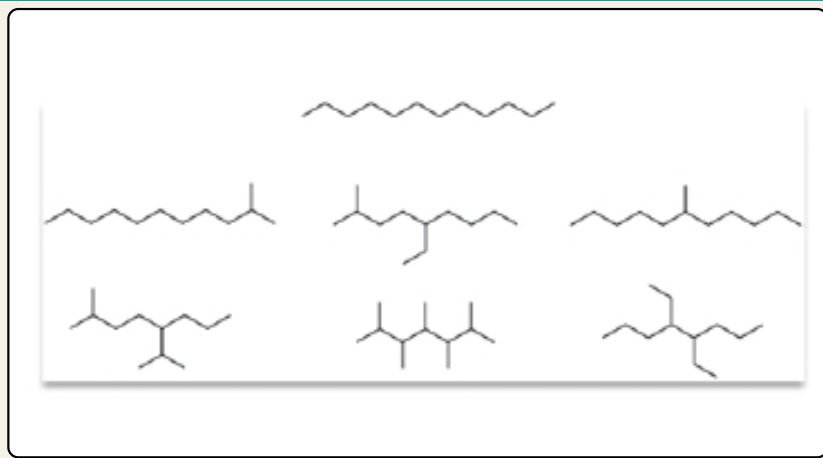
Id. at 12. And Streitwieser explains that:

The IUPAC system of alkane nomenclature is based on the simple fundamental principle of considering all compounds to be derivatives of the longest single carbon chain present in the compound. *Appendages to this chain are designated by appropriate prefixes.* This chain is then numbered from one end to the other. The end chosen as number 1 is that which gives the smaller number (a locant) at the first point of difference.

Id. (emphasis added). Thus, under the IUPAC system for naming chemical compounds, it is the branched structures that must be labeled with an appropriate prefix—in the case of a straight-chain alkane, there is no need to include a prefix (including the “n-” prefix).

Reply (-00466) at 13; Ex. 1078 at ¶17.

Dr. Brown's "355 Isomers" Theory Ignores the Standard IUPAC Nomenclature



Reply (-00466) at 14; Ex. 2074 at ¶72, Ex. 1078 at ¶19.

Dr. Donovan Reply Declaration:

Id. According to Dr Brown, “*n*-dodecane is the linear isomer depicted at the top of this figure, but dodecane can adopt 354 other isomeric forms, only a few of which are depicted above. Other than *n*-dodecane, every other isomer of dodecane is branched in one or more locations.” *Id.* But only one structure depicted in Dr. Brown’s figure is actually named “dodecane” under the IUPAC rules, which Dr. Brown agreed with during his deposition. See, e.g., Ex. 1077 (Brown Dep. Tr.) at 119:13-121:22.

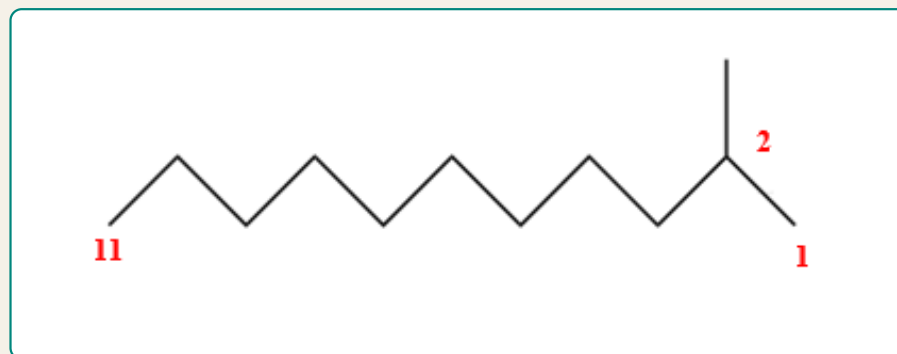
Reply (-00466) at 14; Ex. 1078 at ¶19.

Branched Compounds Would Not Be “Dodecane”

Dr. Donovan Reply Declaration:

Ex. 2074 at ¶ 72 (red numbers added by me). Following the IUPAC nomenclature rules, the first step is to determine the longest single carbon chain present in the compound—as shown above, the longest single carbon chain in Dr. Brown’s compound is 11 carbons long. And as discussed in Streitwieser and the IUPAC rules, this 11-carbon chain is named based on Greek numbers—here, the root of Dr. Brown’s compound would be named “undecane” (Greek for 11) based on the 11-carbon chain, not “dodecane” (which would indicate a 12-carbon chain). The side-chain (i.e., branched structure) at carbon number 2 would then be added as a prefix, specifying that it is a “methyl” group that branches off of the second carbon. Thus, this compound from Dr. Brown’s figure would in fact be named 2-methylundecane.

Reply (-00466) at 14; Ex. 1078 at ¶20.



Reply (-00466) at 14; Ex. 2074 at ¶72; Ex. 1078 at ¶20.

Based on the Standard IUPAC Nomenclature, Only One 12-Carbon Compound is “Dodecane”

Dr. Donovan Reply Declaration:

21. Thus, I disagree with Dr. Brown that a POSA would somehow interpret a compound named “dodecane” (or a compound that includes a “dodecyl” moiety in its name) to somehow refer to *all* of the compounds identified in his figure. The fact that all of the compounds in Dr. Brown’s figure have 12 carbon atoms does not somehow mean they are all named “dodecane” as Dr. Brown opines. Rather, if an article or prior art reference were discussing “dodecane” or a compound containing a “dodecyl” moiety (i.e., without the “n-” prefix), a POSA would have understood that, based on the IUPAC rules and their common knowledge, it was a reference to a straight chain alkane having 12 carbon atoms. In contrast, a branched alkane, including those depicted in Dr. Brown’s figure, would be appended with an appropriate prefix to indicate both *where* the branched side-chain is located and *what* chemical moiety is extending from that position.

Reply (-0466) at 15; Ex. 1078 at ¶21.

The '414 and '786 Patent Specifications Confirm the Same Nomenclature

'786 FH:

48. (New) A pharmaceutical solution for nasal administration consisting of:
 diazepam or a pharmaceutically acceptable salt thereof;
 one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof,
 in an amount from 30% to 95% (w/w);
 one or more alcohols in an amount from 10% to 70% (w/w); and
 n-dodecyl beta-D-maltoside.

Reply (-00466) at 15; Ex. 1002 (-00466) at 176; Ex. 1078 at ¶22.

Upon entry of this Preliminary Amendment, claims 1-47 have been cancelled and new claims 48-67 will be pending in this application. Applicant asserts that no new matter has been added to the application through this amendment and that all claims submitted herewith are fully supported by the specification as filed.

Reply (-00466) at 15; Ex. 1002 (-00466) at 179; Ex. 1078 at ¶22.

'786 Specification:

rose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α - or β -D-maltoside, -glucoside or sucroside. In some embodi-

Reply (-00466) at 15; Ex. 1001 (-00466) at 31:17-21; Ex. 1078 at ¶22.

Dr. Brown's Position that Anomers and Stereochemistry Add to the Number of Isomers Fails

Padagis.

Dr. Donovan Reply Declaration:

24. I note that Dr. Brown also opines about the chemical structures and nomenclature rules for saccharides and glycosides. *See, e.g.*, Ex. 2074 at ¶¶ 74-80. Specifically, Dr. Brown opines that certain saccharides were well-known and common, and that they have both alpha and beta anomers. *Id.* Dr. Brown also opines that “[w]hen a saccharide is chemically connected to another chemically distinct moiety, the resulting molecule is often termed a ‘glycoside.’” *Id.* at

Reply (-00466) at 15-16; Ex. 1078 at ¶24.

glycosides that a POSA would have been aware of or considered. *See, e.g., id.* at ¶ 81. In my opinion, Dr. Brown's discussion of these additional chemical nomenclature and structural issues is irrelevant at least because Meezan expressly discloses the use of dodecyl-β-D-maltoside specifically, as discussed below and in my opening declaration. *See, e.g.*, Ex. 1062 (Donovan Op. Decl.) at ¶¶ 147-153. In other words, Dr. Brown's discussion about the beta and alpha anomers, the potential for D or L stereochemistry, as well as other generalizations about the broad genus of alkyl maltosides, has no bearing on the issues in this IPR because Meezan specifically identified dodecyl-β-D-maltoside.²

Reply (-00466) at 15-16; Ex. 1078 at ¶25.

