IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 24-562 (MN)
	)	
PADAGIS LLC, PADAGIS US LLC and PADAGIS ISRAEL PHARMACEUTICALS LTD.,	)	
	)	
Defendants.	)	

DEFENDANTS' PRELIMINARY INVALIDITY CONTENTIONS

Defendants Padagis LLC, Padagis US LLC and Padagis Israel Pharmaceuticals Ltd. ("Padagis") hereby provide the following Preliminary Invalidity Contentions to Plaintiff Neurelis, Inc. ("Plaintiff") regarding claims 1-22 of U.S. Patent No. 8,895,546 ("the '546 patent"), claims 1-3, 5-13, 15-18 of U.S. Patent No. 11,241,414 ("the '414 patent"), and claims 1-3, 5-9, 11-13, 15-27 of U.S. Patent No. 11,793,786 ("the '786 patent") (the claims, collectively, the "Asserted Claims," and the '546, '414, and '786 patents, collectively, the "Asserted Patents").

I. INTRODUCTION

Padagis makes these disclosures based on its current knowledge, recognizing that investigations are continuing and discovery is just beginning. Moreover, facts, documents, and things now known may be imperfectly understood and, accordingly, such facts, documents and things may not be included in the following Preliminary Invalidity Contentions. Padagis reserves the right to amend these contentions and supplement this production to the full extent consistent with the Court's Rules and Orders and in view of any information discovered during litigation. Further, these contentions are provided without prejudice to the rights of Padagis to introduce at trial expert opinions relating to currently known facts and subsequently discovered facts, and

subsequently-discovered evidence of currently known facts; and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of currently known and subsequently-discovered facts.

Padagis incorporates, in full, all prior art references cited in the prosecution histories or post-grant proceedings of the Asserted Patents or any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority, the prosecution histories themselves, as well as all references and arguments made by the Examiners during prosecution.

Discovery in this case is in its early stages, claim terms of the Asserted Patents have not yet been identified for construction by the parties or construed by the Court in this case, and Padagis's investigation is ongoing. Padagis therefore reserves the right to further supplement or alter the positions taken and information disclosed in these Preliminary Invalidity Contentions including, without limitation, the prior art and grounds of invalidity set forth herein, to take into account information or defenses that may come to light as a result of these continuing efforts. Padagis further expressly reserves the right to amend or supplement these contentions in view of any evidence regarding secondary considerations that Plaintiff may be permitted to raise.

Padagis only addresses the Asserted Claims—that is, the claims that Plaintiff has asserted against Padagis in this litigation. To the extent that Plaintiff is permitted to assert additional claims not presently identified in its disclosure of Asserted Claims, Padagis reserves the right to address the invalidity of such claims. Padagis expressly reserves the right to amend, supplement, or modify any of these contentions should Plaintiff attempt to modify the Asserted Claims and/or Asserted Patents.

Padagis's preliminary invalidity positions in these contentions may be in the alternative and do not constitute any concession or admission for purposes of invalidity, enforceability, claim

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construction, and/or infringement. *See, e.g., Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000). For example, Padagis's Section 112 arguments may be in the alternative to its obviousness arguments and should not be viewed, in any way, to be concessions about the prior art or knowledge of one of ordinary skill in the art. Likewise, the suggested obviousness combinations are in the alternative to any contentions based on anticipation. The obviousness contentions set forth herein should not be construed to suggest that any reference is not anticipatory by itself.

The information set forth below is provided without waiving: (1) the right to object to the use of any statement or evidence for any purpose, in this action or any other action, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided. The contentions of each dependent claim incorporate the contentions of each claim from which the dependent claim depends. This includes all prior art and non-prior art defenses, including all defenses available under 35 U.S.C. §§ 101, 102, 103, and 112.

Padagis objects to the disclosure of information that is protected by the attorney-client privilege, attorney work-product immunity, the common interest privilege or any other applicable privilege or immunity. To the extent Padagis inadvertently discloses information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common interest privilege or any other applicable privilege or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

In these Preliminary Invalidity Contentions, Padagis takes no position, one way or the other, as to whether any particular claim phrase or term should be construed as bearing on the

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scope of any asserted claim by, for example, acting as a limitation or creating an exclusion. These Preliminary Invalidity Contentions are based, at least in part, on Padagis's present understanding of the plain and ordinary meaning of the Asserted Claims of the Asserted Patents. Padagis takes no position regarding the plain and ordinary meaning of any claim terms in these Preliminary Invalidity Contentions. Any statement herein describing or tending to describe any claim element is provided solely for the purpose of understanding the relevant prior art or other basis for invalidity.

These Preliminary Invalidity Contentions may be made in the alternative and are not necessarily intended to be consistent with each other. Furthermore, Padagis's inclusion of prior art that would render a claim anticipated or obvious based on a particular scope of the claim, including that apparently applied by the Plaintiff in its initial infringement contentions, is not, and should in no way be seen as, an adoption or admission as to the scope of the claim or a claim term's plain and ordinary meaning. Padagis reserves all rights to further supplement or modify the positions and information in these Preliminary Invalidity Contentions, including without limitation, the prior art and grounds of invalidity set forth herein.

It should be recognized that a person of ordinary skill in the art at the time of the purported invention ("POSA") would generally read a prior art reference as a whole and in the context of other publications, literature, and general knowledge in the field. To understand and interpret any specific statement or disclosure in a prior art reference, a POSA would rely upon other information including other publications and general scientific or engineering knowledge. Padagis therefore reserves the right to rely upon other unidentified portions of the prior art references and on other publications and expert testimony to provide context and to aid understanding and interpretation of any identified portions. Padagis also reserves the right to rely upon other portions of the prior

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art references, other publications, and the testimony of experts to establish that the alleged inventions were inherently disclosed in the prior art, and/or would have been obvious to a POSA, including on the basis of modifying or combining certain cited references. Padagis also reserves the right to rely upon any prior art or admissions relating to prior art in the prosecution histories of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. In addition, Padagis reserves the right to rely on all prior art produced by Padagis, Plaintiff, or any other party in any other proceeding including re-examinations, oppositions, and *inter partes* review involving any of the Asserted Patents.

II. ASSERTED PATENTS AND CLAIMS

A. The ’546 Patent

Based on Plaintiff’s initial infringement contentions, Padagis understands Plaintiff is asserting claims 1-22 of the ’546 patent.

