

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AQUESTIVE THERAPEUTICS, INC.

Petitioner

v.

NEURELIS, INC.

Patent Owner

IPR2019-00451

U.S. Patent No. 9,763,876

DECLARATION OF DANIEL P. WERMELING, Pharm.D.

AQUESTIVE EXHIBIT 1150

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DECLARATION OF DANIEL P. WERMELING, Pharm.D.

I, Daniel P. Wermeling, do hereby make the following declaration:

1. I have been retained by Hoffmann & Baron, LLP counsel for Petitioner, Aquestive Therapeutics, Inc., to provide my expert opinion in connection with the Petition for *Inter Partes* Review of U.S. Patent No. 9,763,876 (“the ‘876 Patent”) in IPR2019-00451. My *Curriculum Vitae* is attached hereto as Appendix A.
2. My opinions in this expert declaration support Petitioner’s Reply to Patent Owner’s Response to the Petition (Paper No. 16), based on the Petition, that all the challenged claims of the ‘876 Patent are obvious in view of the combination of Gwozdz (Exhibit 1014) and Meezan’962 (Exhibit 1011) for claims 1-16 and 24-36 and the combination of Gwozdz, Meezan’962 and Cartt’784 (Exhibit 1015) for claims 17-23. A POSA would be motivated to combine these references based (at least) on the POSA’s general knowledge of routine pharmaceutical and formulation chemistry (including the well-known requirements related to nasal delivery).
3. I am being compensated at my ordinary and customary consulting rate for my work. My compensation is in no way contingent on the nature of my findings, the presentation of my findings in testimony, or the outcome of this or any other proceeding. I have no other interest in this proceeding.

I. BASIS FOR OPINION

4. In forming my opinion herein, I have relied on my own education, work experiences and knowledge, and on other bases such as textbooks, articles and other references as described herein. This declaration states my current opinions, which could change if additional information or analyses becomes available.

5. I have reviewed the Peppas Dec. (Exhibit 1041), and I agree with the ultimate conclusions reached by Dr. Peppas that (1) the combination of Gwozdz and Meezan'962 renders claims 1-16 and 24-36 obvious, and (2) the combination of Gwozdz, Meezan'962, and Cartt'784 renders claims 17-23, obvious.

6. I have reviewed the Declaration of Professor Sveinbjörn Gizurarson, Exhibit 2012 ("Gizurarson Dec.") and Patent Owner Response ("POR"), and I disagree with their conclusions overall and as described in detail below.

7. In forming my opinion herein, I have also relied on review of the following documents:

<u>EXHIBIT NO.</u>	<u>EXHIBIT DESCRIPTION</u>
Exhibit 1001	U.S. Patent No. 9,763,876, Administration Of Benzodiazepine Compositions, filed October 29, 2014 ('876 Patent)
Exhibit 1002	File History for '876 Patent, Ser. No. 14/527,613 ('876 FH)

- Exhibit 1008 Provisional Patent Application No. 61/040,558, filed March 28, 2008 ('558 Provisional)
- Exhibit 1011 Meezan et al., U.S. Patent Application Publication No. US 2006/0046962, *Absorption Enhancers for Drug Administration*, Serial No. 11/127,786, published March 2, 2006 (Meezan'962)
- Exhibit 1014 Gwozdz et al., WO 2009/120933, *Pharmaceutical Solutions And Method For Solubilizing Therapeutic Agents*, published October 1, 2009, International Filing Date March 27, 2009 (PCT/US2009/038518) (Gwozdz)
- Exhibit 1015 Cartt et al., U.S. Patent Application Publication No. US 2008/0279784, *Nasal Administration Of Benzodiazepines*, Serial No. 12/116,842, published November 13, 2008 (Cartt'784)
- Exhibit 1025 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)

- Exhibit 1028 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. Epub 2009 May 14 (Ivaturi)
- Exhibit 1031 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 (Rowe)
- Exhibit 1041 Declaration of Dr. Nicholas A. Peppas
- Exhibit 1042 PDR 54th Edition 2000, DIASTAT® (diazepam rectal gel); MIACALCIN® (Calcitonin Nasal Spray); VALIUM® (diazepam injection), Physicians’ Desk Reference.
- Exhibit 1043 Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. *Br J Clin Pharmacol.* 2002; 53: 501-507.
- Exhibit 1069 Florida Regional Common EMS Protocols Field Guide, Jones and Barlett Publishers, MA (2005).

- Exhibit 1070 Gizurarson, Patent Application Publication No. US
2008/0275030, Nov. 6, 2008.
- Exhibit 1072 Nayzilam Product Label and Instructions for Use
- Exhibit 1074 Hardman, et al, Editors, *Goodman & Gilman's, The
Pharmacological Basis of Therapeutics*, 10th Edition (2001).
- Exhibit 1076 Budavari, et al, Editors, *The Merck Index*, 12th Edition (1996).
- Exhibit 1077 Ritchel, W.A., et al., *Handbook of Basic Pharmacokinetics
Including Clinical Applications*, 6th Edition, 2004.
- Exhibit 1078 USP/NF 2003, *The Official Compendia of Standards, Ethanol*,
Copyright 2002.
- Exhibit 1080 Valium® Tablet Label, Roche, January 2008.
- Exhibit 1081 Drug Prices from Internet
- Exhibit 1082 Chien, Y.W., et al., “Nasal Systemic Drug Delivery”, Chapter
1, *Anatomy and Physiology of the Nose*, Drugs and the
Pharmaceutical Sciences, Vol. 39, Marcel Decker, 1989.
- Exhibit 1101 Lowenstein DH, Alldredge BK. *Status epilepticus*. N Eng J
Med 1998; 338: 970-976.
- Exhibit 1102 Lowenstein DH, Bleck T, Macdonald RL. *It's time to revise
the definition of status epilepticus*. Epilepsia 1999; 40: 120-
122.

- Exhibit 1103. Wang HC, Chang WN, Chang HW, et al. *Factors predictive of outcome in posttraumatic seizures*. J Trauma 2008; 64: 883-888.
- Exhibit 1104 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.
- Exhibit 1105 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.
- Exhibit 1106 Feen ES, Bershad EM, Suarez JJ. *Status Epilepticus*. South Med J 2008; 101: 400-406.
- Exhibit 1107 Pang T, Hirsch L. *Treatment of convulsive and nonconvulsive status epilepticus*. Cur Treat Options Neurol 2005; 7: 247-259.
- Exhibit 1108 Smith B. *Treatment of status epilepticus*. Neurol Clin 2001; 19: 347-369.
- Exhibit 1109 Ericksson K, Kalviainen R. *Pharmacologic management of convulsive status epilepticus in childhood*. Expert Rev Neurotherapeutics 2005; 5: 777-783.

- Exhibit 1110 Wolfe T, Macfarlane T. *Intranasal midazolam therapy for pediatric status epilepticus*. Am J Emerg Med 2006; 24: 343-346.
- Exhibit 1111 Meierkord H, Engelsen B, Gocke K, et al. *EFNS guideline on the management of status epilepticus*. Eur J Neurol 2006; 13: 445-450.
- Exhibit 1112 Prasad K, Krishnan P, Al-Roomi K, et al., *Anticonvulsant therapy for status epilepticus*. Br J Clin Pharmacol 2007; 63: 640-647.
- Exhibit 1113 Illum L. *Nasal Clearance in Health and Disease*. J Aerosol Med 2006; 19: 92-99.
- Exhibit 1114 Merkus P, Ebbens FA, Muller B, Fokkens WJ. *Influence of anatomy and head position on intranasal drug deposition*. Eur Arch Otorhinolaryngol 2006; 263: 827-832.
- Exhibit 1115 Illum L. *Transport of drugs from the nasal cavity to the central nervous system*. Eur J Pharm Sci 2000; 11: 1-18.
- Exhibit 1116 Illum L. *Is nose to brain transport of drugs a reality?*. JPP 2004; 56: 3-17.

- Exhibit 1117 Merkus F, van den Berg MP. *Can nasal drug delivery bypass the blood-brain barrier? Questioning the direct transport theory.* Drugs 2007; 8: 133-144.
- Exhibit 1118 Constantino HR, Illum L, Brandt G, et al. Intl J Pharmaceutics 2007; 337: 1-24.
- Exhibit 1119 Davis GA, Rudy AC, Archer SA, Wermeling DP, McNamara PJ. *Effect of fluticasone propionate nasal spray on bioavailability of hydromorphone hydrochloride in patients with allergic rhinitis.* Pharmacotherapy 2004; 24: 26-32.
- Exhibit 1120 Davis GA, Rudy AC, Archer SM, Wermeling DP, McNamara PJ. *Bioavailability and pharmacokinetics of intranasal hydromorphone in patients experiencing vasomotor rhinitis.* Clin Drug Invest 2004; 24: 1-7.
- Exhibit 1121 Holsti M, Sill B, Firth S, et al., *Prehospital intranasal midazolam for the treatment of pediatric seizures.* Ped Emerg Care 2007; 23: 148-153.
- Exhibit 1122 Rudy AC, Coda BA, Archer SM, Wermeling DP. *A multiple dose phase 1 study of intranasal hydromorphone hydrochloride in healthy volunteers.* Anesth Analg 2004; 99: 1379-1386.