Under IUPAC Rules, Meezan's "Dodecyl- β -D-Maltoside" Includes a Straight Chain Alkyl Group

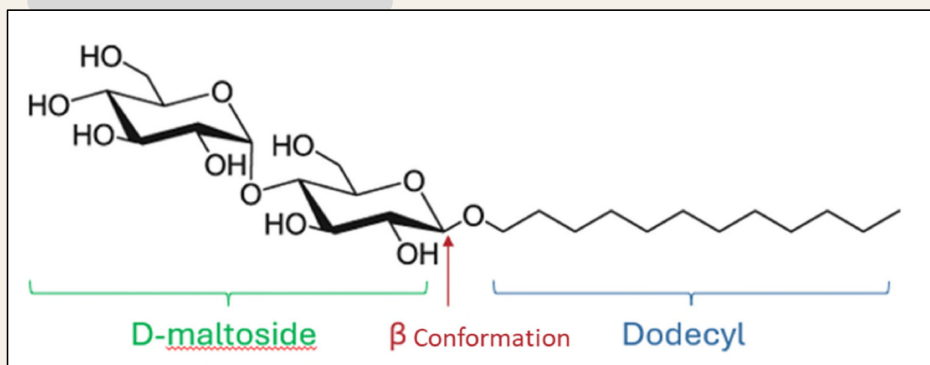
Padagis.

Dr. Donovan Reply Declaration:

41. Applying the correct nomenclature rules, a POSA would understand that Meezan's express disclosure of "dodecyl- β -D-maltoside" refers to the following structure (prepared and annotated by me):

Reply (-00466) at 13; Ex. 1078 at ¶41.

Dodecyl- β -D-Maltoside



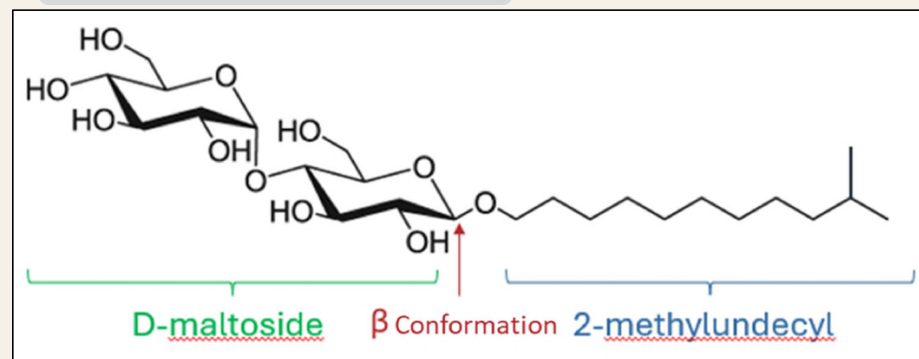
Reply (-00466) at 13; Ex. 1078 at ¶41.

Dr. Donovan Reply Declaration:

entirely different names. For example, as explained above, one of the 12-carbon alkanes that Dr. Brown opines would be named "dodecyl" is in fact named "2-methylundecane," as Dr. Brown himself acknowledged during his deposition. Ex. 1077 at 119:13-121:22. If that isomer were attached to a β -D-maltoside moiety, it would have the following structure and moieties (prepared and annotated by me):

Reply (-00466) at 13; Ex. 1078 at ¶42.

2-methylundecyl- β -D-Maltoside



Reply (-00466) at 13; Ex. 1078 at ¶42.

Neurelis's "Highly Branched" Argument Relies on Deleted Text

FH for Meezan:

Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or **branching length** of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other **highly-branched long** alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

Reply (-00466) at 15; Ex. 1078 at ¶47.

Dr. Donovan Reply Declaration:

on this issue are incorrect. Rather, **the correct Meezan specification emphasizes and supports my opinions: a POSA would understand that Meezan discloses alkyl glycosides having straight-chain (i.e., "long") alkyl groups, *not* branched structures.** Indeed, the corrected language above *specifically* emphasizes that "DDM" has a "long alkyl chain[]." *Id.*

Reply (-00466) at 15; Ex. 1078 at ¶47.

Patent Owner's Own Inventor, Dr. Maggio, Used the Terms Interchangeably

Sworn Declaration of Dr. Edward Maggio:

5. The present invention is based on the discovery that the alkyl glycoside, dodecyl- β -D-maltoside (also referred to as n-dodecyl- β -D-maltoside), increases absorption of therapeutic agents to the cerebral spinal fluid (CSF) of the central nervous system (CNS) of a subject upon nasal administration.

Reply (-00466) at 15; Ex. 1076 at 2; Ex. 1078 at ¶150.

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - Collateral Estoppel
 - Priority Date and Gwozdz Status as Prior Art
 - No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”
 - Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside
 - ***Motivation to Combine and Reasonable Expectation of Success***
 - Cartt Status as Prior Art (Ground 2 in the -00466 IPR)
 - USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)
- Motions to Strike and Exclude Evidence

Motivation to Combine and Reasonable Expectation of Success Arguments

- ***Motivation to Combine Gwozdz and Meezan Based on Known Problems and Motivation to Modify Gwozdz***
- Interactions Between Excipients Do Not Negate the Motivation to Combine Gwozdz and Meezan
- The Absence of “Penetration Enhancer” in Gwozdz Does Not Defeat Motivation to Combine
- Meezan is Not Limited to Large Molecule Drugs and a Motivation Existed to Combine Meezan’s Alkyl Glycosides with Tocopherol/Alcohol Carriers
- A Motivation Existed to Use Meezan’s Dodecyl Maltoside

Motivation to Improve Solubility Based on Known Problems in the Art – As Admitted by Patent Owner

Padagis.

PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342 (2007)

“Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness. See *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988)

Reply (-00466) at 18.

Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.

Pet. (-00466) at 28; Reply (-00466) at 18; Ex. 1001 at 1:44-49; Ex. 1062 ¶101.

Suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient’s intimate acquaintances and the patient’s professional medical caretakers.

Pet. (-00466) at 28; Reply (-00466) at 18; Ex. 1001 at 2:1-6; Ex. 1062 ¶101.

The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount may be metabolized. Thus, it may require large doses to achieve therapeutic plasma levels. Furthermore, due to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally.

Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles.

Pet. (-00466) at 28; Reply (-00466) at 18; Ex. 1001 at 1:50-67; Ex. 1062 ¶101.

Gwozdz Did Not “Solve” the Formulation Issue – A Motivation Existed to Modify Gwozdz’s Formulations

Padagis.

Gwozdz

solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

Pet. (-00466) at 31-32; Reply (-00466) at 19; Ex. 1009 at 10:9-16; Ex. 1062 at ¶104.

Meezan

[0004] The present invention is based, in part, on the development of a therapeutic composition containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug. In particular, the drug

Pet. (-00466) at 29; Reply (-00466) at 19; Ex. 1010 at ¶0004; Ex. 1062 at ¶104.