The ’546 patent was filed on June 13, 2012, as Application No. 13/495,942 and issued on November 25, 2014. The ’546 patent claims priority as a continuation-in-part of Application No. 12/431,439, filed on March 27, 2009, which claims priority to Provisional Application No. 61/497,017, filed June 14,2011, and Provisional Application No. 61/570,110, filed on December 13, 2011.

Based on presently available information, and in view of the early stage of this case, Padagis states that the Asserted Claims of the ’546 patent are entitled to a priority date of no earlier than the March 27, 2009 filing date of the ’439 Application, which contains the first support for alkyl glycosides. Padagis expressly reserves the right to assert that one or more of the claims may only be entitled to an effective filing date later than March 27, 2009.

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B. The ’414 Patent

Based on Plaintiff’s initial infringement contentions, Padagis understands Plaintiff is asserting claims 1-3, 5-13, 15-18 of the ’414 patent.

The ’414 patent was filed on May 27, 2021, as Application No. 17/332,800 and issued on February 8, 2022. The ’414 patent claims priority as a continuation of Application No. 17,228,514, filed on April 12, 2021, which is a continuation of Application No. 15/995,397, filed on April 17, 2018, which is a continuation of Application No. 12/413,439, filed on March 27, 2009, which claims priority to Provisional Application No. 61/040,558, filed on March 28, 2008.

Based on presently available information, and in view of the early stage of this case, Padagis states that the Asserted Claims of the ’414 patent are entitled to a priority date of no earlier than the March 27, 2009 filing date of the ’439 Application, which contains the first support for alkyl glycosides. Padagis expressly reserves the right to assert that one or more of the claims may only be entitled to an effective filing date later than March 27, 2009.

C. The ’786 Patent

Based on Plaintiff’s initial infringement contentions, Padagis understands Plaintiff is asserting claims 1-3, 5-9, 11-13, 15-27 of the ’786 patent.

The ’786 patent was filed on April 12, 2021, as Application No. 17,228, 514 and issued on October 24, 2023. The ’786 patent claims priority as a continuation of Application No. 15/995,397, filed on April 17, 2018, which is a continuation of Application No. 12/413,439, filed on March 27, 2009, which claims priority to Provisional Application No. 61/040,558, filed on March 28, 2008.

Based on presently available information, and in view of the early stage of this case, Padagis states that the Asserted Claims of the ’786 patent are entitled to a priority date of no earlier than the March 27, 2009 filing date of the ’439 Application, which contains the first support for

alkyl glycosides. Padagis expressly reserves the right to assert that one or more of the claims may only be entitled to an effective filing date later than March 27, 2009.

III. LEGAL FRAMEWORK

A. Anticipation

A patent is invalid for anticipation under 35 U.S.C. § 102 if a single prior art reference discloses each and every limitation of the claimed invention. *See Schering Corp. v. Geneva Pharm.,* 339 F.3d 1373, 1377 (Fed. Cir. 2003). A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference. *See id.*

B. Obviousness

A claim is invalid for obviousness if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). For example, the refinement of ranges does not typically impart patentability of a claimed invention over the prior art. *See, e.g., Merck & Co. Inc. v. Biocraft Labs Inc.*, 874 F.2d 804 (Fed. Cir. 1989); *In re Geisler*, 116 F.3d 1465 (Fed. Cir. 1997). Absent a demonstration of criticality, variation in a concentration, temperature, or other such feature does not indicate nonobviousness over prior art disclosing a different value for the same parameter. *See In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990). In particular, a claim is obvious if it teaches a range that, while not overlapping with the prior art, is close enough that a POSA would expect them to have the same properties. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985).

A claimed modification of a prior art product is "obvious to try" where there are a "finite number of identified, predictable solutions," and if such modification is successful, "it is likely the

product not of innovation but of ordinary and common sense." *KSR, Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). Accordingly, if the prior art explicitly teaches an array of features, and the prior art components "provide only their known properties, to produce results shown or predicted in the prior art," then such combinations would have been obvious. *See Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc. USA*, 748 F.3d 1354, 1360–61 (Fed. Cir. 2014). Moreover, whether a particular feature or embodiment is identified as "preferred" in a prior art reference does not limit the scope of the overall reference as disclosure against a later claim. *See Id.*

A claim may also be shown to be obvious in view of the prior art. Although the ultimate determination of obviousness under § 103 is a question of law, the evaluation is based on several underlying factual factors, often referred to as "the Graham factors," including: "(1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, such as commercial success, long-felt need, and the failure of others." *Innovention Toys, LLC v. MGA Entm't, Inc.*, 637 F.3d 1314 (Fed. Cir. 2011) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). However, even secondary considerations of nonobviousness may be inadequate to overcome a strong prima facie case of obviousness. *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

The Supreme Court's decision in *KSR* further indicates that the *Graham* factors are to be evaluated flexibly and in view of common sense. Specifically, *KSR* indicates that pressure to solve a known problem, the presence of a limited number of predictable solutions, and anticipated success are all relevant factors in determining whether an invention is obvious. The inquiry may be referred to as the "common sense" standard, and is described below.

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103. . . . Rigid preventative rules that deny fact finders recourse to common sense, however, are neither necessary under our case law nor consistent with it.

KSR, 550 U.S. at 418-19.

The common-sense standard provides that the motivation to combine references may be present in the nature of the problem to be solved or known by one of skill in the art. In establishing any of the contentions set forth herein, Padagis may rely on common sense and/or the knowledge of a POSA at the time of the alleged inventions.

C. Section 112

Under 35 U.S.C. § 112, the specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112.

1. Written Description

Under 35 U.S.C. § 112(a), "The specification shall contain a written description of the invention." The inventor must describe the invention so that the public will know what it is and that he or she has truly made the claimed invention. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002) ("The [ ] requirements must be satisfied before issuance of the patent, for exclusive patent rights are given in exchange for disclosing the invention to the public. What is claimed by the patent application must be the same as what is disclosed in the specification. . . ." (internal citations omitted)).