- Exhibit 1125 Loftsson T, Gudmundsdottir H, Sigurjonsdottir JF, et al.
Cyclodextrin solubilization of benzodiazepines: formulation of midazolam nasal spray. Int J Pharm 2001; 212: 29-40.
- Exhibit 1127 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.
- Exhibit 1128 Dale O., Nilsen T., Loftsson T. *Intranasal midazolam: a comparison of two delivery devices in human volunteers.* J Pharmacy Pharmacol 2006; 58: 1311-1318.
- Exhibit 1129 Burstein AH, Modica R, Hatton M, et al. *Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration.* J Clin Pharmacol 1997; 37: 711-718.
- Exhibit 1130 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.
- Exhibit 1131 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.

- Exhibit 1133 Lau SWJ, Slattery JT. Intl J Pharmaceutics. *Absorption of diazepam and lorazepam following intranasal administration.* Int J Pharmaceutics 1989; 54: 171-174.
- Exhibit 1134 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.
- Exhibit 1135 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.
- Exhibit 1136 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.
- Exhibit 1137 Mittal P, Manohar R, Rawat A. *Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures.* Ind J Pediatrics 2006;73: 975-978.

- Exhibit 1138 Mahmoudian T, Zadeh M. *Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children*. Epilepsy and Behavior 2004; 5: 253-255.
- Exhibit 1139 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.
- Exhibit 1140 Bhattacharyya M, Kalra V, Gulati S. *Intranasal midazolam vs rectal diazepam in acute childhood seizures*. Pediatric Neurology 2006; 34: 355-359.
- Exhibit 1141 Wilson, M.T., S. Macleod, and M.E. O'Regan, *Nasal/buccal midazolam use in the community*. Arch Dis Child, 2004. 89(1): p. 50-1.
- Exhibit 1142 Harbord, M.G., et al., *Use of intranasal midazolam to treat acute seizures in paediatric community settings*. J Paediatr Child Health, 2004. 40(9-10): p. 556-8.
- Exhibit 1143 Jeannet, P.Y., et al., *Home and hospital treatment of acute seizures in children with nasal midazolam*. Eur J Paediatr Neurol, 1999. 3(2): p. 73-7.

- Exhibit 1144 Ahmad S, Ellis J, Kamwendo H, et al. *Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open label trial*. Lancet 2006; 367: 1591-1597.
- Exhibit 1145 Wolfe T, Bernstone T, Intranasal Drug Delivery: *An Alternative to Intravenous Administration in Selected Emergency Cases*, J Emerg Nurs. 2004 Apr;30(2):141-7.
- Exhibit 1146 FDA GUI FINAL, *Determining Whether to Submit an ANDA or a 505(b)(2) Application*, Published May 2019, <https://www.fda.gov/media/123567/download>
- Exhibit 1147 CDER 2019-09-19-Abbreviated Approval Products: 505(b)(2) or ANDA? <https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/abbreviated-approval-pathways-drug-product-505b2-or-anda-september-19-2019-issue>
- Exhibit 1148 FDA GUIDANCE FOR INDUSTRY (1999), *Applications Covered by Section 505(b)(2)*, <https://www.fda.gov/media/72419/download>
- Exhibit 1149 Transcript of the January 14, 2020 deposition of Dr. Gizararson,

- Exhibit 1151 Wermeling, D.P., *Intranasal delivery of antiepileptic medications for treatment of seizures*, Neurotherapeutics, April 2009, Volume 6, Issue 2, pp 352–358
- Exhibit 2006 SIGMA Chemical Company Catalog (1988)
- Exhibit 2012 Declaration of Dr. Sveinbjorn Gizurarson, Ph.D.
- Exhibit 2014 D. Wermeling, U.S. Patent No. 6,610,271, issued August 26, 2003.

<u>PAPER NO.</u>	<u>PAPER DESCRIPTION</u>
3	Petition
8	PTAB Decision to Institute the IPR

II. RELEVANT CONSIDERATIONS

8. I provide my opinions in this declaration as informed below.
9. I have been informed that to be entitled to an earlier priority date each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure, in this case Provisional Application Serial No. 61/040,558, Exhibit 1008 (“the ‘558 Provisional application”).

10. I have been informed that a claim is interpreted by giving its terms the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.

11. I have been informed that to benefit from a claim of priority to an originally filed disclosure, the originally filed disclosure must contain a written description of the invention as claimed in the later applications, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person of ordinary skill in the art to make and use the invention as claimed. I have been informed that to meet this requirement, the originally filed disclosure must reasonably convey to one of skill in the art that the inventor possessed the later-claimed subject matter at the time the parent application was filed. I have been further informed, a disclosure in a parent application (the originally filed disclosure) that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure itself must describe the claimed invention with all its limitations.

12. I have been informed that for a disclosure to be enabling it must teach those in the art enough that they can make and use the invention without “undue experimentation” and that in determining whether a disclosure is enabling I should consider: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the disclosure; (3) the presence or absence of working

examples in the disclosure; (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. I was informed that these are called the *Wands*' factors and that only those factors relevant to the claim scope need be considered.

13. I have been further informed that in order to determine if the later application (i.e., the '876 Patent, Ex. 1001) is to receive the benefit of an earlier filed application or patent (i.e., the '558 Provisional, Ex. 1008), the question is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application (i.e., the '876 Patent, Ex. 1001) as of the filing date of the earlier filed application or patent (i.e., the '558 Provisional, Ex. 1008). The disclosure as originally filed in the earlier applications or patent (i.e., '558 Provisional, Ex. 1008) must convey with reasonable clarity to those skilled in the art that the inventor was in possession of the invention. That is, one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims.

14. I have been informed that these requirements for written support, possession of the invention and enablement, are referred to as § 112(a) requirements. I have further been informed that if a patent's claims do not have § 112(a) support, it is unpatentable and invalid.

15. I have been informed that a claimed invention is unpatentable if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having ordinary skill in the art to which the subject matter pertains. I have also been informed that an obviousness analysis takes into account factual inquiries including the level of a person of ordinary skill in the art, the scope and content of the prior art, and the differences between the prior art and the claimed subject matter, as well as secondary considerations such as commercial success, long felt but unsolved needs, failure of others and unexpected results.

16. I have also been informed that objective evidence or “secondary considerations,” such as unexpected results, commercial success, long felt need, failure of others, copying by others, licensing, and skepticism of experts can be relevant to the issue of obviousness. However, where the differences between the claimed invention and the prior art are “minor,” objective evidence of non-obviousness may not be sufficiently compelling to support the patentability of a claim. I have also been informed that to be considered the secondary considerations must have a nexus to claims.

17. I have also been informed that in order for the results to be unexpected the claimed invention must exhibit some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected and

that to establish unexpected results over a claimed range, the patent owner must compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range.

18. I have been informed that there are several accepted rationales for combining references or modifying a reference to show obviousness of the claimed subject matter. Some of these rationales include the following: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; a predictable use of prior art elements according to their established functions; applying a known technique to a known device to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

19. I have been informed that “a person of ordinary skill in the art”, a POSA, is not a specific, real individual, but rather a hypothetical individual or team of individuals working closely together, who is presumed to have known the relevant art at the time of the invention. In defining the POSA, I have been informed to consider factors such as the educational level and years of experience not only of

the person or persons who have developed the invention that is the subject of the case, but also others working in the pertinent art at the time of the invention; the types of problems encountered in the art; the teachings of the prior art; patents and publications of other persons or companies; and the sophistication of the technology.

A. POSA

20. Patent Owner and Dr. Gizurarson take issue with Petitioner’s description of a POSA. See POR, Paper 16, p. 15-17; and Gizurarson Dec. ¶¶ 25-33, Exhibit 2012.

21. Petitioner’s definition (which was objected to by Patent Owner), see Petition, Paper 3, p. 4, reads as follows:

“As of the earliest priority date that the Challenged Claims of ‘876 Patent are entitled to, a person of ordinary skill in the art (“POSA”) would have been a medicinal chemist, pharmaceutical chemist, chemist, or biologist involved in the research and development of pharmaceutical formulations and/or delivery. The POSA would have at least a bachelor’s degree in chemical, biological, or pharmaceutical sciences or a medical degree, and several years of experience in the field of transmucosal (including intranasal, rectal, vaginal, ocular, lacrimal, nasolacrimal, buccal, sublingual, urethral, inhalation, and auricular) pharmaceutical formulation development and/or delivery, the amount of post-graduate experience depending upon the level of

formal education. The individual would also have some experience in design and testing of formulations for mucosal delivery (and particularly in intranasal formulations) of systemic-acting drugs.”

22. It is my opinion that at least the following of Dr. Gizurarson’s statements in his declaration (Exhibit 2012) regarding the definition of a POSA must be corrected:

- (a) in response to Gizurarson Dec. ¶ 31, it is necessary to add “transmembrane” to “intranasal” because all the other routes listed in (b) below are transmembrane;
- (b) in response to Gizurarson Dec. ¶ 32, I agree that experience formulating “rectal, vaginal, ocular, lacrimal, nasolacrimal, buccal, sublingual, urethral, inhalation, and auricular” formulations can be very “informative”. In fact, such experience can be very useful to formulating intranasal products, and further the use of rectal formulations of diazepam (a commercially available product) for intranasal administration would give POSA clues and direction as to what could and should work in intranasal formulations.