Dr. Donovan Original Declaration:

improve the solubility of drugs with poor solubility. Gwozdz notes that the pharmaceutical solutions described therein may further incorporate additional pharmaceutically acceptable additives, including, “acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.” *Id.*, 10:12-

Pet. (-00466) at 29; Reply (-00466) at 19; Ex. 1062 at ¶104.

avoiding various adverse toxic effects of drug.” Meezan, Ex. 1010, ¶0004. Thus, while Gwozdz was focused on pharmaceutical solutions developed to improve the solubility of drugs with solubility issues, Meezan presented a distinct approach of utilizing compounds that increase the absorption (i.e., absorption enhancers) and bioavailability of drug compounds. Based on this, a POSA was motivated to apply the teachings of Meezan related to alkyl glycosides to the pharmaceutical solutions of Gwozdz.

Pet. (-00466) at 29; Reply (-00466) at 19; Ex. 1062 at ¶104.

The Board Agreed that a Motivation Existed to Modify Gwozdz's Formulations

'451 FWD

Patent Owner also contends that Gwozdz provides no motivation to modify its disclosed formulations. PO Resp. 28. Specifically, Patent Owner asserts that Gwozdz dealt with the issue of bioavailability of benzodiazepines for intranasal administration by focusing on solubility and “left no room for modification in its precipitation sensitive formulations.”

Pet. (-00466) at 68; Reply (-00466) at 19; Ex. 1040 at 40.

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

Pet. (-00466) at 68; Reply (-00466) at 19; Ex. 1040 at 41.

Motivation to Combine and Reasonable Expectation of Success Arguments

- Motivation to Combine Gwozdz and Meezan Based on Known Problems and Motivation to Modify Gwozdz
- ***Interactions Between Excipients Do Not Negate the Motivation to Combine Gwozdz and Meezan***
- The Absence of “Penetration Enhancer” in Gwozdz Does Not Defeat Motivation to Combine
- Meezan is Not Limited to Large Molecule Drugs and a Motivation Existed to Combine Meezan’s Alkyl Glycosides with Tocopherol/Alcohol Carriers
- A Motivation Existed to Use Meezan’s Dodecyl Maltoside

Antimicrobial Properties of Ethanol and Benzyl Alcohol Would Not Be Materially Impacted by Alkyl Glycosides for a One-Time Use Nasal Spray

Padagis.

Dr. Donovan Reply Declaration:

55. First, an intranasal formulation (i.e., a nasal spray) as contemplated by Gwozdz would require a formulation in a final package that has virtually no bacteria present in the formulation. While the possibility of microbial contamination is always a consideration in pharmaceutical formulation development, for an emergency, one-time use product like a diazepam nasal spray, whether or not the antimicrobial properties of ethanol and benzyl alcohol are decreased or inactivated would not be seen as a limitation since single-use nasal spray devices able to deliver preservative-free nasal sprays were known in the art. These single-use devices would be also be suitable for the administration of diazepam in the emergency treatment of seizure.

Reply (-00466) at 19-20; Ex. 1078 at ¶155.

The Low Concentration of Dodecyl- β -D-Maltoside Would Not Inactivate Antimicrobial Properties of Ethanol and Benzyl Alcohol

Padagis.

Dr. Donovan Reply Declaration:

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

Reply (-00466) at 19-20; Ex. 1078 at ¶156.

The Board Agreed in the '451 FWD

'451 FWD:

glycosides. PO Resp. 30. First, Patent Owner asserts that Petitioner has not shown a reasonable expectation of success in adding a penetration enhancer such as alkyl glycoside to the Gwozdz formulation. *Id.* at 31. According to Patent Owner, alkyl glycosides are known nonionic surfactants and “[t]he Handbook of Pharmaceutical Excipients (“Handbook”) (Ex. 1031) teaches that non-ionic surfactants interact to the detriment of the disclosed solvents.”

Reply (-00466) at 20; Ex. 1040 at 48.

'451 FWD:

Ex. 1150 ¶ 154. Furthermore, according to Dr. Wermeling, the benzodiazepine formulation in the final package has to be aseptic so there are no bacteria to kill. Ex. 1150 ¶ 155. Therefore, we credit Dr. Wermeling’s testimony and agree with Petitioner that “whether or not the antimicrobial properties are inactivated is irrelevant and a POSA would not be led away from considering nonionic surfactants.” Reply 17 (citing

Reply (-00466) at 20; Ex. 1040 at 49.

Ex. 1150 ¶ 155). Even if such antimicrobial properties were important, we credit the testimony of Dr. Wermeling that “a POSA would not expect that the very small amounts of nonionic surfactants being used would be sufficient to inactivate the antimicrobial properties of high concentrations of ethanol and/or benzyl alcohol being used here.” Ex. 1150 ¶ 156.

Reply (-00466) at 20; Ex. 1040 at 49.

Alleged Instability of Tocopherols Would Not Prevent a POSA from Modifying the Gwozdz Formulation

Padagis.

Gwozdz:

Summary of the Invention

An aspect of the present invention relates to 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. In some

Reply (-00466) at 20; Ex. 1009 at 4:13-17.

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, e.g., saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to,

Reply (-00466) at 20; Ex. 1009 at 10:9-16.

Motivation to Combine and Reasonable Expectation of Success Arguments

- Motivation to Combine Gwozdz and Meezan Based on Known Problems and Motivation to Modify Gwozdz
- Interactions Between Excipients Do Not Negate the Motivation to Combine Gwozdz and Meezan
- ***The Absence of “Penetration Enhancer” in Gwozdz Does Not Defeat Motivation to Combine***
- Meezan is Not Limited to Large Molecule Drugs and a Motivation Existed to Combine Meezan’s Alkyl Glycosides with Tocopherol/Alcohol Carriers
- A Motivation Existed to Use Meezan’s Dodecyl Maltoside

A POSA Had Ample Reasons to Combine Gwozdz and Meezan

Dr. Donovan Original Declaration

102. In view of these shortcomings, a known problem existed related to the solubility of benzodiazepine drug compounds, and the dosage forms that could be developed based on this limited solubility. Consequently, a POSA was motivated to identify strategies to improve the solubility of benzodiazepine drugs, to allow for the development of additional dosage forms that would be an improvement over the known shortcomings of oral, intravenous, and suppository dosage forms.

Pet. (-00466) at 28; Ex. 1062 at ¶102.

solubility of drugs with solubility issues, Meezan presented a distinct approach of utilizing compounds that increase the absorption (i.e., absorption enhancers) and bioavailability of drug compounds. Based on this, a POSA was motivated to apply

Pet. (-00466) at 29; Reply (-00466) at 19; Ex. 1062 at ¶104.

1. Known water solubility issues limited diazepam formulations

2. Meezan teaches that alkyl glycosides increase bioavailability

Dr. Donovan Original Declaration

113. Meezan also discloses using alkyl glycosides in non-aqueous systems:

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

Meezan, Ex. 1010, ¶ 74.

Pet. (-00466) at 33; Reply (-00466) at 21; Ex. 1062 at ¶113.

3. Meezan’s alkyl glycosides are compatible with non-aqueous carriers, including alcoholic or oleaginous carriers

The Board Agreed There Were Ample Reasons to Combine Gwozdz and Meezan

Institution Decisions

Patent Owner counters that, because Petitioner relies in its motivation-to-combine analysis on a “single statement” in Gwozdz that is *not prior art*, the motivation for combining Gwozdz and Meezan is defective and institution should be denied. Prelim. Resp. 33–39. More specifically, Patent

Paper 13 at 34 (-00466).

Meezan.”). To the contrary, Petitioner provides additional reasoning that does not appear to turn on Gwozdz’s disclosure of “penetration enhancers” among a list of additives. Petitioner cites, *inter alia*, known solubility issues with diazepam limiting delivery of sufficient drug to the tissues desired, Meezan’s teachings about increasing bioavailability of drugs meant for nasal administration by the addition of absorption-enhancing alkyl glycosides, and Meezan’s suggestion that its formulations are compatible with non-aqueous solvent systems (such as Gwozdz’s solvents for intranasal delivery) and suitable for use with small-molecule drugs (like diazepam). *See, e.g.*, Pet.