The Federal Circuit has made it clear that the description must allow one of ordinary skill in the art to recognize that the inventor had possession of the claimed subject matter at the time of filing. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[I]t is the specification itself that must demonstrate possession." *Id.* at 1352. Assessing possession as shown in in the disclosure requires "an objective inquiry into the four corners of the specification." *Id.* at 351. Ultimately, "the specification must describe an invention understandable to [a person of ordinary skill in the art] and show that the inventor actually invented the invention claimed." *Id.* For the purposes of written description, the invention is "whatever is now claimed." *See, e.g., PowerOasis, Inv. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1311 (Fed. Cir. 2008). A "mere wish or plan" for obtaining the claimed invention is not adequate written description. *Regents of the Univ. of Cal. v. Eli Lilly Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

The written description "must do more than merely disclose that which would render the claimed invention obvious." *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1377 (Fed. Cir. 2009). Each claim limitation must be described in the specification. *Id.* at 1347. The level of detail required to satisfy the written description requirement depends on the scope of the claims and predictability of the relevant technology. *See Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1344 (Fed. Cir. 2011). In an unpredictable art, a higher level of detail is required to show that the inventors possessed what was claimed. *See, e.g., Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1229 (Fed. Cir. 1994).

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable. *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997); *see also Centocor*, 636 F.3d at 1350-53 (claim to provisional application filing date rejected for lack of disclosure of the claimed subject matter).

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Thus, "the lack of any disclosure of examples may be considered when determining whether the claimed invention is adequately described." *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011). Moreover, a patentee may not rely on information "well-known in the art" to supply the lacking written description in an unpredictable art. *See, e.g., Univ. of Rochester*, 358 F.3d at 927.

2. Indefiniteness

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.,* 134 S. Ct. 2120, 2124 (2014). "[A] patent must be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them." *Id.* at 2129 (quotations and citations omitted). The analysis to determine if a claim is invalid for indefiniteness examines the claims, specification, and prosecution history "to ascertain if they convey to one of skill in the art with reasonable certainty the scope of the invention claimed." *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015).

3. Enablement

A patent's specification must describe the invention and "the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains ... to make and use the same." 35 U.S.C. § 112(a). Claims are not enabled when, at the effective filing date of the patent, a POSA could not practice their full scope without undue experimentation. *See Wyeth & Cordis Corp. v. Abbott Labs*., 720 F.3d 1380, 1384 (Fed. Cir. 2013). In addition, the scope of enablement must be commensurate with the full scope of the claim. *Id.* at 1384–85; *see also AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). The Federal Circuit has provided several factors that may be utilized in determining whether a

disclosure would require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

IV. INVALIDITY OF THE ASSERTED CLAIMS

A. Level of Ordinary Skill in the Art

A POSA as to Asserted Patents would have been a pharmaceutical chemist, chemist, or biologist involved in the research and development of pharmaceutical formulations and/or delivery, and would have at least a Bachelor's degree with at least 5 years of experience, or a Master's, Ph.D. or Pharm.D. degree with several years of experience. A POSA would have had knowledge of benzodiazepine structure and function, and would further have knowledge and practical experience working with intranasal and transmembrane formulations, including knowledge of the physiology and anatomy of the nasal cavity, with relevant experience in developing intranasal formulations. A POSA is considered to be aware of all relevant prior art, including the prior art described below, and would have had the capability to draw inferences from the references, including combining the references and then drawing additional inferences from the combined teachings.

B. Background of Technology

Acute isolated seizure, repetitive or recurrent seizures and status epilepticus are all deemed medical emergencies. Mortality and "worse neurologic outcome" (as referred to in the literature) are directly associated with the duration of seizure activity. A number of reviews have described consensus statements regarding the pharmacologic treatment protocols for seizures when patients are in pre-hospital, institutional and home-bound settings. Benzodiazepines such as lorazepam,

diazepam, midazolam and clonazepam are considered medications of first choice. The rapidity by which a medication can be delivered to the systemic circulation and then to the brain plays a significant role in reducing the time needed to treat seizures and reduce opportunity for damage to the central nervous system. Intranasal transmucosal delivery of benzodiazepines is useful in reducing time from drug administration to cessation of seizures. A POSA would look to various factors when developing a benzodiazepine for intranasal administration, including formulation considerations, as well pharmacology and PK/PD profiles.

Additional references that may be relied upon to demonstrate the state of the art include:

Reference	**Publication Date**	**Short Cite**
U.S. Patent No. 9,763,876, *Administration Of Benzodiazepine Compositions*	October 29, 2014	’876 patent
Ritschel, *Handbook of Basic Pharmacokinetics*, Chapter 36 (Bioavailability and Bioequivalence), Drug Intelligence Publications, Illinois	1992	Ritschel
Osborne et al., *Skin Penetration Enhancers Cited in the Technical Literature*, Pharmaceutical Technology	November 1997	Osborne
Lindhardt et al., *Electroencephalographic effects and serum concentrations after intranasal and intravenous administration of diazepam to healthy volunteers*, Blackwell Science Ltd Br J Clin Pharmacol, 52, 521-527	2001	Lindhardt
Ivaturi et al., *Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers*, Acta Neurol Scand. 2009 Nov;120(5):353-7. doi: 10.1111/j.1600-0404.2009.01170.x.	May 14, 2009	Ivaturi
Rowe et al., editors, *Handbook of Pharmaceutical Excipients*, Fourth Edition (2003), Monographs for “Alcohol” (i.e., ethanol), “Alpha Tocopherol”, “Benzyl Alcohol”, “Glycerin”, “Olive Oil”, “Polyethylene Glycol”, “Propylene Glycol”, “Sesame Oil”, and “Triacetin”, American Pharmaceutical Association, Washington DC	2003	Rowe
PDR 54th Edition 2000, DIASTAT® (diazepam rectal gel); MIACALCIN® (Calcitonin Nasal Spray); VALIUM® (diazepam injection), Physicians’ Desk Reference	2000	PDR
Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam	2002	Knoester