1. Ethanol Versus Dehydrated Ethanol

23. I have been asked to consider what a POSA would understand the terms “ethanol” and “dehydrated ethanol” to mean. A POSA would understand that the ordinary meaning of the terms “ethanol” and “dehydrated ethanol” would be the meanings given in the U.S. Pharmacopeia (“USP”). See Ex. 1078, pp. 0004-0005.

24. Thus, a POSA would understand that ethanol “contains not less than 92.3% and not more than 93.8%, by weight, corresponding to not less than 94.9% and not more than 96.0%, by volume, at 15.56°, of C₂H₅OH.” *Id.* A POSA would understand the remaining 4-5% (by volume) to be mostly – if not all – water.

25. Thus, a POSA would understand that dehydrated ethanol “contains not less than 99.2 percent, by weight, corresponding to not less than 99.5 percent, by volume, at 15.56°, of C₂H₅OH.” *Id.*, p. 0005. A POSA would understand the remaining percent (up to 0.5% by volume) to be mostly – if not all – water.

26. Based on my reading of the ‘876 Patent, the inventors understood the difference between “ethanol” and “dehydrated ethanol.” “In some embodiments, the alcohol or glycol is free of water (dehydrated, USP). In some embodiments, the alcohol is ethanol (dehydrated, USP).” See ‘876 Patent, Ex. 1001, 7:40-42, p. 0013.

27. Moreover, the patent also refers to different embodiments having either ethanol or dehydrated ethanol. See, for example, those terms used at the following locations in the ‘876 Patent: **ethanol** (2:59; 2:62; 2:63; 3:11; 3:17; 3:21; 3:24; 3:61;

3:64; 3:65; 4:13; 4:20; 4:23; 4:27; 6:63; 7:34; 10:31; 11:21; 11:22; 33:61; 38:48; 38:56; 46:65; 47:23; 47:39; 47:47; 47:66; 62:26-27; 62:29; 62:32; Claim 1 [63:33]; Claim 8 [63:60]; Claim 13 [64:9]; Claim 14 [64:13]; Claim 15 [64:17]; Claim 27 [64:57]; Claim 29 [64:64]; Claim 30 [65:2]; Claim 31 [65:6]; Claim 32 [65:11]; and Claim 33 [65:16]); **dehydrated ethanol** (7:42; 10:34; 38:49; 39:14; 47:61; 60:17; Claim 28 [64:62]; **dehydrated alcohol, USP** (Fig. 4).

28. Therefore, a POSA would understand that the ordinary meaning of “ethanol” in the claims includes several percent of water.

29. Therefore, a POSA would understand that the ordinary meaning of “dehydrated ethanol” in the claims can include some water.

30. Patent Owner makes many arguments that the ‘876 Patent claims do not allow for any water at all. See, for example, POR, Paper 16, pp. 13, 37 and 38; Gizurarson Dec. ¶¶ 41, 98 (fn.15). However, as discussed above, the ‘876 Patent claims not only do allow for a certain amount of water, the “ethanol” claims require it to be present. Patent Owner’s choice of the term “ethanol” in its claims, requires, by USP definition, that the “ethanol” contains several percent of water dissolved/mixed with the actual ethanol molecule. Again, Patent Owner’s recitation of “ethanol” in their claims (instead of specifying “dehydrated ethanol”, as they did in other places) means that there is some water present. It was Patent Owner’s choice of words, and I suspect that Patent Owner knew what they were

claiming by using the term “ethanol” instead of “dehydrated ethanol” (which was used elsewhere in the patent, proving they were aware of the term “dehydrated ethanol”).

III. QUALIFICATIONS AND BACKGROUND

31. I am currently an Emeritus Professor at the University of Kentucky, College of Pharmacy, where I served for 30 years.

32. I obtained Bachelor and Doctor Pharmacy degrees from the University of Kentucky in 1982 and 1983. The College is, and has been, one of the top 5-10 Colleges of Pharmacy in the country if not the world. I then completed a 2-year clinical pharmacy residency at the Albert B Chandler Medical Center at the University of Kentucky. Subsequently I completed a 2-year drug development fellowship in the Drug Product Evaluation Unit at the University of Kentucky College of Pharmacy. Three years after completing the fellowship I was recruited to be the second director of the program.

33. In 1990 I was recruited back to the University of Kentucky College of Pharmacy as an assistant professor, to direct the Drug Product Evaluation Unit and the Hospital Investigational Drug Service. I was promoted to Associate Professor

in 1994 and to tenured Associate Professor in 1998. I was promoted to full professor in 2010.

34. Operating a human clinical pharmacology and clinical trials program. I have been the principal or co-investigator for over 100 clinical studies involving medications and/or drug delivery systems. The research involved studies in healthy volunteers and patients. As it relates to the matter at hand, I have conducted a number of studies of antiepileptic medications and delivery systems, including nasal delivery, in healthy volunteers and in patients who suffered from epileptic seizures. I have also run investigational studies involving intravenous administration to patients having seizures and oral administration to patients having epilepsy.

35. My role as a clinical pharmacist. One of my roles at the University of Kentucky was to act in the capacity of a clinical pharmacist at various times. University of Kentucky Hospital pharmacists administer medications to patients as part of patient care. In this regard, I administered to seizing patients, under physicians' orders, anti-epileptic medications for loading and maintenance dosing. I also designed a mobile pharmacy program to prescribe and dispense both naloxone injection products administered intranasally with a mucosal atomization device and FDA-approved naloxone nasal spray products, throughout the

Commonwealth of Kentucky, to individuals and families where there was a high risk of opioid overdose.

36. Organizing and operating an Investigational Drug Service. University of Kentucky Hospital Department of Pharmacy had one of the first academic medical centers that provided: i) centralized health system management tools for protocol implementation, ii) drug storage, ii) drug preparation and formulation, and iii) dispensing and providing hospital staff with the information for proper administration and monitoring of all medications, including antiepileptic medications, formulations, and related delivery systems.

37. Educating pharmacy, medicine, nursing, physician assistant and other students regarding medications, delivery systems and certain aspects of patient care. Similarly, I trained post-graduate students who were residents in pharmacy or medicine or graduate students in the College of Pharmacy. I taught Drug Development and FDA Regulation as a graduate level course for all clinical pharmacology Ph.D. students and others who had interest. I taught pain management and therapeutics, opioid overdose prevention and treatment, and many other topics to College of Pharmacy and College of Medicine students.

38. Acting as a serial entrepreneur through start-up companies intending to commercialize University intellectual property. I started Intranasal Technology, which was a company that traversed the University incubation system and

progressed to a separate off campus facility (i.e., the University Coldstream Research Park campus). As the COO, I participated in the creation of a 10,000 square foot custom sterile manufacturing facility for the production of sterile unit dose nasal sprays for our products and similar to the formulations and products in the '876 Patent. I also founded a second intranasal company, AntiOp, which commercialized naloxone nasal spray (NALSCUE™) for the treatment of opioid overdose, another medical emergency that requires immediate treatment. Prior to commercialization of naloxone nasal spray, EMS services in large cities used naloxone injection in conjunction with a mucosal atomization device to intranasally administer naloxone injection formulations. In response to our national opioid overdose crisis, I began a NIH grant application series and FDA IND submissions to develop a nasal spray for naloxone in accordance with typical nasal spray designs. AntiOp received over \$7M in funding and other development compensation and then licensed the NALSCUE™ product to Indivior PLC, a large pharmaceutical company.

39. Serving as a consultant to pharmaceutical companies, from start-up stage, through large public and private commercial companies. My services range from being the Pharmacist in Charge, to scientific consulting, to opining in (and being an expert for) medical malpractice suits and patent litigation suits. I have served on industry expert advisory panels. I am an approved expert on The National

Institutes of Health's Special Emphasis Panels as a grant reviewer. These panels cross over all medical disciplines and frequently involve not only new medications, but novel delivery systems, which I evaluate for competitive funding.

40. Since 1996, I have continuously been engaged in – and focused on – the science, development and commercialization of nasal sprays. Most of the product design intentions and resultant formulations were for acute medical conditions such as severe pain (hydromorphone), migraine headache (butorphanol), opioid overdose (naloxone), extinguish craving for alcohol (naltrexone and ondansetron), acute psychosis and agitation (haloperidol and lorazepam), and especially epileptic seizures using water-insoluble and water-soluble benzodiazepines. All of these products went through formulation development, had regulatory approvals to initiate human studies, and had clinical studies performed. Naloxone nasal spray was commercialized as NALSCUE™.

IV. GROUNDS FOR INVALIDATING THE '876 PATENT CLAIMS

41. I have been informed that Petitioner has argued that all the claims of the '876 Patent are invalid as obvious based on the prior art set forth in the following grounds.

Ground	References	Basis	Claims Challenged
1	Gwozdz (Exhibit 1014) and Meezan'962 (Exhibit 1011)	§103(a) Obviousness	1-16, 24-36
2	Gwozdz (Exhibit 1014), Meezan'962 (Exhibit 1011), and Cartt'784 (Exhibit 1015)	§103(a) Obviousness	17-23

42. As discussed below, it is my opinion the differences between the invention and the references cited in the grounds are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having ordinary skill in the art to which the subject matter pertains. A POSA would have been motivated to combine Gwozdz, Meezan'962, and Cartt'784 because, *inter alia*, they all relate to optimizing the intranasal administration of drugs.