Paper 13 at 36 (-00466).

'451 FWD

Resp. 27–29, 35–38. Patent Owner and Dr. Gizurarson assert that a POSA would not look to both (1) increase drug solubility and (2) use penetration enhancers to increase the permeability of the nasal mucosa in order to increase the permeation problems associated with intranasal administration.

Reply (-00466) at 18; Ex. 1040 at 39.

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

Reply (-00466) at 18; Ex. 1040 at 39.

Neurelis Ignores the Full Scope of Gwozdz's Disclosure, Including the Inclusion of "Wetting" Materials

Padagis.

Gwozdz:

solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

Reply (-00466) at 21; Ex. 1009 at 10:9-16.

Meezan:

[0053] The therapeutic composition of the invention includes a drug and a drug absorption enhancing agent, for example, a surfactant. The term "surfactant" is any surface active agent that modifies interfacial tension of water. Typically, surfactants have one lipophilic and one hydrophilic group in the molecule. Broadly, the group includes soaps, detergents, emulsifiers, dispersing and wetting agents, and several groups of antiseptics. More specifically, surfactants

Reply (-00466) at 22; Ex. 1010 at ¶0053.

Dr. Donovan Original Declaration:

104. Moreover, a POSA was motivated to combine the teachings of Meezan related to alkyl glycosides with the pharmaceutical solutions described in Gwozdz. As noted, Gwozdz is directed to pharmaceutical solutions that are designed to improve the solubility of drugs with poor solubility. Gwozdz notes that the pharmaceutical solutions described therein may further incorporate additional pharmaceutically acceptable additives, including, "acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials." *Id.*, 10:12-

Reply (-00466) at 21; Ex. 1062 at ¶104.

Gwozdz's Discussion of "Other Pharmaceutically Acceptable Additives" Includes Non-Aqueous Formulations and Is Not Limited to Injectables

Padagis.

Gwozdz

also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, e.g., saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to,

Reply (-00466) at 21; Ex. 1009 at 10:9-16.

Formulations suitable for parenteral administration can be aqueous or non-aqueous injection solutions, which are generally isotonic with the blood of the intended recipient.

Reply (-00466) at 22; Ex. 1009 at 11:17-18.

Gwozdz

subcutaneous routes. Specifically, pharmaceutical compositions of the present invention can be administered by any of the following nonlimiting exemplary routes, intraabdominal, intraarterial, intraarticular, intracapsular, intracervical, intracranial, intraductal, intradural, intralesional, intralocular, intralumbar, intramural, intranasal, intraocular, intraoperative,

Reply (-00466) at 22; Ex. 1009 at 9:2-9.

Motivation to Combine and Reasonable Expectation of Success Arguments

- Motivation to Combine Gwozdz and Meezan Based on Known Problems and Motivation to Modify Gwozdz
- Interactions Between Excipients Do Not Negate the Motivation to Combine Gwozdz and Meezan
- The Absence of “Penetration Enhancer” in Gwozdz Does Not Defeat Motivation to Combine
- ***Meezan is Not Limited to Large Molecule Drugs and a Motivation Existed to Combine Meezan’s Alkyl Glycosides with Tocopherol/Alcohol Carriers***
- A Motivation Existed to Use Meezan’s Dodecyl Maltoside

Meezan's Alkyl Glycosides May Be Used with Small Molecule Drugs

Meezan

[0130] Therapeutic agents or drugs of the present invention can be peptides or proteins, medically or diagnostically useful, of small to medium size, e.g. up to about 15 kD, 30 kD, 50 kD, 75 kD, etc., or a protein having between about 1-300 amino acids or more. The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.

Pet. (-00466) at 33; Reply (-00466) at 23; Ex. 1010 at ¶130.

[0052] Other drugs or therapeutic compounds, molecules and/or agents include compounds or molecules of the central nervous system affecting neurotransmitters or neural ion channels (i.e. antidepressants (bupropion)), selective serotonin 2c receptor agonists, anti-seizure agents (topiramate,

Reply (-00466) at 23; Ex. 1010 at ¶0052.

Dr. Donovan Original Declaration:

112. Similarly, Meezan teaches that alkyl glycosides will increase the bioavailability of small molecules, and identifies molecules having molecular weight below 1.5 kDaltons as candidates for improved bioavailability. Meezan, Ex. 1010, ¶ [0130]. Diazepam is a small molecule, having a molecular weight of 284.74 (i.e., 0.28474 kDaltons). See PDR, Ex. 1017, p. 2676. Thus, a POSA would understand Meezan's teachings as motivating the use of alkyl glycosides with small molecule compounds, such as benzodiazepines, and, in particular diazepam.

Pet. (-00466) at 33; Reply (-00466) at 23; Ex. 1062 at ¶112.

Meezan is Not Limited to Aqueous Carriers and a Motivation Existed to Use Alkyl Glycosides in Non-Aqueous Carriers – the Board Agreed

Padagis.

Dr. Donovan Original Declaration

113. Meezan also discloses using alkyl glycosides in non-aqueous systems:

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

Meezan, Ex. 1010, ¶ 74.

Pet. (-00466) at 33; Reply (-00466) at 21; Ex. 1062 at ¶113.

’451 FWD:

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

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

Reply (-00466) at 24; Ex. 1040 at 46.

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

Reply (-00466) at 24; Ex. 1040 at 47.

Motivation to Combine and Reasonable Expectation of Success Arguments

- Motivation to Combine Gwozdz and Meezan Based on Known Problems and Motivation to Modify Gwozdz
- Interactions Between Excipients Do Not Negate the Motivation to Combine Gwozdz and Meezan
- The Absence of “Penetration Enhancer” in Gwozdz Does Not Defeat Motivation to Combine
- Meezan is Not Limited to Large Molecule Drugs and a Motivation Existed to Combine Meezan’s Alkyl Glycosides with Tocopherol/Alcohol Carriers
- ***A Motivation Existed to Use Meezan’s Dodecyl Maltoside***

Meezan Focuses on a Small Number of Preferred Alkyl Glycosides, Including Dodecyl Maltoside

Padagis.

Meezan:

[0157] Several other alkylmaltosides are also effective as absorption enhancers for ocular administration of insulin including 0.5% tridecylmaltoside (see Table III) and 0.125% (Table II) and 0.5% tetradecyl maltoside. These studies show that alkylmaltosides with the longer alkyl chains (or number of carbon atoms), e.g., dodecyl-, tridecyl- and tetradecyl- β -D-maltosides, are more effective. The increase in the number of carbon atoms also contributes to the greater hydrophobic/hydrophilic structural balance and absorption enhancing effect. The shorter alkyl chains (fewer carbon atoms) e.g.,

Reply (-00466) at 24; Ex. 1010 at ¶0157.

Dr. Donovan Original Declaration:

94. Meezan explains that alkyl glycosides in concentrations ranging from about 0.01% to about 6% by weight (and in particular 0.125% and 0.25% by weight) resulted in enhanced absorption of the drug and increased bioavailability. *Id.* Additionally, Meezan again identifies dodecyl maltoside (i.e., “DDM”) as one of the preferred alkyl glycosides having an absorption-enhancing and bioavailability-increasing effect on the drug compound. *Id.*

Reply (-00466) at 25; Ex. 1062 at ¶94.