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administered as a concentrated intranasal spray. A study in healthy volunteers. Br J Clin Pharmacol. 2002; 53: 501-507		
Florida Regional Common EMS Protocols Field Guide, Jones and Barlett Publishers, MA	2005	EMS
Valium® Tablet Label, Roche	January 2008	Valium Label
Wolfe T, Macfarlane T. *Intranasal midazolam therapy for pediatric status epilepticus.* Am J Emerg Med 2006; 24:43-346	2006	Wolfe
Holsti M, Sill B, Firth S, et al., *Prehospital intranasal midazolam for the treatment of pediatric seizures.* Ped Emerg Care 2007; 23: 148-153	2007	Holsti
Greenblatt D, Gan L, Harmatz, et al. *Pharmacokinetics and pharmacodynamics of single-dose triazolam: EEG compared with digital symbol substitution test.* Br J Clin Pharmacol 2005; 60: 244-248	2005	Greenblatt
O'Regan M, Brown J, Clarke M. *Nasal rather than rectal benzodiazepines in the management of acute childhood seizures.* Develop Med and Child Neurol 1996; 38: 1037-1045	1996	O'Regan
Bhattacharyya M, Kalra V, Gulati S. *Intranasal midazolam vs rectal diazepam in acute childhood seizures.* Pediatric Neurology 2006; 34: 355-359	2006	Bhattacharyya
SIGMA Chemical Company Catalog	1988	Sigma Catalog
Wermeling DP, et al., Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures, Neurotherapeutics: The Journal of the American Society for Experimental Neurotherapeutics, Vol. 6, 352-353	April 2009	Wermeling I
Hardman, et al., Editors, Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 10th Edition	2001	Goodman & Gilman
Loftsson T, Gudmundsdottir H, Sigurjonsdittur JF, et al. Cyclodextrin solubilization of benzodiazepines: formulation of midazolam nasal spray. Int J Pharm 2001; 212:29-40	2001	Loftsson
Gudmundsdottir H, Sigurjonsdottir JF, Masson M, et al. *Intranasal administration of midazolam in a cyclodextrin based formulation: bioavailability and clinical evaluation in humans.* Pharmazie 2001; 56: 963-966	2001	Gudmundsdottir
Dale O., Nilsen T., Loftsson T. *Intranasal midazolam: a comparison of two delivery devices in human volunteers.* J Pharmacy Pharmacol 2006; 58: 1311-1318	2006	Dale
Burstein AH, Modica R, Hatton M, et al. *Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration.* J Clin Pharmacol 1997; 37: 711-718	1997	Burstein

Wermeling, D, Record K, Kelly T, et al., *Pharmacokinetics and pharamcodynamics of a new intranasal midazolam formulation in healthy volunteers.* Anesth Analg 2006; 103: 344-349	2006	Wermeling II
Schols-Hendriks MWG, Lohman JJHM, Janknegt R, et al. *Absorption of clonazepam after intranasal and buccal administration.* Br J Clin Pharmacol, 1995; 39: 449-451	1995	Schols-Hendricks
Lau SWJ, Slattery JT. Intl J Pharmaceutics. *Absorption of diazepam and lorazepam following intranasal administration.* Int J Pharmaceutics 1989; 54: 171-174	1989	Lau
Wermeling DP, Miller JL, Archer SM, et al. *Bioavailability and pharmacokinetics of lorazepam after intranasal, intravenous, and intramuscular administration.* J Clin Pharmacol, 2001; 41: 1225-1231	2001	Wermeling III
Budavari, et al., Editors, The Merck Index, 12th Edition	1996	Merck Index
Lowenstein DH, Alldredge BK. *Status epilepticus*, N Eng J Med 1998; 338:970-976	1998	Lowenstein I
Lowenstein DH, Bleck T, Macdonald RL. *It's time to revise the definition of status epilepticus*. Epilepsia 1999: 40:120-122	1999	Lowenstein II
Wang HC, Chang WN, Chang HW, et al., *Factors predictive of outcome in postraumatic seizures*. J Trauma 2008; 64: 883-888	2008	Wang
Stavem K, Bjornaes H, Langmoen IA. *Long-term seizures and quality of life after epilepsy surgery compared with matched controls*. Neurosurgery 2008; 62: 326-334	2008	Stavem
Logroscino G, Hessdorffer DC, Cascino G, et al., *Time Trends in incidence, mortality, and case-fatality after first episode of status epilepticus*, Epilepsia 2001; 42:1031-1035	2001	Logroscino
USP 26/NF 21, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville, 2003	2003	USP 2003
Feen ES, Bershad EM, Suarez JI, *Status Epilepticus,* South Med J 2008; 101: 400-406	2008	Feen
Pang T, Hirsch L, *Treatment of convulsive and nonconvulsive status epilepticus*, Cur Treat Options Neurol 2005; 7:247-259	2005	Pang
Smith B, *Treatment of status epilepticus*, Neurol Clin 2001; 19:347-369	2001	Smith
Ericksson K, Kalviainen R. *Pharmacologic management of convulsive status epilepticus in childhood*, Expert Rev Neurotherapeutics 2005; 5:777-783	2005	Ericksson
Meierkord H, Engelsen B, Gocke K, et al., *EFNS guideline on the management of status epilepticus*, Eur J Neurol 2006; 13: 445-450	2006	Meierkord

Prasad K, Krishman P, Al-Roomi K, et al., *Anticonvulsant therapy for status epilepticus*, Br J Clin Pharmacol 2007; 63:640-647	2007	Prasad
Illum L., *Nasal Clearance in Health and Disease*, J Aerosol Med 2006; 19:92-99	2006	Illum II
Constantino HR, Illum L, Brandt G et al., *Intranasal delivery: Physicochemical and therapeutic aspects*, Intl J Pharmaceutics 2007; 337:1-24	2007	Constantino
Rudy AC, Coda BA, Archer SM, et al., *A multiple dose phase I study of intranasal hydromorphone hydrochloride in healthy volunteers*, Anesth Analg 2004; 99:1379-1386	2004	Rudy
Mittal P, Manohar R, Rawat A, *Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures*, Ind J Pediatrics 2006; 73:975-78	2006	Mittal
Mahmoudian T, Zadeh M, *Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children*, Epilepsy and Behavior 2004; 5:253-255	2004	Mahmoudian
Lahat E, Goldman M, Barr J, et al., *Comparison of intranasal midazolam with intravenous diazepam in treating febrile seizures in children: prospective randomized study*, BMJ 2000; 321:83-87	2000	Lahat
Sharma S, et al., *Permeation enhancers in the transmucosal delivery of macromolecules*, Pharmazie 2006; 61(6): 495-504	2006	Sharma
Ahsan F. et al., *Effects of the permeability enhancers, tetradecylmaltoside and dimethyl-β-cyclodextrin, on insulin movement across human bronchial epithelial cells*, Eur J Pharm Sciences 2003; 20:27-34	2003	Ahsan
U.S. Patent No. 5,661,130 to Meezan and Pillion	1997	Meezan II
U.S. Patent No. 6,610,271 to Wermeling	2003	Wermeling IV

C. Identification of Invalidating Prior Art

Padagis identifies the following prior art that, alone or in combination with other references, renders obvious the Asserted Claims of the Asserted Patents. Padagis reserves the right to rely upon additional prior art or documents as discovery progresses, to the extent not addressed herein. Defendants reserve the right to rely on all prior art cited or discussed during the prosecution of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. As such, Padagis incorporates by reference, in

full, all prior art references cited in any of the Asserted Patents or in any of the prosecution histories of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. Padagis further reserves the right to identify and rely on additional art or teachings or disclosures within the art in the event that Padagis' evaluation of the prior art teachings or disclosures is in any way contested.