43. In particular, and as discussed below, it is my opinion that all the claims of U.S. Patent No. 9,763,876 would have been obvious to a POSA in view of Gwozdz and Meezan'962 for claims 1-16 & 24-36 and in view of Gwozdz, Meezan'962 and Cartt'784 for claims 17-23.

44. Moreover, these references could be readily varied by a POSA in predictable ways, without undue experimentation and with a reasonable expectation of success to obtain the claimed intranasal solutions.

45. Finally, I disagree that the “secondary considerations” of patentability, including unexpected results, failure of others and a long-felt but unmet need apply to the ‘876 Patent claims. Commercial success is not delimited by the alleged solubility question posed by Patent Owner. In my personal experience, the need for intellectual property protection was the most significant limiting factor to attract adequate capital for development to have an FDA approved intranasal product for administering benzodiazepines and in particular - diazepam. In my opinion, commercial success was also limited by the FDA’s relative inexperience with such products in their regulatory and clinical research design experience. Moreover, based on the small market size and the availability of cheaper off-label intranasal benzodiazepines sprays employed in the practice of medicine, including for diazepam, the question of whether sufficient returns could be engendered deterred the required investment to get the products to market. See discussion below.

V. THE HISTORY OF INTRANASAL BENZODIAZEPINE DELIVERY

46. I disagree generally with the opinions of Dr. Gizurarson regarding the history of benzodiazepines administered intranasally. See Gizurarson Dec. ¶¶ 44-67, Exhibit 2012. The declaration ignores the literature and mischaracterizes, in a very narrow manner, what the actual history is. There is a rich history in the medical and pharmaceutical literature that is missing from the report. This section, which recapitulates portions of an article of mine, provides the appropriate context and references for what was known about nasal delivery of benzodiazepines such as diazepam and others prior to 2009. See Exhibit 1151 for the full article.

A. Summary

47. 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. Overall speed of delivery (including i.v. setup, administration of the drug and time to therapeutic effect), particularly outside of the hospital, is enhanced when nasal routes of delivery, on or off label, are employed in place of an intravenous or an intramuscular injection.

48. Intranasal transmucosal delivery of benzodiazepines is useful in reducing time to drug administration and cessation of seizures in the pre-hospital setting, when actively seizing patients arrive in the emergency room, and at home where caregivers treat their dependents. This section summarizes factors to consider when choosing a benzodiazepine for intranasal administration, including formulation and device considerations, pharmacology and PK/PD profiles. A review of the most relevant clinical studies in epilepsy patients will provide context for the relative success of this technique with a number of benzodiazepines and relatively less sophisticated nasal preparations.

B. Introduction

49. Patients with a life-threatening or unstable condition presenting to pre-hospital, emergency service field personnel or hospital emergency facilities will have an intravenous (IV) line established, if possible, for rapid administration of medications. See also EMS, Ex. 1069, p. 0030. Other routes of administration are

employed in the field, as clinically indicated, including intramuscular injection and transmucosal approaches such as rectal, nasal, buccal and endotracheal administration. Organized health care has developed standards of care, and assessment and treatment protocols, for a variety of conditions to stabilize the patient as rapidly as possible. The development of clinical treatment protocols for Emergency Medical Services is frequently supervised by a state emergency medical board and implemented by a local municipal medical director. Clearly, patients experiencing epileptic seizures have a medical emergency and require prompt medical care. See Exhibits 1101-1104. Several consensus statements have been published describing pharmacologic treatment protocols for patients presenting with seizures or in status epilepticus. The guidelines recognize the need for prompt treatment and recommend various transmucosal routes of benzodiazepine delivery when IV access has not yet been established. See Exhibit 1105-1109. The marketing of diazepam rectal gel recognizes the need for non-injection based delivery – however, the aesthetics of rectal delivery are not popular with patients and caregivers.

50. Intranasal administration of antiepileptic medications, in particular benzodiazepines, has been studied with various preparations. For example, intranasal midazolam has been extensively studied in children and adults for sedation in preparation for procedures, in delivery of anesthesia and in epilepsy

patients and is recommended in some consensus guidelines as an alternative drug delivery technique for prompt seizure treatment. See Exhibits 1110-1112.

51. An understanding of nasal anatomy and physiology is required to appreciate the operating limitations of intranasal drug administration. Ad-hoc preparations (e.g., as by EMS) and products for registration must consider designs that integrate the medication and its chemistry, the formulation and the administration device to work successfully. Early stage studies in healthy volunteers are important steps in determining if appropriate pharmacokinetic and pharmacodynamic properties and safety profiles will lend themselves to treating seizures. Clinical experience in treating epileptic patients with various preparations demonstrates that intranasal drug delivery is a rapid-acting and effective drug delivery alternative.

C. Nasal Anatomy As Related to Intranasal Drug Delivery

52. Intranasal sprays of medication intended for systemic drug absorption are generally designed to target the turbinates on the medial wall of the nasal cavity (see Figure 1 below).

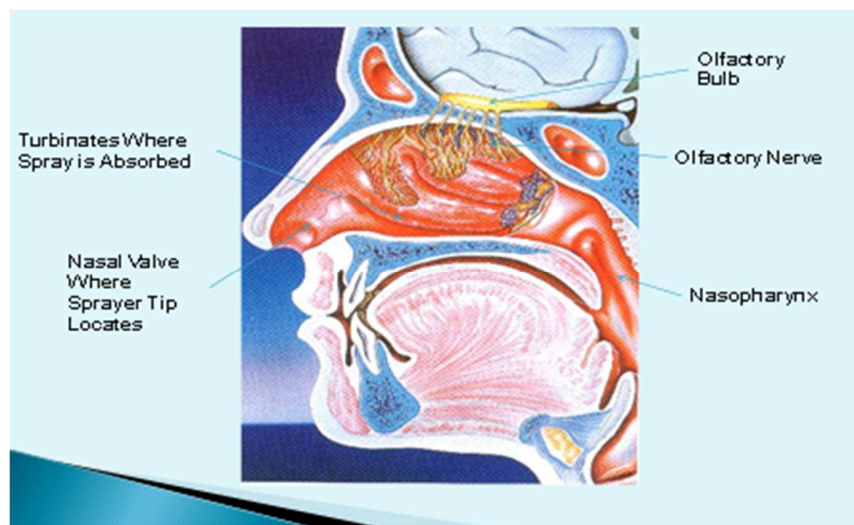


Figure 1. Anatomy of the Nasal Cavity and Relation to the Brain

Wermeling, Ex. 1151, p. 0002.

53. The turbinates serve as a baffle in which inspired air is humidified and filtered. This region of the nasal cavity is covered with a thin mucus layer, a monolayer ciliated epithelium, with an abundant underlying blood supply. See Exhibit 1113. These conditions are ideal to permit passive diffusion (transcellular) of medications with certain chemical characteristics across cell membranes and into the bloodstream. Some medications also transit to the blood stream by passing through the tight-cell junctions between cells (paracellular).

54. To reach the turbinates the nasal spray device must be inserted fully into the nasal vestibule with the atomizer tip placed at the nasal valve, and then aimed laterally toward the turbinates. See Exhibit 1114. Activation of the device ejects

the liquid as an atomized spray or plume. The bulk of the spray impacts the anterior and inferior portions of the nasal cavity as a simple ballistic missile. The smallest particles or droplets, less than 10 microns in size, may be carried by air currents more superiorly in the nasal cavity and impact on the superior turbinate and possibly reach the olfactory region and nerve. See Exhibits 1115-1116. There is substantial evidence in animals, and some evidence in humans, that the olfactory nerve can absorb or actively transport medications to the central nervous system via the olfactory bulb (“nose to brain theory”). Differences in animal and human nasal apparatus anatomy, and certain characteristics of the medication, seem to play roles as to whether medication is transported to the brain via this mechanism and if a pharmacologic effect is observed. See Exhibit 1117.

55. Under ideal conditions, most medication is absorbed from the nasal cavity and into the bloodstream within 15-20 minutes, thus generally avoiding the gut first-pass metabolism. See Exhibit 1118. Medication remaining in the nasal cavity beyond this time is subject to elimination via various enzyme systems present within the nasal mucus and by swallowing. A second absorption phase can be observed with nasally administered medications having incomplete nasal absorption that are not subject to high first pass gut metabolism. Diazepam is 100% bioavailable when swallowed. Ritschel, p. 376, Ex. 1077, 0006; Goodman &

Gillman, Ex. 1074, p. 0003; Valium® 2008 product label (>90%), Ex. 1080, p. 0001.

56. Nasal physiologic changes during pathologic conditions, such as polyposis and allergic and vasomotor rhinitis, could theoretically alter the biopharmaceutics of intranasal medications intended for systemic drug administration. See Exhibit 1113. Physical obstruction of the nasal passage(s) due to prior trauma and subsequent deflection of the passageways is another possibility. Lastly, increases in mucus production and changes in mucociliary clearance rates could affect bioavailability.