Dr. Donovan Reply Declaration:

52. In any case, as explained in my opening declaration, Meezan expressly disclosed dodecyl maltoside (i.e., dodecyl- β -D-maltoside) as a “preferred” alkyl glycoside and reported that it was effective at increasing the permeability of drugs. *See, e.g.*, Ex. 1010 at ¶¶ [0150]-[0151], [0157]-[0159], Table I. Thus, Meezan expressly disclosed that dodecyl- β -D-maltoside was a

Reply (-00466) at 25; Ex. 1078 at ¶52.

Motivation to Combine is Not Limited to the Most Preferred Option

In re Fulton, 391 F.3d 1195, 1200 (Fed. Cir. 2004)

“[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention. “[T]he question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination,” not whether there is something in the prior art as a whole to suggest that the combination is the *most desirable* combination available. See *In re Beattie*, 974 F.2d at 1311 (internal quotation omitted; emphasis added).

Reply (-00466) at 24.

Meezan Discloses that DDM Showed Significant Absorption and Efficacy

Meezan

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

Time (min)	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Blood Glucose Concentrations (mg/dl)				
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

Pet. (-00466) at 41; Reply (-00466) at 24; Ex. 1010 at ¶0157.

Dr. Donovan Reply Declaration

preferred and effective penetration enhancer. The fact that TDM *may* have been more effective than dodecyl-β-D-maltoside does not mean that dodecyl-β-D-maltoside would not have been an obvious penetration enhancer to choose. Indeed, Meezan shows that it would have been an excellent choice. In particular, Example 3 of Meezan reported that dodecyl-β-D-maltoside concentrations of 0.25%, 0.375%, and 0.5% all achieved a dramatic improvement in absorption and efficacy (as evidenced by the decreased blood glucose concentrations reported in Table I). EX1010, ¶[0158]. Although Dr. Brown relies heavily on his argument that Meezan did not demonstrate that a concentration of 0.125% dodecyl-β-D-maltoside was effective, this would not have discouraged a POSA from using dodecyl-β-D-maltoside in the greater concentrations that did show a significant improvement in absorption and efficacy. And, the challenged claims of the '786

Reply (-00466) at 25; Ex. 1078 at ¶52.

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - Collateral Estoppel
 - Priority Date and Gwozdz Status as Prior Art
 - No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”
 - Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside
 - Motivation to Combine and Reasonable Expectation of Success
 - ***Cartt Status as Prior Art (Ground 2 in the -00466 IPR)***
 - USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)
- Motions to Strike and Exclude Evidence

Cartt Qualifies As Prior Art Under 35 U.S.C. §§ 102(a) and/or 102(e)(1)

- Cartt is prior art against the '786 patent:
 - o Proper priority date of the '786 patent: March 27, 2009.
 - o Cartt is prior art under §102(a) because it was published on Nov. 13, 2008.
 - o Cartt is also prior art under §102(e)(1) because it was filed on May 7, 2008 and claims priority to the '550 provisional, filed on May 7, 2007.

(19) United States	(10) Pub. No.: US 2008/0279784 A1
(12) Patent Application Publication	(43) Pub. Date: Nov. 13, 2008
Cartt et al.	
(54) NASAL ADMINISTRATION OF BENZODIAZEPINES	Related U.S. Application Data
(75) Inventors: Steve Cartt, Union City, CA (US); David Medeiros, South San Francisco, CA (US)	(60) Provisional application No. 60/916,550, filed on May 7, 2007.
Correspondence Address: WILSON SONSINI GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050 (US)	Publication Classification
(73) Assignee: QUESTCOR PHARMACEUTICALS, INC., Union City, CA (US)	(51) Int. Cl. A61K 9/12 (2006.01) A61K 31/5513 (2006.01) A61P 25/00 (2006.01) A61K 31/5517 (2006.01)
(21) Appl. No.: 12/116,842	(52) U.S. Cl. 424/43; 514/221; 514/220; 514/219
(22) Filed: May 7, 2008	(57) ABSTRACT Particulate formulations of benzodiazepines, such as diazepam, are used for nasal administration of diazepam drugs to patients. Multimodal particulate formulations of benzodiazepines and methods for their use, e.g. by nasal administration for the treatment of seizure, are also provided.

Ex. 1065 at 1.

The Board Previously Determined That Cartt Was Prior Art

- Cartt was also relied on by Petitioner in the 451 IPR:

F. Instituted Grounds of Unpatentability

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

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

⁴ U.S. Pub. No. 2008/0279784 A1, published November 13, 2008 (Ex. 1015, “Cartt '784”).

Ex. 1040 at 5.

The Board Previously Determined That Cartt Was Prior Art

- The Board determined that Cartt was prior art in the 451 IPR:

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

Ex. 1040 at 23.

Patent Owner's §103(c)(1) Arguments Do Not Affect Cartt's Prior Art Status

- Cartt is prior art under §102(a), which cannot be disqualified under §103(c)(1):

35 U.S.C. §103(c)(1)

“Subject matter developed by another person, which qualifies as prior art only under one or more of **subsections (e), (f), and (g)** of section 102...”

- Patent Owner has not contested that point—if the Board determines that the '786 patent's priority date is March 27, 2009, it is undisputed that Cartt is §102(a) prior art against the '786 patent.

Patent Owner's §103(c)(1) Arguments Do Not Affect Cartt's Prior Art Status

- Cartt is also prior art under §102(e)(1):
 - o The Board previously determined that Cartt is prior art under §102(e)(1):

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

Ex. 1040 at 23.

Patent Owner's §103(c)(1) Arguments Do Not Affect Cartt's Prior Art Status

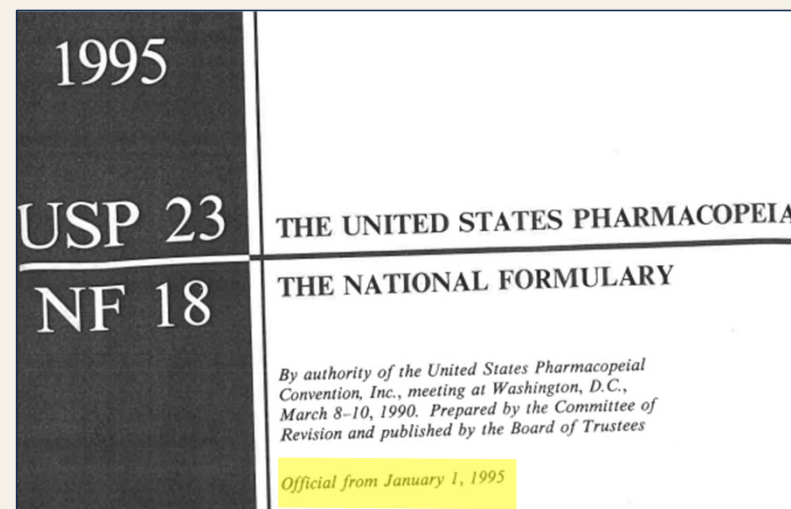
- Cartt is also prior art under §102(e)(1):
 - o The assignment records of the '786 patent and Cartt contradict Patent Owner's position.
Exs. 1084-1086, 1089.
 - o Patent Owner did not respond to Petitioner on this point or offer any additional explanation to rebut Petitioner in its sur-reply.

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - Collateral Estoppel
 - Priority Date and Gwozdz Status as Prior Art
 - No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”
 - Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside
 - Motivation to Combine and Reasonable Expectation of Success
 - Cartt Status as Prior Art (Ground 2 in the -00466 IPR)
 - ***USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)***
- Motions to Strike and Exclude Evidence

USP 23/NF 18 Qualifies As Prior Art Under 35 U.S.C. § 102(b)

- USP 23/NF 18 is 102(b) prior art against the '786 patent:
 - o Proper priority date of the '786 patent: March 27, 2009.
 - o USP 23/NF 18 was published in 1995.



Ex. 1066 at 2.