Padagis reserves the right to rely on these cited or uncited references as well as other teachings or disclosures in the field to demonstrate the state of art and/or the knowledge and level of skills of a person of ordinary skill in the art at the relevant times. Padagis intends to rely upon each reference in its entirety to the extent relevant and/or appropriate, including references cited in and/or referenced within the references identified below.

Prior art not included in these Preliminary Invalidity Contentions may become relevant depending upon the positions Plaintiff asserts (*e.g.*, the infringement or claim construction positions asserted by Plaintiffs), the claim constructions adopted by the Court, and the priority date(s) determined for any of the Asserted Patents. In addition, Padagis may uncover additional prior art and/or relevant information during discovery. Padagis reserves the right to supplement, modify, or amend these Preliminary Invalidity Contentions with additional prior art, or different versions of the references listed herein, as discovery continues in light of information provided by Plaintiff concerning its infringement allegations, claim constructions, or alleged earliest priority dates of the Asserted Patents, or in light of the Court's claim construction or other rulings and orders.

D. References Relied Upon for Invalidity

Padagis intends to rely on at least the following Prior Art References:

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Prior Art Reference	Effective Publication Date	Short Cite
WIPO Publication No. WO 2009/120933 to Gwozdz et al.	March 28, 2008	Gwozdz
U.S. Publication No. 2006/0046962 to Meezan et al.	March 2, 2006	Meezan
U.S. Pub. No. 2008/0279784 to Cartt et al.	November 13, 2008	Cartt
USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville, 1995	1995	USP

E. Preliminary Summary of the Prior Art References

1. Gwozdz

WIPO Publication No. WO 2009/120933 to Gwozdz et al. entitled "Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents" published October 1, 2009 (hereinafter "Gwozdz"). Gwozdz claims priority to U.S. Prov. App. No. 61/040,281 (hereinafter "the '281 provisional"), filed March 28, 2008. Based on the filing date of the '281 provisional, Gwozdz constitutes prior art against the Asserted Patents under § 102(e)(1).

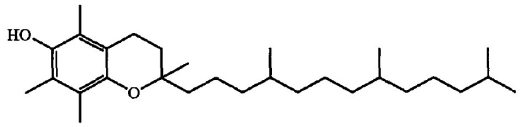
Gwozdz is directed to pharmaceutical solutions for solubilizing therapeutic agents in "one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combination thereof." (Gwozdz at 4:13-17). Gwozdz states that the therapeutic agent may include various compounds, including diazepam, stating:

> Exemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to, steroids such as Dexamethasone, 17-beta-Estradiol; benzodiazepenes such as Diazepam, alprazolam, bromazepam, chlordiazepoxidem, clonazepam, estazolam, flunitrazepam, flurazepam, lorazepam, lormetazepam, mexazolam, nitrazepam, oxazepam, temazepam, and triazolam; Rapamycin and analogues; Taxol (paclitaxel) and analogues; Actinomycin D; Prostaglandins (PGEl) ; Vitamin A; Probucol; Batimastat; Statins (HMG-CoA Reductase Inhibitors; Trapidil (and other anti-proliferative Growth Factor Inhibitors); Cytochalasin B; and microtubule binding agents such as epothilones, elutherobin and discodermolide.

(Gwozdz at 8:6-18).

In fact, Gwozdz identified diazepam (a benzodiazepine) as a preferred therapeutic agent for use in the solubilizing solutions described therein, stating that the solubility of diazepam can be increased from less than or equal to 6.67% (in ethanol) to "approaching the 10% level" (when incorporating tocopherol into the solution). (Gwozdz at 7:12-16).

Regarding the components of the solubilizing solutions, Gwozdz states the following:

> The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents.
>
> …
>
> Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds, and it has the following chemical structure:
>
> 
>
>
> Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. Use of the phrase tocopherol (s) and/or tocotrienol (s) herein is meant to be inclusive of any member of this family alone or in combination. In one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol.
>
> 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 tocotrienol with an alcohol or glycol dramatically reduces the inherent viscosity of the tocopherol or tocotrienol thereby allowing for generation of sprayable formulations.

(Gwozdz at 4:29-33, 5:33-7:2).

Gwozdz states that the solubilizing solutions described therein include a combination of "of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols." Additionally, Gwozdz identifies alpha-tocopherol as a preferred tocopherol, and ethanol and benzyl alcohol as potential alcohol components.

Regarding the combination of the tocopherol and alcohols, Gwozdz states:

> In accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent. In some embodiments, the tocopherol (s) and/or tocotrienol (s) is in an amount from about 30% to about 99% (w/w) and the alcohol (s) and/or glycol (s) is in an amount about 1% to about 70% (w/w).
>
> As a non-limiting example, the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol : 30% ethanol (200 proof) , Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol : 5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.
>
> Accordingly, preferred for some embodiments is that alpha-tocopherol and ethanol constitute 60% to 99% and 1% to 40%, respectively, of the pharmaceutical solution. In other embodiments, the alpha-tocopherol and ethanol constitute approximately 70% to 90% and 10% to 30%, respectively, of the pharmaceutical solution. In still other embodiments, the tocopherol and ethanol are used at ratios of approximately 95:5, 90:10, 85:15, 80-20, 75:25, 70:30, 65:35, or 60:40, respectively.

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(Gwozdz at 7:3-19).

Gwozdz explains that the tocopherol component is generally present in amounts ranging from about 30% to about 99% by weight, and the alcohol component is generally present in amounts ranging from about 1% to about 70% by weight. Additionally, Gwozdz notes that preferred alpha-tocopherol concentrations range from 60-99% by weight, and preferred alcohol (e.g., ethanol) concentrations range from 1-40% by weight.

Moreover, Gwozdz states that additional components may be incorporated into the solubilizing solution, stating:

> 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

(Gwozdz at 10:3-16).