57. Pharmaceutical regulatory agencies have required studies of the effect of rhinitis on nasal drug delivery biopharmaceutics. It has been demonstrated that there is a lack of effect of nasal mucosal inflammation on the absorption of hydromorphone, butorphanol, buserelin and triamcinolone acetonide – an exception was reported for desmopressin. See Exhibits 1113, 1119, 1120. Inconsistent results have been reported on the biopharmaceutical disposition of these medications when pretreatment with oral or topical decongestants was administered. Small but statistically measureable changes in rate or extent of absorption have been reported when decongestants were co-administered. See Exhibit 1113.

58. Increased nasal mucus production is commonly observed with actively seizing patients and could be clinically relevant to intranasal drug administration for treatment of seizures. Holsti (Exhibit 1121) recognized this consideration in their pre-hospital treatment protocol that called for suction of mucus from the nasal cavity prior to administration of intranasal administration of midazolam injection in the field. Pre-treatment nasal cavity suctioning was likely contributory to the success observed in rapidly aborting seizure activity after intranasal midazolam administration.

VI. COMMERCIAL SUCCESS AND LONG-FELT NEED IN THE DESIGN OF NASAL PRODUCTS FOR SYSTEMIC DRUG ADMINISTRATION INCLUDES TECHNICAL CONSIDERATIONS AS WELL AS MARKETING CONSIDERATIONS

A. Exclusion of Market Considerations

59. To begin, I disagree with Dr. Gizurarson's discussion of long-felt need insofar as it excludes any consideration of market forces, including: size of the market, cost of product development, cost of clinical trials, costs associated with other regulatory requirements, intellectual property protection considerations, costs to produce and sell at wholesale and retails levels and market acceptance of costs. See Gizurarson Dep., Ex. 1149, 28:2-31:4. As discussed below, marketing considerations are very important in determining whether a product will be

commercialized; commercialization appears to be Dr. Gizurarson's sole test for determining whether a product finally solves a "long-felt need." Dr. Gizurarson disregards the fact that there were many different solutions suitable for administering benzodiazepines intranasally. As discussed herein, these were disclosed in the literature and used in the field prior to 2009.

B. Patent Owner's Expert Testified That he was Unaware of the Composition of Patent Owner's Intranasal Diazepam Spray, Valtoco, and He Could Not Answer Whether Valtoco Satisfied any Long-Felt Need

60. I also note that Dr. Gizurarson recognized the necessity for establishing a nexus between the '876 Patent claims and Patent Owner's Valtoco product (which Dr. Gizurarson argues fulfills the long-felt need), unfortunately he did not do so.

61. First, Dr. Gizurarson sets forth his understanding of the necessity for providing evidence of the nexus.

"I understand from counsel that the proponent of that evidence must establish a 'nexus' or a sufficient connection or tie between that evidence and the merits of the claimed invention, which I understand specifically incorporates any novel element(s) of the claimed invention. I also understand from counsel it is the patentee that has the burden of proving that a nexus exists."

Gizurarson Dec., Ex. 2012, ¶ 21.

62. Second, Dr. Gizurarson states that the “eventual approval of Neurelis’ NDA for NRL-1 (Valtoco®),...will fill a long-felt and unmet need for an alternative to rectal and intravenous diazepam products...” Gizurarson Dec., Ex. 2012, ¶¶ 36, 116.

63. However, Dr. Gizurarson had no evidence that Patent Owner’s Valtoco product fell within the scope of the ‘876 Patent claims, simply because Dr. Gizurarson testified that he did not know the formulation of Valtoco.

“Q Okay. What do you know about Valtoco?

A As far as I know, that is what Neurelis is going -- that is the name Neurelis will use on their product.

Q Okay. What do you know about the product that goes by the name of Valtoco?

MS. MORGAN: Objection. Form.

THE WITNESS: **I only know what is described in the patent that we are discussing.**

BY MR. CHAKANSKY:

Q Do you know the formulation for Valtoco?

MS. MORGAN: Same objection.

THE WITNESS: I know what is described in the patent. And, if they have -- I expect that they are using that formulation within a certain range, I expect.

BY MR. CHAKANSKY:

Q **Do you have any independent knowledge of the formulation of Valtoco?**

A **No. Nothing except what is described in this document.**

Q How do you know that Valtoco is described in what we've called this patent, Exhibit 1001? And it's given the designation **U.S. Patent No. 9,763,876.**

MS. MORGAN: Objection. Form.

BY MR. CHAKANSKY:

Q Is this the patent you were talking about?

A This is the patent I was talking about, yes.

Q Okay. I'll ask the question again. How do you know that Valtoco is described in this patent, Exhibit 1001?

MS. MORGAN: Objection. Form.

THE WITNESS: I have not looked at the application for this trade name, **so I cannot say 100 percent that it -- that is the -- what the formulation is."**

Gizurarson Dep., Ex. 1149, 19:6-20:15 (**emphasis added**).

64. Moreover, in contrast to his Declaration at ¶¶ 36, 67, 111, and 116, Dr.

Gizurarson testified at his deposition that he didn't know if Valtoco satisfied any long-felt need:

“Q So, in your opinion, does Valtoco satisfy a long-felt need?

A Here I would like to say that I have not seen what Valtoco is -- the description of Valtoco, so I cannot say what that drug is supposed to do.”

Gizurarson Dep., Ex. 1149, 21:16-20.

C. Commercial Success Factors – Formulation and Commercial Considerations

65. Furthermore, I disagree with Dr. Gizurarson that solubility is “**the**” most significant factor in determining whether a nasal benzodiazepine formulation could be commercially successful. See, e.g., Gizurarson Dec. ¶¶ 47-50, Exhibit 2012. Rather, it is “**a**” factor among other equally important factors that help determine formulation and commercial success. Factors leading to formulation and commercial success are discussed throughout this document.¹

¹ I note that Patent Owner has alleged that there are challenges to formulating an intranasal solution. “These included at least: (1) limited delivery volume because of the small volume of the nasal cavity – requiring an effective dose 5-10 times more concentrated than with intravenous administration (EX2012, ¶56); (2) mucosal and ciliary clearance mechanisms – limiting residence time of a solution placed in the nasal cavity (*id.*, ¶¶57-59); and (3) nasal cell anatomy – known to

66. I disagree with Dr. Gizurarson that the absence of an approved commercial intranasal benzodiazepine products establishes any “secondary considerations” of patentability. See Gizurarson Dec., Ex. 2012, ¶¶ 110-113. Failure to produce a commercial product is not determined solely by the solubility question posed by Dr. Gizurarson. As I stated above, in my personal experience, the need for intellectual property protection was the most significant limiting factor to attract adequate capital for development. Producing an FDA approved intranasal product was also limited by FDA’s relative inexperience with such products and their regulatory and clinical research design requirements. Lastly, there was some question about market size and whether sufficient returns could be engendered given a modest population that was described to FDA to garner an Orphan Drug

physically block foreign agents from entering through the cell wall (*id.*, ¶60).”

POR, Paper 16, p. 7. However, it is my understanding that Patent Owner bases its “unexpected results” claim on the bioavailability of its diazepam solution. The factors recited in Patent Owner’s quote would not have an effect on the bioavailability of diazepam because (as discussed throughout this declaration) the absorption of the diazepam solution is nasal-oral (“nas-oral”) – which is about 100%.

Designation request (that had been granted for Diastat™). A much larger population would have required off label use beyond cluster seizures.

67. An additional economic question is whether there is a willingness to pay for these new products. Injectable diazepam given IM (Valium™ and others) costs \$ 27.02 at Walgreens whereas Diastat rectal gel charge is \$ 317.69. See Drug Price List, Ex. 1081, pp. 0001, 0003. The UCB list price for midazolam nasal spray (Nayzilam™) is \$ 550. See Drug Price List, Ex. 1081, p. 0005 (<https://ucb-usa.com/Responsibility/Affordability/Nayzilam-Pricing-Info>). The cost of a MAD Nasal kit manufactured by Wolfe Tory Medical (currently a Subsidiary of Teleflex) was \$2.45 in 2004. See Wolfe, Exhibit 1145, p. 0002. The MAD Nasal kit was also used with Diazepam IV formulations at least as far back as 2005. See EMS, Exhibit 1069, p. 0030. The University of Kentucky Pharmacy compounds midazolam injection into nasal spray kits for under \$50.

1. Product Design Considerations

68. As further discussed in Wermeling, Ex. 1151, many intranasal delivery products are designed to serve certain purposes or unmet medical needs. Clearly, a nasal spray can remove the needle from drug administration, as is the case with the conversion of the protein calcitonin from a daily injection to a nasal spray. Furthermore, beyond just removing the needle from delivery, intranasal products

are designed for rapid action, such as those products designed to treat migraine headache (sumatriptan, butorphanol, zolmitriptan, dihydroergotamine) or pain in general (fentanyl, hydromorphone). Exhibit 1118 and 1122. In addition to these medications, a number of others, like midazolam and sufentanil injection, were administered successfully to patients as nasal drops or nasal sprays, off label and using improvised or suitable devices. See Wolfe, Ex. 1145.

69. What makes each of the aforementioned nasal sprays successful is that their approach satisfied several fundamentals necessary for intranasal delivery (see Table 1 below). See Exhibit 1118.