USP 23/NF 18 Qualifies As Prior Art Under 35 U.S.C. § 102(b)

- The record in this proceeding shows that USP 23/NF 18 is prior art:
 - o Dr. Donovan testified that USP 23/NF 18 is a foundational compendium that POSAs were aware of and used in 1995.

It is my opinion that a person of ordinary skill in the art (“POSA”) would have known and understood that USP 23/NF 18 was published in 1995. As of that time, the United States Pharmacopeia/National Formulary was among the core, industry-standard references used in pharmaceutical dosage-form development, including for standards relating to drug substances, excipients, formulations, and related quality attributes. A POSA would have regarded USP–NF as a foundational compendium that was routinely consulted in the ordinary course of pharmaceutical development work.

regularly accessed and used this reference in physical, printed form. As a result, a POSA would have worked with the printed volume itself and would have readily appreciated its publication year and edition designation from the reference as published and used in the field. In fact, in my own experience, I can recall seeing and having access to the printed version of USP23/NF18 after 1995 (and prior to the earliest priority date of the '786 patent). Accordingly, in my opinion, a POSA would have understood USP 23/NF 18 to be a well-known, publicly available printed publication in 1995.

IPR2025-00466, Paper 2 at 25; Paper 43 at 27; Ex. 1078 at ¶¶58-59.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

USP 23/NF 18 Qualifies As Prior Art Under 35 U.S.C. § 102(b)

- The record in this proceeding shows that USP 23/NF 18 is prior art:
 - o A 1996 Final Rule from FDA explained that USP 23/NF 18 became official in 1995.

[Federal Register Volume 61, Number 27 (Thursday, February 8, 1996)]
[Rules and Regulations]
[Pages 4822-4823]

capacity test procedures in USP XXII/N.F. XVII. Since the proposal was published, USP 23/N.F. 18 became official on January 1, 1995. The test procedures in both editions of the USP are the same. Therefore, the agency is referencing USP 23/N.F. 18 in this final rule.

Ex. 1087 at 1, 4.

USP 23/NF 18 Qualifies As Prior Art Under 35 U.S.C. § 102(b)

- The record in this proceeding shows that USP 23/NF 18 is prior art:
 - o A patent issued in 2002 discussed USP 23/NF 18.

A preferred Vitamin E composition for use in the emulsions of the present invention is α -tocopherol as described in the United States Pharmacopoeia, Volume 23, 1995 which is also known as all-rac- α -tocopherol. This material can be obtained from Roche Products Ltd., Heanor, UK.

Ex. 1088 at 3:30-34.

Topics of Discussion

- Overview of Known Problems and Solutions for Diazepam Formulations Discussed in the Prior Art
- **Contested Issues:**
 - Collateral Estoppel
 - Priority Date and Gwozdz Status as Prior Art
 - No Inconsistency in Claim Construction with Litigation and the Prior Art Teaches “Consisting Of”
 - Meezan Discloses and Renders Obvious n-Dodecyl-B-D-maltoside
 - Motivation to Combine and Reasonable Expectation of Success
 - Cartt Status as Prior Art (Ground 2 in the -00466 IPR)
 - USP 23/NF 18 Status as Prior Art (Ground 3 in the -00466 IPR)
- ***Motions to Strike and Exclude Evidence***

Petitioner's Motions to Strike (All IPRs)

Petitioner's Motions to Strike

- Petitioner moved to strike the declarations of Steve Cartt (EX2045), Mark Mitchnick (EX2046), and David Hale (EX2047).
- Patent Owner was required, but refused, to make the declarants available for cross-examination before Petitioner's Reply:

Consolidated Trial Practice Guide

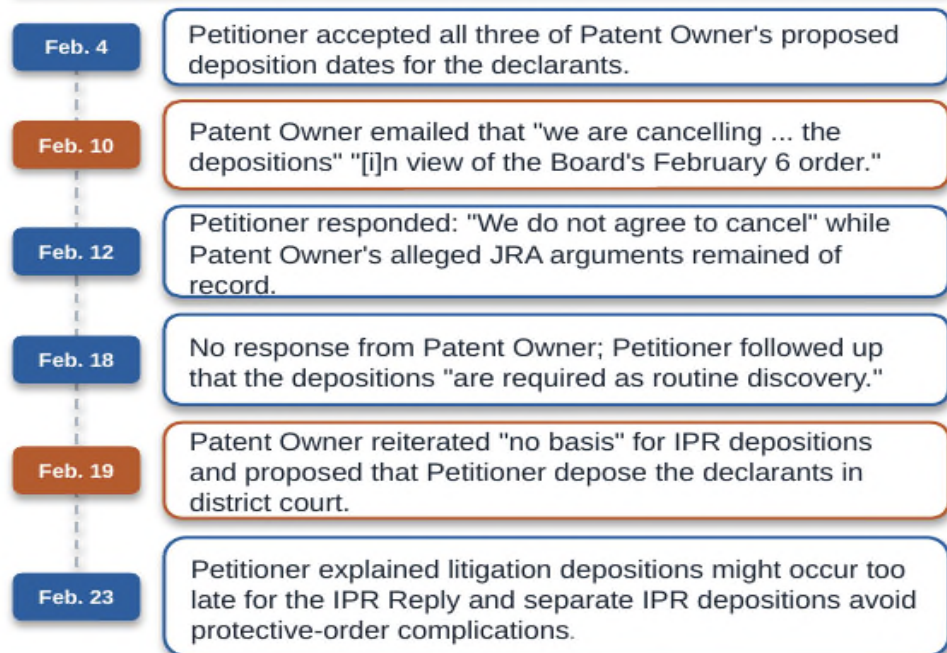
Routine discovery includes ... the cross-examination of the other sides declarants ... Routine discovery places the parties on a level playing field and streamlines the proceeding.

37 C.F.R. §42.53(d)(2)

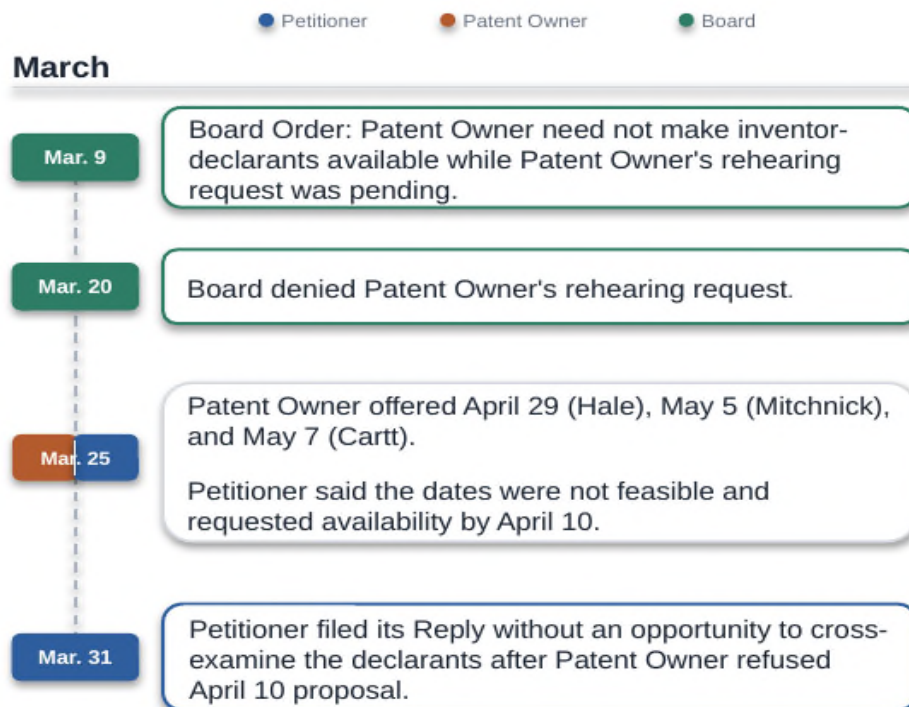
Cross-examination should ordinarily take place after any supplemental evidence relating to the direct testimony has been filed and more than a week before the filing date for any paper in which the cross-examination testimony is expected to be used.