Gwozdz explains that additional pharmaceutically suitable additives may be included in the solubilizing solutions, including, among others, solubilizing agents, penetration enhancers, and wetting materials.

Further, Gwozdz explains that the solubilizing solutions are preferably used for the nasal administration of therapeutic agents, stating:

> 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

> slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve hydrophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

(Gwozdz at 9:19-10:2).

As noted above, Gwozdz states that the pharmaceutical solutions of the instant invention are preferably utilized to deliver drugs to the nasal mucosa via the nasal route, which provides faster achievement of systemic therapeutic agent concentrations. Gwozdz explains that the therapeutic agent may be administered to the nasal mucosa utilizing known delivery mechanisms, such as metered dose inhalers, nebulizers, or nasal mist sprayers.

2. Meezan

U.S. Patent Application Publication No. US 2006/0046962 to Meezan et al. (hereinafter "Meezan") is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006. Meezan published more than one year prior to the earliest possible priority date for the Asserted Patents (March 27, 2009), and constitutes prior art under §102(b).

Meezan is directed to non-irritating compositions designed for improved bioavailability of therapeutic agents. Meezan states:

> The invention relates generally to non-irritating, non-toxic compositions providing enhanced bioavailability and more specifically to alkyl glycoside or saccharide alkyl ester compositions for delivery of therapeutic agents to a subject.

(Meezan at [0002]).

Meezan states that the invention is directed to alkyl glycoside or saccharide alkyl ester compositions that provide enhanced bioavailability of therapeutic agents. In particular, Meezan states the following regarding the alkyl glycoside component:

> Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside….
>
> …
>
> Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

(Meezan at [0056]-[0058]).

Meezan states that the preferred alkyl glycoside includes "nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside," as these compounds are non-toxic and amphipathic.

Moreover, Meezan states that the alkyl glycoside compounds can be utilized with a wide variety of therapeutic agents, in a wide variety of dosage forms, stating:

> [T]he present invention provides compositions, including alkyl glycosides and/or saccharide alkyl esters and a therapeutic agent (e.g. small molecule organic drug molecules, low molecular weight peptides such as Exenatide, GLP-1 and the like, proteins, and non-peptide therapeutic polymers such as 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.

(Meezan at [0004]).

Meezan explains that the alkyl glycoside compositions can be used to enhance the bioavailability of "small molecule organic drug molecules," indicating that the compositions can be utilized with a broad array of potential drug compounds. Additionally, Meezan states that the compositions may be utilized to administer drug compounds via the nasal delivery route, among others.

Regarding the amount of the alkyl glycoside or saccharide alkyl ester to be utilized in the compositions, Meezan states:

> Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects…For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug….

(Meezan at [0004]).

Meezan explains that alkyl glycosides in concentrations ranging from about 0.01% to about 6% by weight resulted in "good stabilization of the drug." Additionally, Meezan again identifies dodecyl maltoside (i.e., "DDM") as one of the preferred alkyl glycosides having a stabilizing effect on the drug compound.

3. Cartt

U.S. Pub. No. 2008/0279784 to Cartt et al. titled "Nasal Administration of Benzodiazepines" published November 13, 2008 (hereinafter "Cartt"). As noted above, the earliest possible priority date for the '546, '414, and '786 patents is March 27, 2009, meaning Cartt constitutes prior art under §102(a) and/or §102(e)(1).

Cartt is directed to nasal formulations for the administration of benzodiazepine drug compounds, including diazepam. (Cartt at [0028]). In particular, Cartt explains exemplary doses of diazepam to be delivered to patients per dose via nasal administration:

> 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….

(Cartt at [0063]).

Cartt explains that the administration of doses of about 1 mg to about 20 mg of diazepam was found to be therapeutic. Cartt further states the following regarding the typical concentrations of diazepam in the nasal formulations:

> In some embodiments, the benzodiazepine or pharmaceutically acceptable salt thereof is present in a concentration of from about 0.05 mg/mL up to about 600 mg/mL.

Thus, Cartt states that the benzodiazepine is formulated in concentrations ranging from about 0.05 mg/mL to about 600 mg/mL.

4. USP

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville, 1995 (hereinafter "USP"), published in 1995 and constitutes prior art under §102(b).

USP provides the official monograph for vitamin E, stating:

> Vitamin E is a form of alpha tocopherol (C29H50O2). It includes the following d- or dl-alpha tocopherol (C29H50O2); d- or dl-alpha tocopheryl acetate (C31H52O3); d- or dl-alpha tocopheryl acid succinate (C33H54O5). It contains not less than 96.0 percent and not more than 102.00 percent of C29H50O2, C31H52O3, or C33H54O5, respectively.

(USP at 1631).

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USP explains that Vitamin E USP represents a form of alpha tocopherol that may include d- or dl-alpha tocopherol (C29H50O2); d- or dl-alpha tocopheryl acetate (C31H52O3); d- or dl-alpha tocopheryl acid succinate (C33H54O5).

F. Prior Art Reference Claim Charts.

The following table summarizes the references and corresponding claim chart exhibits incorporated by reference in these Preliminary Invalidity Contentions.

Exhibit	Prior Art References	Patent
1	Gwozdz in view of Meezan	’546 patent
2	Gwozdz in view of Meezan	’414 patent
3	Gwozdz in view of Meezan Gwozdz in view of Meezan further in view of Cartt Gwozdz in view of Meezan further in view of USP	’786 patent

G. The Asserted Claims are Invalid as Obvious

1. Obviousness

To the extent the Asserted Claims are not indefinite, Padagis contends that the Asserted Claims of the Asserted Patents are invalid as obvious in light of the Prior Art References, either alone or in combination with the knowledge of a POSA or each other. It would have been obvious to a POSA as of the priority date of each of the Asserted Claims of the Asserted Patents to combine the various cited Prior Art References so as to practice the Asserted Claims. Moreover, the Prior Art References render the Asserted Claims obvious because, to the extent a Prior Art Reference may not expressly teach or disclose a component of the system claimed or recited in the Asserted Claims, such “missing” component was nevertheless known in the art and adding the well-understood “missing” component would yield predictable results, so that the subject matter of the claim as a whole would have been obvious to a POSA at the time the invention was made. *See generally KSR,* 550 U.S. 398.