• Potent medication, less than 20 mg per dose • Molecular weight < 1000 Daltons • Excellent water solubility • <u>pKa</u> and pH control of aqueous solutions • Osmolality – isotonic to slightly hypertonic • Stability in processing and storage • Compatibility with sprayer components • Use of special excipients to manage ○ Solubility ○ Stability ○ Permeation
--

Table 1 - Chemistry and formulation issues affecting intranasal medication

bioavailability and tolerability. See Wermeling, Ex. 1151, p. 0003

70. First, there must be selection of drug candidates based on their pharmacologic and therapeutic properties. In the case of benzodiazepines, there are at least four reasonable alternatives to consider: diazepam, lorazepam, clonazepam and midazolam.

71. Physical-chemical properties of the candidates must also be considered. Solubility is important for formulation considerations. Log P, derived from the octanol/water partition coefficient, is a surrogate for lipophilicity and measures the potential for compounds to diffuse across biologic membranes. Benzodiazepines have sufficient lipophilic character to readily cross biologic membranes.

72. Benzodiazepines satisfy the potency requirement in that typical doses are all less than 20 mg. The dose must have sufficient solubility to be administered in approximately 100 μ L to 200 μ L (1 spray per naris (nostril) of solution; with the understanding that the total dose may be delivered in smaller doses delivered to each nasal cavity, etc. The nasal cavity can retain 100 to 150 μ L without causing immediate run-off out the front of the nose or down the naso-pharynx. Water is generally the preferred solvent, but many medications, including the benzodiazepines, do not have sufficient water solubility to formulate a nasal product and, therefore, a POSA would look towards non-aqueous solvents. Moreover, a POSA would also consider additional solubilization strategies,

including the use of particular organic co-solvents, stabilizers, preservatives and surface-active agents.

73. Design of the formulation must account for other factors as well. It is useful to design the formulation to be isotonic to slightly hypertonic to optimize absorption and tolerability. Viscosity enhancing agents such as methylcellulose can promote retention in the nasal cavity by slowing the ciliary movement of mucus. Surfactants or polymers can be employed to enhance transmembrane permeation. Lastly, the drug and formulation have to be stable in the device during processing, i.e., sterilization and storage, and thus may require stabilizers.

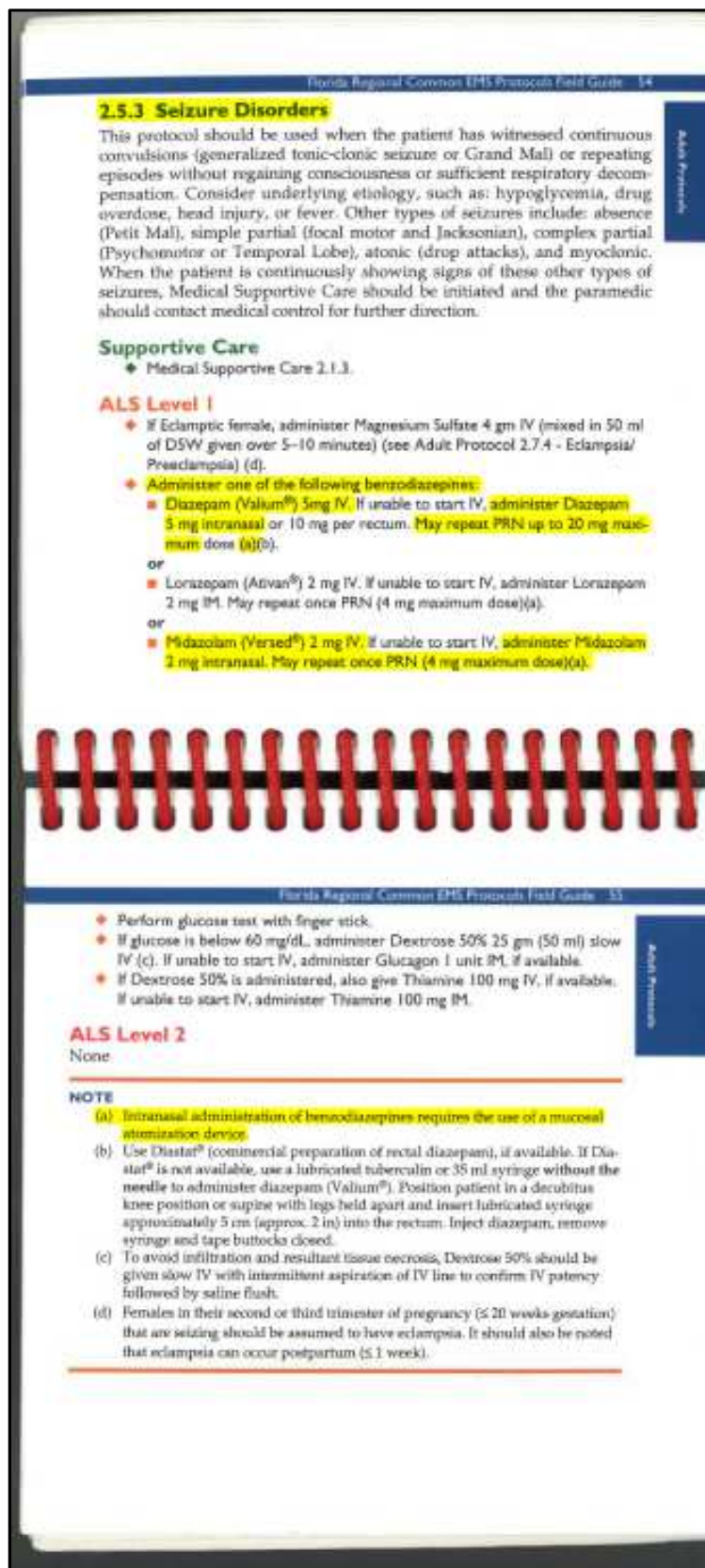
74. The choice of delivery device for the medication is another critical consideration. The following figure depicts a number of different nasal spray devices that I am familiar with that were available prior to 2008.



See Wermeling, Ex. 1151, p. 0004.

75. Squeeze bottles have been available but have no metering device appropriate to administer potent systemic medications such as benzodiazepines. Multi-dose bottles have been available for chronic drug administration – however, this is not a likely consideration with regard to seizure emergencies. A standard syringe with Luer fitting to accept a mucosal nasal atomizer (Mucosal Atomization Device™; Teleflex) has been used to draw up and administer injection-based drug solutions into the nasal cavity for opiate overdoses, acute pain and to deliver midazolam, lorazepam, and (significantly) diazepam injections to the nasal cavity of a seizing

patient. *See, e.g.*, Ex. 1069, EMS, p. 0030 (which is copied below again for convenience; *see also* pp. 0029 and 0037-0039):



AQUESTIVE EXHIBIT 1150

76. Unit-dose devices used for migraine treatment are also available and I used them prior to 2000 in the development of benzodiazepine nasal spray products. The choice of device depends upon factors such as intended clinical use, setting, stability with the drug and formulation, among others.

77. Due to the water insoluble nature of benzodiazepines, a common approach to nasal delivery formulations is to employ organic solvents or co-solvents with or without water. For acute use, there is a risk of transient irritation from such formulations. However, the risk-benefit assessment clearly still favors use of such products in treatment of life-threatening circumstances such as seizures.

2. Pharmacokinetics And Pharmacodynamics Of Nasal Benzodiazepines In Healthy Volunteers

78. Frequently, the first reports or studies of medications (including benzodiazepines) administered nasally to a patient is use of an injection device (with needle removed) coupled with the MAD nasal spray device off label. Data on clinical outcomes or pharmacokinetic and pharmacodynamic data have been collected – frequently showing success with benzodiazepines, e.g., diazepam. See Ex. 1025, 1043, 1125, 1127-1131, 1133, 1134. Further studies of intranasal delivery of benzodiazepine formulations were performed in healthy volunteers. The purpose of the trials was to generate systemic exposure and local tolerance

data for various formulation approaches. Table 2 provides some comparative data that examines formulations for intranasal delivery and the resulting pharmacokinetic parameters. See Exhibits 1025, 1043, 1125, 1127-1131, 1133, 1134; see also ¶¶ 191-194, below.

<u>Drug</u>	<u>Dose (mg)</u>	<u>Formulation</u>	<u>C_{max} (ng/mL)</u>	<u>t_{max} (min)</u>	<u>F (%)</u>
Clonazepam	1.0	B-CDE/H ₂ O	6.3	17.5	45
Lorazepam	2.0	Prop. Gly.	21.4	30	77.7
Lorazepam	4.0	Cremophor El	18.7	135	51
Midazolam	5.0	PEG400/Prop. Gly.	80	10	72.5
Midazolam	5.0	Prop. Gly./H ₂ O	71	14	83
Midazolam	3.4	SBE-CDE	51	15	71
Midazolam	0.25mg/kg	Aqueous Injection	147	25	50
<u>Diazepam</u>	<u>7.0</u>	<u>PEG 300</u>	<u>179</u>	<u>42</u>	<u>42</u>
C _{max} = maximum plasma concentration; t _{max} = time to maximum plasma concentration; F = absolute bioavailability comparing nasal dose to an intravenous dose					

TABLE 2. Pharmacokinetics of Selected Benzodiazepine Formulations (Aqueous and Non-aqueous) Administered Intranasally. See Wermeling, Ex. 1151, p. 0004.