Timeline of Deposition Discussions

February



March



Petitioner Has Been Prejudiced by Lack of Cross-Examination

- Late depositions would not have cured prejudice to Petitioner.

Adobe Inc. v. Rah Color Technologies, LLC,
IPR2019- 00627, Paper No. 124 at 23-24
(PTAB Aug. 31, 2020)

“Notwithstanding, we need not consider how or why Petitioner came to rely on Dr. Green; the fact that he was not available for a timely deposition is the relevant consideration for our inquiry.”

We also have considered the potential for prejudice to Patent Owner if we were to overlook Dr. Green’s belated availability ... Under the circumstances of this case, it would have been unfair to require or expect Patent Owner to readdress Dr. Green’s declaration in its Sur-reply.”

Netflix Inc. et al. v. DivX, LLC, IPR2020-00646,
Paper No. 34 at 5 (PTAB April 26, 2021)

“Additionally, we are persuaded that Petitioner would be prejudiced by allowing Patent Owner to introduce the new exhibit. Regardless of the extent of material quoted in Dr. Bajaj’s declaration, Petitioner is entitled to depose Dr. Bajaj after the exhibit has been filed and more than a week before its Reply deadline. See 37 C.F.R. § 42.53(d)(2) ... Accordingly, given the impending Reply deadline and lack of opportunity to cross examine Dr. Bajaj on the new exhibit, Petitioner would be prejudiced by the filing of the exhibit.”

Petitioner Has Been Prejudiced by Lack of Cross-Examination

- The inventor declarations are relevant to prior art status of Gwozdz, which remains a live issue that Patent Owner intends to appeal:

35 U.S.C. §103(c)(2)

For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if —

(A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;

(B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

IPR2025-00464, Paper 44 at 8-9; Paper 47 at 1-2

Patent Owner's Motions to Strike (All IPRs)

Patent Owner's Motion to Strike

- Patent Owner moved to strike:
 - o Exhibits that Patent Owner argues “were not discussed or even cited” in Petitioner’s Reply:

Document	Exhibit No.
Dr. Brown’s Textbook	1073
U.S. Pat. No. 6,962,691	1074
Meezan Specification Amendment	1075
Dr. Maggio’s Declaration	1076
IUPAC Nomenclature Recommendations	1079
U.S. Pat. No. 8,278,292	1080

Patent Owner's Motion to Strike

- Patent Owner moved to strike:
 - o Portions of Petitioner's Reply and of Dr. Donovan's Reply Declaration that allegedly raise "new invalidity theories."

Document	Exhibit/Paper No.	Disputed Portions
Meezan Specification Amendment	1075	All
Dr. Maggio's Declaration	1076	All
Donovan Reply Decl.	1078	¶¶ 11, 15-19, 21-23, 37-43, 45, 47-50
IUPAC Nomenclature Recommendations	1079	All
Petitioner's Reply	43	Pages 13-15, 17-18, 21-22

Board Should Not Strike Exhibits Relied on in Expert Testimony

- All challenged exhibits except Exhibit 1080 were discussed in expert testimony:

Ex. No.	Cited in Dr. Brown Deposition (Ex. 1077)	Cited in Dr. Donovan Reply Declaration (Ex. 1078)
1073	130:21-142:3	¶¶ 37-38
1074	160:4-164:10	N/A
1075	171:18-178:12	¶¶ 47-48
1076	184:17-192:12	¶¶ 49-50
1079	N/A	¶ 18

Board Should Not Strike Exhibits Relied on in Expert Testimony

- Exhibits cited in an expert declaration or a deposition should not be stricken:

TwinStrand Biosciences, Inc. v. Guardant Health, Inc., IPR2022-01400, Paper 41 at 47 (PTAB Jan. 26, 2024)

“Here, Dr. Spellman and Dr. Satija rely on the identified exhibits in their declarations. As such, they are relevant to understanding the weight to be given the declarants’ testimony.”

Intex Recreation Corp. v. Team Worldwide Corp., IPR2018-00875, Paper 129 at 88 (PTAB Sept. 11, 2019)

“We also deny Petitioners’ motion as to the other Uncited Exhibits (Exhibits 2031, 2032, and 2033) as moot. As Patent Owner explains, these exhibits were used in conducting Dr. Beaman’s December Deposition (Ex. 2040) and the complete deposition transcript is in the record.”

Board Should Not Strike Exhibits Relied on in Expert Testimony

- An expert's reference to an exhibit not cited in the papers does not constitute a new argument

SK Hynix Inc. v. Netlist, Inc., IPR2017-00561,
Paper 36 at 61-62 (PTAB July 5, 2018)

The testimony regarding Exhibit 1022 is relevant to why Averbuj would be modified to the configuration in claim 2 in which the components are on separate ICs. This argument is fully explored in the Petition despite the lack of specific citation to Exhibit 1022. See Pet. 51–55 (citing, *inter alia*, Ex. 1003 ¶¶ 197–198 (citing Exhibit 1022)). We do not find that Dr. Mazumder's reference to this Exhibit introduces argument that was not contained in the Petition or introduces material that was either excessive or material that the relevance of which is not explained.

Reply Maintains the Same Legal Theories Raised in the Petition

- Petitioner's and Dr. Donovan's Replies rely on the same legal theories raised in the Petition and merely rebut issues raised in Patent Owner's Response:

Apple Inc. v. Gesture Tech. Partners, LLC,
127 F.4th 364, 372 (Fed. Cir. 2025)

In its final written decision with respect to claim 4, the Board ignored Apple's expert's testimony, reasoning that Apple's IPR petition "[did] not reference any such analysis in connection with the subject matter of claim[] 4." J.A. 34. But under our precedent, Apple's expert's testimony was sufficiently confined to the argument made in Apple's IPR petition to warrant consideration by the Board, since a party is not barred from elaborating on its arguments on issues previously raised.

Apple Inc. v. Andrea Elecs. Corp., 949 F.3d
697, 706–07 (Fed. Cir. 2020)

It is unreasonable to hold petitioners to such a high standard that, if they choose to rely on one example of an algorithm, they must either discuss all potential permutations of the variables or risk waiving the opportunity to further discuss other relevant examples in their reply. *Chamberlain Grp., Inc. v. One World Techs., Inc.*, 944 F.3d 919, 925 (Fed. Cir. 2019) ("Parties are not barred from elaborating on their arguments on issues previously raised.").

Reply Maintains the Same Legal Theories Raised in the Petition

- Petitioner's and Dr. Donovan's Replies rely on the same legal theories raised in the Petition and merely rebut issues raised in Patent Owner's Response:

Petition

Accordingly, as observed by Dr. Donovan, “based on Meezan’s teaching of 0.25% alkyl glycoside, including dodecyl maltoside, and the fact that the amount and identity of the alkyl glycoside is not critical, a POSA would routinely select [n-dodecyl beta-D-maltoside] to add to Gwozdz’s solution.” EX1062, ¶151.

IPR2025-00466, Paper 2 at 41.

Reply

Patent Owner and Dr. Brown argue that Meezan does not teach the claimed “n-dodecyl beta-D-maltoside” because Meezan discloses “dodecyl beta-D-maltoside” without the “n-” designation and that disclosure supposedly covers more than 355 isomeric species. POR, 39-42. That is wrong.

IPR2025-00466, Paper 43 at 13.

Reply Maintains the Same Legal Theories Raised in the Petition

- Petitioner and Dr. Donovan have always asserted that Meezan's disclosure of dodecyl maltoside was a disclosure of n-dodecyl-β-D-maltoside.