The disclosures and teachings that render the Asserted Claims obvious are identified in the

claim charts attached hereto as **Exhibits A–C** (collectively, the "Invalidity Charts"). Each Invalidity Chart provides an element-by-element disclosure of where specifically, in each Prior Art Reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the Invalidity Charts does not exclude other combinations. Padagis contends that it would have been obvious to a POSA to combine any of the Prior Art References so as to practice any of the Asserted Claims. The Prior Art References are analogous art as each reference is from the same field of endeavor, is reasonably pertinent to the particular problem with which the inventor is involved, or both. To the extent Plaintiff contends that an embodiment within a particular Prior Art Reference does not fully disclose all limitations of a claim, Padagis reserves the right to rely on other embodiments in that Prior Art Reference, or other information, to show obviousness.

2. Motivation to Combine

(a) All Asserted Claims

A motivation existed to combine the teachings of Gwozdz and Meezan. A motivation to combine references may be present in the nature of the problem to be solved. Here, the Asserted Patents admit and acknowledges the known problem in the art regarding the inability to administer benzodiazepine drugs (e.g., diazepam) due to the limited solubility of the drug compounds. The Asserted Patents state:

> 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.
>
> 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.
>
> 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

(e.g., ’414 patent at 1:47-2:8).

The Asserted Patents admit that, due to the limited solubility of benzodiazepine drugs, only certain types of dosage forms were possible, including oral, intravenous, and suppository dosage forms. However, each of these dosage forms suffered from considerable shortcomings: oral dosage forms take considerable time to reach therapeutic drug levels, and suffer from significant liver metabolism; intravenous dosage form administration is primarily limited to trained health care professionals, and maintaining sterility of the dosage form; and suppository dosage forms are inconvenient to administer, given the requirement for rectal administration.

Gwozdz provides this guidance, and would have been a lead reference in the development of benzodiazepine formulations with improved solubility. Gwozdz specifically states that “[p]harmaceutical 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." (Gwozdz at 7:29-34). In addition, Gwozdz states that the pharmaceutical solutions "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." (Gwozdz at 9:19-22). As such, Gwozdz was focused on formulations for nasal administration, which provided an improvement over the known issues with oral, intravenous, and suppository formulations for benzodiazepines, as noted previously. For at least these reasons, a POSA would have first looked to Gwozdz as the lead reference for strategies to improve the solubility of benzodiazepine drugs in an effort to develop new dosage forms, including nasally administered formulations.

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." (Gwozdz at 10:12-16). In view of this, a POSA would have also looked to additional references for guidance regarding additive compositions to improve the efficacy of the pharmaceutical solutions of Gwozdz. Meezan provides such a teaching, as it is directed to "therapeutic composition[s] 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." (Meezan at [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.,

penetration 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.

Finally, a reasonable expectation existed that the Gwozdz formulations could be successfully developed to improve the solubility of benzodiazepine drugs (including diazepam), and that the alkyl glycoside compounds of Meezan (including dodecyl beta-D-maltoside) could be successfully incorporated into the Gwozdz pharmaceutical solution. Obviousness requires only a reasonable expectation of success- absolute certainty is not required. *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success."). Gwozdz states that the pharmaceutical solutions described therein were shown to improve the solubility of diazepam specifically, stating "[a]s a non-limiting example, the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol[;] [h]owever, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level." (Gwozdz at 7:12-14). Based on this disclosure, a POSA would have at least a reasonable expectation that the Gwozdz formulations could successfully improve the solubility of benzodiazepine drug compounds, particularly diazepam.

Additionally, as noted, Gwozdz expressly teaches that additional pharmaceutically acceptable additives may be added to the pharmaceutical solutions described therein, including permeation enhancers. Meezan expressly teaches the use of compounds that enhance the absorption of drug compounds (i.e., permeation enhancers). Meezan also teaches that the formulations and compounds described therein can be utilized with a wide variety of drug compounds. (Meezan at [0004]). Accordingly, a POSA would have at least a reasonable

expectation that the alkyl glycoside compounds of Meezan (including dodecyl beta-D-maltoside) could be successfully incorporated into the pharmaceutical solutions of Gwozdz.

(b) Additional Motivations as to Claims 17 and 18 of the '546 Patent

A POSA was motivated to pursue the claimed solution containing about 10% w/v diazepam. A motivation to combine references may be present in the nature of the problem to be solved. As discussed, there as a known problem in the art related to benzodiazepine drug formulations (including tablets, intravenous injections, and suppositories), owing to the limited solubility of benzodiazepines (including diazepam). Consequently, a POSA was motivated to develop pharmaceutical dosage forms with increased benzodiazepine solubility that would allow for the development of new and improved dosage forms. Here, Gwozdz expressly states that diazepam concentrations "approaching the 10% level" can be achieved by utilizing the pharmaceutical solutions described therein. Based on this teaching, a POSA was motivated to experiment with and optimize the pharmaceutical solutions of Gwozdz to achieve a diazepam solubility/concentration of "about 10% (w/v)," and would have had at least a reasonable expectation that such a concentration could successfully be achieved.

(c) Additional Motivations as to Claims 20 and 21 of the '786 Patent

Based on Gwozdz's teaching that diazepam concentrations of 10% w/v (i.e., 100 mg/mL) can be achieved with the pharmaceutical solutions, in view of Cartt's teaching that a "therapeutic" dose of diazepam is typically 1-20 mg, a POSA was motivated to develop the pharmaceutical solution rendered obvious by Gwozdz and Meezan to deliver a volume of the solution that would provide an amount of 1-20 mg of diazepam to the patient per nasal spray administration. As such, Gwozdz and Meezan, in view of Cartt, render obvious the claimed requirement that "the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 5 to about 20 mg" (claim 20) and "the therapeutically

effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 1 mg to about 20 mg" (claim 21).

Further, a POSA was motivated to combine the teachings of Cartt with those of Gwozdz and Meezan to deliver diazepam to the patient in amounts of 1-20 mg. As noted, Cartt is directed to benzodiazepine nasal formulations. Given the similarity in teachings between Gwozdz, Meezan, and Cartt, a POSA would have been motivated to combine the teachings of the three references, and would have had at least a reasonable expectation that pharmaceutical solution could be developed to deliver diazepam doses of 1-20 mg.

(d) Additional Motivations as to Claims 26 and 27 of the '786 Patent

A POSA was motivated to utilize vitamin E USP in the pharmaceutical solution rendered obvious by Gwozdz and Meezan, as USP was an internationally recognized standard for pharmaceutical grade compounds and ingredients. As such, a POSA would have been motivated to utilize vitamin E USP in the pharmaceutical solution rendered obvious by the prior art, and would have had at least a reasonable expectation that the USP grade vitamin E could be successfully incorporated into the formulation.