79. The main considerations from these data include whether early (first 10 minutes) drug concentrations and maximum plasma concentrations represented by $C_{\max}$ are within ranges known to produce pharmacologic effects, and, secondly, whether the concentrations are achieved rapidly enough to be appropriate for treating a seizure. Well-designed nasal preparations may demonstrate a pharmacokinetic profile in which the rate and extent of drug exposure is equal to or superior to intramuscular injection and approximates IV infusion (versus bolus injection) (Figure 3 below). See Exhibit 1130.

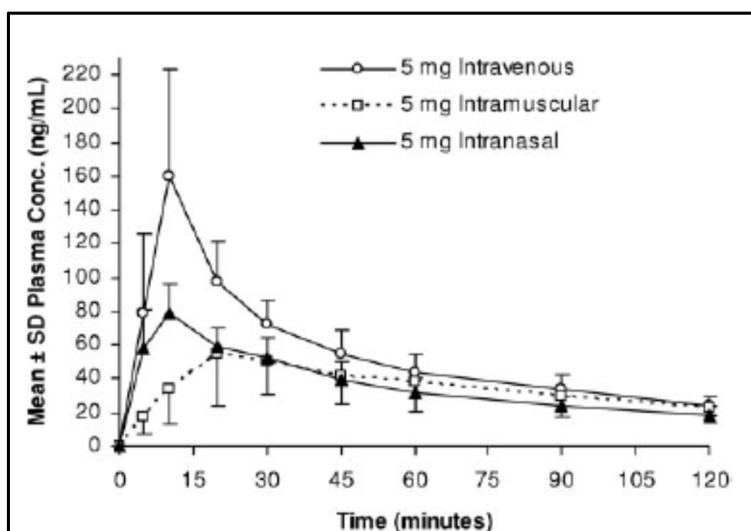


Figure 3. Midazolam Plasma Concentrations after 5 mg IV Infusion, IM and IN Administration. See Wermeling, Figure 3, Exhibit 1151, p. 0005.

80. The extent of absorption of a nasal dose compared to an IV dose may not be as relevant as the rate of absorption of a nasal dose compared to an IM dose. IM administration is an approved delivery route for treatment of seizures and more relevant in comparing the rate and degree of absorption in the early minutes after administration and the treatment of a seizure patient.

81. A POSA would know that the data for intranasal administration of benzodiazepines suggests that certain formulations could be appropriate for treating seizures. The evidence is indirect, in the sense that some formulations produce rapid plasma levels that are associated with IV or other routes of administration. Moreover, some studies collected pharmacodynamic information such as psychomotor or cognitive impairment studies, or sedation scoring, in conjunction with pharmacokinetic sampling. The pharmacodynamic data can be compared to dose and concentration data of the original studies of benzodiazepine effects on EEG beta wave (13 – 30 Hz) activity. Greenblatt (Exhibit 1135) has established that the degree of impairment on digital-symbol substitution tests was directly correlated to the degree of change in new-onset beta wave activity after triazolam administration. Moreover, Lindhardt (Exhibit 1025) demonstrated comparable changes in EEG amplitude in the 16-35 Hz range comparing 4mg intranasal to 5mg intravenous diazepam. Thus, these early studies examining

formulation strategy, biopharmaceutics and local tolerance were suggestive that nasal delivery of benzodiazepines could be successful in treatment of seizures.

D. Prior Art Experience With Intranasal Delivery Of Benzodiazepines For Treatment Of Seizures Prior To 2009

82. Studies demonstrating nasal delivery of midazolam to treat seizures, as compared to other benzodiazepines, are by far the most prevalent in the biomedical literature. O'Regan (Exhibit 1136) was the first to publish success employing this method by administering 0.2 mg/kg of the midazolam injection solution intranasally. The results demonstrated successful abolition of seizures in 14 of 19 children with difficult to treat seizures. There was a 60% reduction in spike counts per minute and the appearance of beta-wave activity within 175 seconds of drug administration.

83. Many additional pre-2009 papers describe intranasal delivery of midazolam in case reports or open-label studies with relatively small numbers of patients. However, in aggregate the studies are universally positive in their patient outcomes of rapid treatment and cessation of seizures. Three papers of similar construct compared intranasal midazolam to intravenous diazepam for cessation of seizures rates and time to cessation. See Exhibits 1137-1139. Each research team reached the same conclusions: 1) midazolam injection administered nasally was equally

effective as IV diazepam in seizure cessation; and, 2) intranasal midazolam reduced time to cessation of seizures by eliminating the need to establish IV access.

84. Bhattacharyya (Exhibit 1140) conducted a controlled trial of intranasal midazolam to rectal diazepam in children. There was a shorter time to seizure cessation in the midazolam group. Intranasal midazolam had a superior tolerability profile with lower incidences of drowsiness, nausea, and respiratory depression.

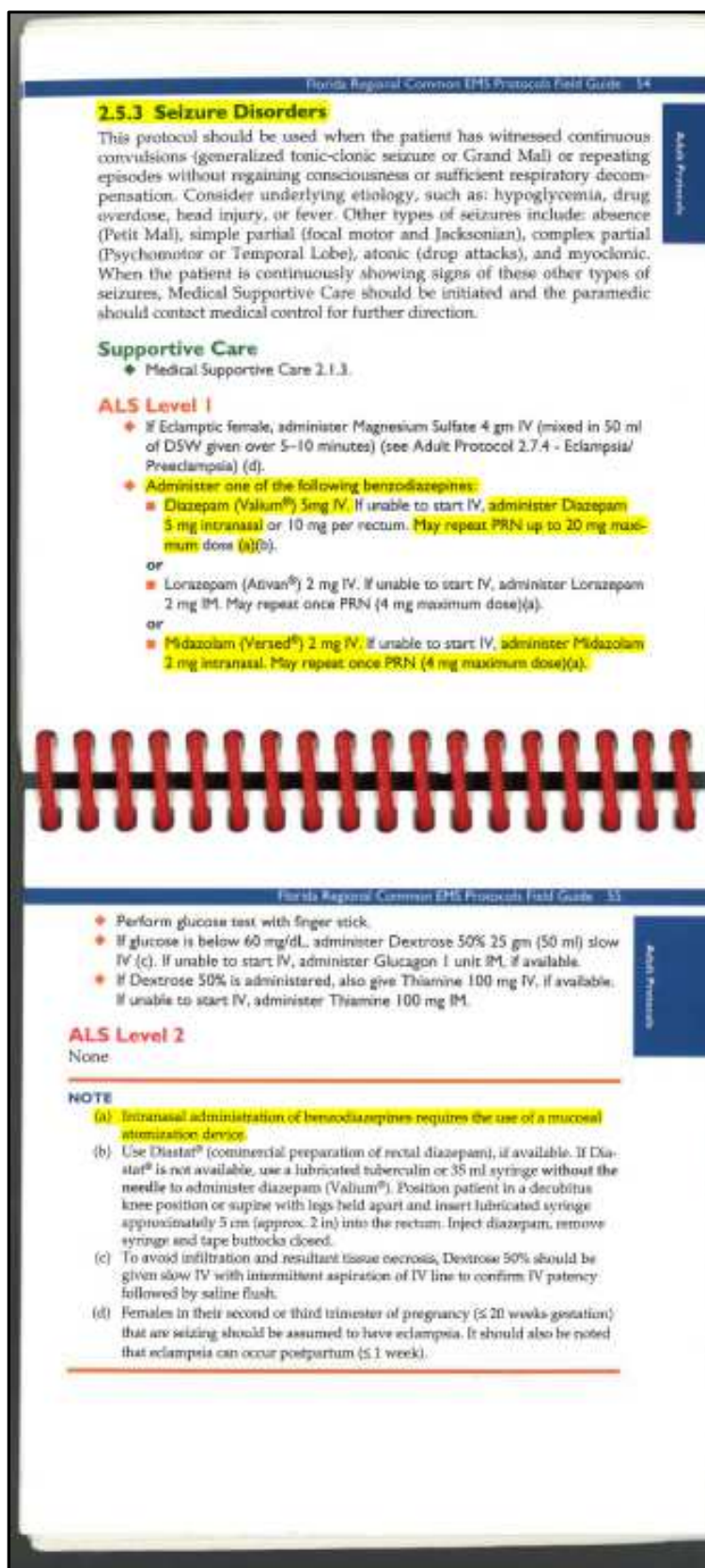
85. Similar outcomes have been reported when 0.2 mg/kg IV midazolam administered intranasally was compared to rectal diazepam in children in the pre-hospital setting. See Exhibit 1121. In addition to the aforementioned advantages from Bhattacharyya, the investigators demonstrated that midazolam treated patients were less likely to be seizing upon presentation to the emergency department, needed less additional seizure medication, had a lower incidence of intubation, or be admitted to the hospital or intensive care unit.