Dr. Donovan Original Declaration

151. Therefore, based on Meezan's teaching of 0.25% alkyl glycoside, including dodecyl maltoside, and the fact that the amount and identity of the alkyl glycoside is not critical (and is, in fact, predictable), a POSA would routinely select n-dodecyl beta-D-maltoside to add to Gwozdz's solution.³

³ The terms dodecyl maltoside and "n-dodecyl beta-D-maltoside" are understood to be the same compound, and the terms are generally considered interchangeable.

Pet. (-00466) at 41; Reply (-00466) at 15; Ex. 1062, ¶151.

Dr. Donovan Reply Declaration

48. Relatedly, as noted in my opening declaration, a POSA would have understood the shortened name "dodecyl maltoside" to refer to n-dodecyl-β-D-maltoside. See, e.g., Ex. 1062 (Donovan Op. Decl.) at ¶¶147-152. The above corrected Meezan specification underscores that point. Indeed, Meezan discloses that "DDM" and "dodecyl maltoside" are shorthand for "n-dodecyl-β-D-maltoside." For example, Meezan discloses an example in which "0.5% dodecyl-β-D-maltoside" was included in an ocular formulation and test results were reported in "Table I." Ex. 1010 (Meezan) at ¶ [0156]. But in Table I, Meezan simply lists "dodecyl maltoside" despite making it clear that Table I was discussing "dodecyl-β-D-maltoside." *Id.* at ¶ [0158], Table I.

Reply (-00466) at 15; Ex. 1078, ¶48.

Reply Maintains the Same Legal Theories Raised in the Petition

- The Petition and Reply both assert that “consisting of” has its conventional meaning, i.e. containing only the claimed ingredients:

Petition

Finally, as noted by Dr. Donovan, “Gwozdz and Meezan render obvious a pharmaceutical solution for nasal administration “consisting of” (i.e., containing only) the claimed benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and an alkyl glycoside.” EX1062, ¶131.

IPR2025-00466, Paper 2 at 36.

Reply

Petitioner has always applied the plain meaning of “consisting of” to the prior art, noting that “Gwozdz and Meezan render obvious a pharmaceutical solution for nasal administration ‘consisting of’ (i.e., containing only) the claimed benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and an alkyl glycoside.” Pet., 36; EX1062, ¶131; EX1078, ¶¶31-33.

IPR2025-00466, Paper 43 at 16.

IPR2025-00466, Paper 49 at 8-9.

Reply Maintains the Same Legal Theories Raised in the Petition

- Petitioner's citation to Gwozdz is proper rebuttal to Patent Owner's argument that Gwozdz fails to disclose a non-aqueous solution:

POR

Just as every embodiment in Gwozdz-PCT includes water, every example in Meezan involves peptides or proteins dissolved in water. EX2074 ¶¶228-230. Petitioner utterly fails to address how these water-based references somehow result in the '786 Patent inventions, which—according to Petitioner in district court—exclude every trace of water.

IPR2025-00466, Paper 28 at 44.

Reply

Patent Owner further argues that Gwozdz's disclosure of "penetration enhancer" supplies the motivation to combine with Meezan and that, because that discussion appears in a section on injectable formulations that may contain water, the Gwozdz formulation must also contain water. POR, 42-44. But Gwozdz never states that water is required. To the contrary, it expressly says that formulations suitable for parenteral (i.e., injection) administration can be aqueous or nonaqueous. EX1009, 11:17-18

IPR2025-00466, Paper 43 at 17-18.

IPR2025-00466, Paper 49 at 8-9.

Patent Owner's Motions to Exclude (All IPRs)

Patent Owner's Motion to Exclude

- Patent Owner moved to exclude exhibits that it also moved to strike: Exhibits 1073-1076.
- Patent Owner argued that:
 - o Exhibits 1073-1076 are not relevant under FRE 401-403.
 - o Exhibit 1075 was incomplete under FRE 106.
 - o Exhibits 1075 and 1076 were hearsay under FRE 801-802.

Patent Owner's Motion to Exclude: Relevance

- Exhibits 1073-1076 are relevant, and are not prejudicial, for the reasons already discussed.
- Regardless, whether an exhibit was expressly cited in a petition or reply relates to how much weight the evidence at issue should be afforded:

BioMarin Pharma Inc., v. Genzyme Therapeutic Prods. L.P., IPR2013-00537, Paper 79 at 25 (PTAB Feb 23, 2015)

“It is better to have a complete record of the evidence submitted by the parties than to exclude particular pieces of evidence.”

Corning Inc. v. DSM IP Assets B.V., IPR2013-00053, Paper 66 at 19 (PTAB May 1, 2014)

“The Board, sitting as a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to evidence presented.”

IPR2025-00466, Paper 59 at 2-3.

Patent Owner's Motion to Exclude: Exhibit 1075 Is Not Incomplete

- Exhibit 1075 was a complete copy of an August 13, 2007 Response to an Office Action and Amendments filed during the prosecution of Meezan.
- Patent Owner argued that Exhibit 1075 was incomplete under FRE 106 but agreed that if Petitioner filed the entire file history of Meezan, the objection would be resolved.
- Petitioner filed the entire file history of Meezan (Ex. 1104) and has therefore resolved this objection.

Patent Owner Motion to Exclude: Exhibits 1075 and 1076 Are Not Hearsay

- Patent Owner argues that Exhibits 1075 and 1076 should be excluded as hearsay.
- Petitioner is not relying on Exhibits 1075 or 1076 for the truth of the matter asserted:

Donovan Reply Declaration

Relatedly, as noted in my opening declaration, a POSA would have understood the shortened name “dodecyl maltoside” to refer to n-dodecyl-β-D-maltoside. See, e.g., Ex. 1062 (Donovan Op. Decl.) at ¶¶147-152. The above corrected Meezan specification underscores that point. Indeed, Meezan discloses that “DDM” and “dodecyl maltoside” are shorthand for “n-dodecyl-β-D-maltoside.”

EX1078 at ¶48.

Donovan Reply Declaration

Dr. Maggio’s position and view supports my own, namely that a POSA would have understood that the recitation of “dodecyl-β-D-maltoside” is a reference to “n-dodecyl-β-D-maltoside.”

EX1078 at ¶150.

Patent Owner Motion to Exclude: Exhibits 1075 and 1076 Are Not Hearsay

- Even if Exhibits 1075 and 1076 are hearsay, they fall within certain hearsay exceptions:
 - o The Meezan Specification Amendment (Ex. 1075) satisfies the business records exception to hearsay under FRE 803(6):
 - A. It was submitted by “someone with knowledge” (the prosecuting DLA Piper attorney);
 - B. “kept in the course of a regularly conducted activity of” patent prosecution duties;
 - C. Made as part of “a regular practice of” patent prosecution activities;
 - D. Signed and certified by the prosecuting attorney; and
 - E. Not shown to be lacking in “trustworthiness.”

Patent Owner Motion to Exclude: Exhibits 1075 and 1076 Are Not Hearsay

- Even if Exhibits 1075 and 1076 are hearsay, they fall within certain hearsay exceptions:
 - o Exhibits 1075 and 1076 also satisfy FRE 807's residual exception to hearsay:
 1. Both are “supported by sufficient guarantees of trustworthiness” because they were signed by an attorney subject to a duty of candor (Ex. 1075) or by a witness under 18 U.S.C. § 1001 (Ex. 1076); and
 2. Both are “more probative on the point” for which they are offered than other evidence because they directly relate to what the Meezan specification describes and because Dr. Maggio is an inventor on both Meezan and the challenged patents.
 - o Dr. Donovan's reliance on Exhibits 1075 and 1076 is also not hearsay under FRE 703.