(e) Reservations

These Preliminary Invalidity Contentions are not intended to provide an exhaustive or comprehensive list of all rationale(s) for why a POSA would be motivated to combine elements of the prior art references to render obvious the Asserted Claims. The fact that other rationale(s) or motivation(s) to combine are not specifically discussed should not be interpreted as an admission or concession that such other rationale(s) or motivation(s) does(do) not apply. This case is in its early stages, significant discovery remains, including expert discovery, which would likely include elaboration of these rationale(s) or motivation(s) or the addition of other rationale(s) or motivation(s). Padagis expressly reserves the right to rely on the knowledge of those skilled in the

art, the testimony of expert witnesses, or other prior art to show that it would have been obvious to include the allegedly missing limitation and to explain the motivation to combine the elements of the prior art references.

3. Secondary Considerations

Padagis contends that no secondary considerations weigh in favor of non-obviousness with respect to any of the Asserted Claims.

Padagis is presently unaware of any secondary considerations that are relevant to any of the Asserted Claims of any of the Asserted Patents. Secondary considerations do not form a part of the *prima facie* case of obviousness. Rather, a patentee may try to rebut a *prima facie* case of obviousness by coming forth with purported evidence of secondary considerations. Padagis therefore has no burden at this stage to address any secondary considerations, or to come forward with any evidence rebutting such considerations. To the contrary, it is Plaintiff's obligation and burden to produce evidence of so-called secondary considerations, if any, on which it intends to rely, Padagis expects that additional discovery directed to any secondary considerations Plaintiff may allege will take place in accordance with the case schedule, and that the evidence will rebut any alleged or claimed secondary considerations in full. As such, if and in the event Plaintiff cites to any alleged secondary considerations, Padagis reserves the right to supplement these contentions.

G. Invalidity under 35 U.S.C. § 112

35 U.S.C. § 112(b) requires a patent applicant to distinctly claim the invention with particularity and definiteness. "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc*., 134 S. Ct. 2120, 2124, 189 L. Ed. 2d 37 (2014). The Federal Circuit has

subsequently applied the *Nautilus* standard to find claims indefinite where a claim recites a limitation that can be determined by more than one method, one of which provides an infringing result, and one of which does not; and the patent claims, specification, and prosecution history fail to indicate which method should be used, and there is no art-recognized standard. *Dow Chem. Co. v. Nova Chems. Corp. (Canada)*, 803 F.3d 620 (Fed. Cir. 2015), request for reh'g en banc den., *Dow Chem. Co. v. Nova Chems. Corp. (Canada)*, No. 2014-1431, 2015 WL 9202304, at *1 (Fed. Cir. Dec. 17, 2015).

All of the Asserted Claims are invalid as indefinite as they fail to inform with reasonable certainty the extent to which they include water, if at all. All of the Asserted Claims recite a "pharmaceutical solution for nasal administration consisting of" a list of recited ingredients. The transition phrase "'consisting of'" is a term of patent convention meaning that the claimed invention contains only what is expressly set forth in the claim." *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016) (quoting *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331 (Fed. Cir. 2004)).

The Asserted Claims all recite a pharmaceutical solution "consisting of" (a) a benzodiazepine drug (or diazepam, specifically); (b) one or more natural or synthetic tocopherols or tocotrienols (in some claims, limited to a specific list); (c) one or more alcohols (or in some cases, specifically at least benzyl alcohol, or specifically ethanol and benzyl alcohol); and (d) an alkyl glycoside (or n-dodecyl beta-D-maltoside, specifically). Due to the "consisting of" transitional phrase, a pharmaceutical solution within the scope of the Asserted Claims may not contain any additional unrecited ingredients.

Additionally, the specification of the Asserted Patents explicitly discloses embodiments whereby water is a component of the carrier system, stating "In some embodiments, a carrier

system in such a composition includes water. In some embodiments, such a liquid carrier system contains water and one or more excipients." '546 Patent at 12:40-43; '414 Patent at 9:36-39. In view of this explicit acknowledgement in the specification that the solvent systems may contain water, the claim language stating that the pharmaceutical solution "consist[s] of" (a) a benzodiazepine drug (or diazepam, specifically); (b) one or more natural or synthetic tocopherols or tocotrienols (in some claims, limited to a specific list); (c) one or more alcohols (or in some cases, specifically at least benzyl alcohol, or specifically ethanol and benzyl alcohol); and (d) an alkyl glycoside (or n-dodecyl beta-D-maltoside, specifically), is understood to require that water is not present in the claimed solution.

However, the specification of the Asserted Patents also expressly acknowledges that various excipients, e.g., the alcohol component, may or may not include water. The specification of the Asserted Patents states "In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof…In some embodiments, the alcohol or glycol is free of water (dehydrated, USP). In some embodiments, the alcohol is ethanol (dehydrated, USP)." '546 Patent at 7:20-29; '414 at 4:35-44.

Consequently, the claims of the Asserted Patents are expressly drafted in a manner that does not allow for the inclusion of water, yet the specification indicates that one or more of the claimed excipients, for example the alcohol components, including ethanol and benzyl alcohol, may include water. In addition, to the extent Plaintiff contends the Asserted Claims encompass pharmaceutical solutions that include water, the Asserted Claims are indefinite as the inclusion of water is not reasonably certain. Moreover, to the extent Plaintiff contends the Asserted Claims

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encompass pharmaceutical solutions that include water, the Asserted Claims are indefinite because the amount of water is not reasonably certain.

For at least these reasons, a POSA does not have reasonable certainty as to whether the Asserted Claims allow for the inclusion of water, and, if so, what amount of water may be included, while still falling within the scope of the claims. Therefore, the Asserted Claims of the Asserted Patents are invalid as indefinite.

V. PRODUCTION OF PRIOR ART

Padagis has produced and/or is producing herewith prior art documents on which it intends to rely to prove the invalidity of the Asserted Claims. Padagis expressly reserves the right to rely on additional documents in furtherance of establishing the invalidity of the Asserted Claims, and to the extent not previously produced, will timely produce such documents to Plaintiff.

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CERTIFICATE OF SERVICE

I hereby certify that on December 20, 2024, I caused copies of the foregoing document to be served upon the following in the manner indicated:

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