86. Intranasal drug delivery has been readily accepted by the layman as demonstrated by the considerable usage of over-the-counter and prescription products. Nasal drug delivery of midazolam for treatment of seizures in the home bound setting has been successful in preliminary studies. See Exhibits 1141-1143. Clearly, morbidity and mortality, the intensity of health-care resources and expenses associated with treatment of epileptic patients could be reduced if an

effective and safe transmucosal treatment was available for use by caregivers. In fact, physicians and pharmacists prepared midazolam injection in syringes, and the syringes were packaged with MAD devices into kits and made available to our patients. For example, at the University of Kentucky Medical Center Departments of Child Neurology and Pharmacy, since at least 2000, prescriptions were issued and compounded by the pharmacy for midazolam injection drawn into syringes and packaged with MAD nasal sprayers for intranasal administration. The product was kept in the home refrigerator for use by caregivers. The cost was less than \$50.00 per kit of midazolam injection solution syringes+MAD sprayers.

87. Lorazepam injection administered by intranasal spray was compared to intramuscular paraldehyde for protracted seizures in children of sub-Saharan Africa. See Exhibit 1144. Children randomized to lorazepam received 100 mcg/kg drawn up into a syringe with a nasal spray adapter. Seventy-five percent of the lorazepam patients had seizures stop within 10 minutes. The most significant finding may have been that there was a great difference in favor of intranasal lorazepam for the reduction of needing two or more additional rescue anticonvulsant agents. The authors believe their intranasal lorazepam system is an ideal primary healthcare facility, first-line anticonvulsant agent by satisfying the following criteria: quick acting, minimal cardio-pulmonary side-effects, long-lasting effect, and inexpensive.

88. Florida Regional Common EMS Protocols Field Guide, Jones & Bartlett Publishers (2005) (Exhibit 1069), prescribed the use of diazepam IV solution to be used with MAD nasal sprayer for intranasal administration of diazepam to treat seizures. See pages 54-55 from EMS (Exhibit 1069, p. 0030) copied below again for convenience.



AQUESTIVE EXHIBIT 1150

Each mL of Valium (Diazepam) IV “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.” PDR, Exhibit 1042, p. 0010 (emphasis supplied).

89. Intranasal delivery of benzodiazepines has been recommended in treatment guidelines when IV access has not yet been established. Table 3 (below) provides a general guideline that clinicians may wish to consider if nasal delivery of benzodiazepines is to be considered in their practice. Many of the key concepts are directly provided from the literature. Most importantly, development of protocols for non-physicians will assist in keeping this a safe drug delivery practice.

VII. THE PATHWAY TO FORMULATING THE SOLUTION

90. Benzodiazepines, although generally water-insoluble, can be designed into appropriate nasal delivery candidates. Preparations for clonazepam, diazepam, lorazepam and midazolam have been described. Clinical researchers have investigated, with considerable success, the potential for injectable benzodiazepine solutions to serve as a surrogate for optimally designed nasal spray formulations to treat seizures. The availability of low-tech nasal spray devices has facilitated this research and permitted translation of this technique into emergency medicine practice in some locales. The emergency medical community is striving to improve

the care of the seizure patient by examining drug delivery techniques to reduce the time to treatment and cessation of seizures. Table 3 below provides a summary of key points available from the literature.

• The choice of medication based on pharmacology, regulatory and clinical experience • Highly concentrated, stable drug solution ○ 100-200 uL delivery volume per spray for commercial products ○ As concentrated as available for injection solution products • Choose an appropriate nasal spray device ○ Atomizers distribute spray across the nasal mucosa ○ Use both naris to increase absorption surface area • Desirable pharmacokinetic and pharmacodynamic profiles ○ Rapid absorption ○ Sufficient duration to permit dosing of other medications • Develop assessment, administration and monitoring protocols and training guides ○ Emergency room and transport settings ○ Home-bound setting for patients and care-givers
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TABLE 3. Key Concepts for Clinical Use of Intranasal Benzodiazepine Delivery.

See Wermeling, Ex. 1151, p. 0006.

91. In contradiction to Dr. Gizurarson's opinion, there is a considerable history for nasal delivery of benzodiazepines that demonstrate clinical success in treatment of a patient. The early art demonstrates that administration of injection solutions to the nose had successful clinical outcomes to eliminate seizures. Pharmacokinetic and pharmacodynamic data from volunteers and patients are instructive to a path forward. A key clinical point of data integration across the studies defines a critical feature of interpretation. The clinical standard for success is the percent of patients treated within 10 minutes. The time to maximum concentration for any of these products is well beyond the 10-minute limit; it is frequently 20-90 minutes to maximum concentration. Therefore, successful treatment of a seizure, within 10 minutes or less, has a drug concentration far below the maximum concentration achieved from common doses. It is more telling that seizures cease with formulations 5-10 times more dilute than those designed for a nasal sprayer and the 100uL delivery volume. Therefore, the time to reaching a critical concentration is the defining factor for success in treating a patient to abort a seizure. Total exposure, or bioavailability as used by Dr. Gizurarson, as compared to another route, is not dispositive to successful treatment. One could have 100% bioavailability and be unsuccessful, such as, with an oral diazepam tablet PK profile.

1. There Were Many Nasal Delivery Systems And Many Non-Technical Problems To Their Commercialization

92. POR and Dr. Gizurason's declaration would have one believe that a POSA would approach the development of a diazepam nasal spray formulation as a single, serial approach of trying a single element at a time and then stopping at early stages, frustrated that one problem might be solved but the next problem makes the issue intractable. Following the logic postulated, their argument is that a POSA would not search for all relevant information and not combine what was known historically from a myriad of sources and use an efficient parallel formulation development approach. I strongly disagree with the position, the logic and the scientific approach in their opinions.

93. My personal experience with many nasal delivery products (see CV, attached hereto as Appendix A), FDA IND submissions (human research initiation request) and one NDA submission (request for approval) is quite different than the approach described in Neurelis expert's declaration. Several of my nasal formulation design products were also the subject of national peer reviewed research applications that were all funded by the National Institutes of Health (See CV, Appendix A hereto). Each of these grants had a scientific scope of work section centered on formulation development, optimization, and early stage clinical evaluation of one or more formulation candidates.

94. The consideration for developing a previously approved medication for a new route of delivery requires a comprehensive assessment, data integration, and formulation of a scientific process to move forward. Sources of data are many and likely include:

- All public domain information available from the innovator company for the medication of interest - information on file at FDA, including and most importantly, the label. Obtain the FDA summary basis of approval under FOIA which includes a by discipline analysis (chemistry of active ingredient and formulation, manufacturing, pre-clinical pharmacology and toxicology, and clinical pharmacology and clinical studies). Obtain listings of inactive ingredients from the FDA repository for each ingredient by route of administration and concentration. Examine the regulatory pathways needed to obtain approval for the innovator and the likely path for the nasal product candidate.
- Patent information on the innovator medication and excipients.
- Patent information on the list of likely excipients to satisfy nasal design parameters (see details further down).

- A complete literature search for the active ingredient including chemistry, formulation, pharmacology, toxicology, clinical pharmacology and clinical studies. Off label delivery considerations are of great interest.
- FDA guidance on Food Drug and Cosmetic Act (FDCA) for 505(b)(2) development plans which are for products in which there is a Reference Listed Drug (RLD) that has already been deemed safe and effective and approved for human medical use in the US.
- FDA guidance for the chemistry and manufacturing considerations for nasally delivered products.
- Specifications, regulatory and approval status for nasal delivery device candidates.

95. The 505(b)(2) regulatory pathway provides for FDA approval of a drug based in part on data that was not developed by the sponsor of the application, including published literature references and data previously reviewed by the FDA for the approval of a separate application. See, e.g., FDA GUI FINAL, *Determining Whether to Submit an ANDA or a 505(b)(2) Application*, Published May 2019, Exhibit 1146 (<https://www.fda.gov/media/123567/download>); CDER 2019-09-19, *Abbreviated Approval Products: 505(b)(2) or ANDA?*; Exhibit 1147 (<https://www.fda.gov/drugs/cder-small-business-industry-assistance->

[sbia/abbreviated-approval-pathways-drug-product-505b2-or-anda-september-19-2019-issue](#)); and FDA GUIDANCE FOR INDUSTRY (1999), *Applications Covered by Section 505(b)(2)*, Exhibit 1148 (<https://www.fda.gov/media/72419/download>).

96. Therefore, the considerations for formulation design are many and not considered in a vacuum. Solubility is but one of many factors for consideration of potential formulation candidates. However, an excellent starting point is to consider what the FDCA 505(b)(2) regulatory pathway means and how it drives all the aspects of the development plan. As a result, in my experience, you are trying to solve two things simultaneously: 1) a product design that follows an efficient 505(b)(2) pathway, research plan, and ability to reference data from the innovator (a critical feature so that preclinical work is not repeated) with as little questions or concerns from FDA as possible; and 2) a product design that will generate patent protection permitting financial investment and market monopoly if ultimately successful.

97. These dual goals can create quite a conundrum. It is relatively easy to design products that can fit 505(b)(2) with excipients and devices that are well known to FDA. Therefore, the scientific inquiry then becomes a critical one of knowing exactly what is in the prior art world-wide including patent applications,

issued patents and the scientific literature. A POSA is unable to design without this knowledge and to avoid infringing on other's property rights.

98. This conundrum has created, in general, companies who specialize in considering old excipients not used in pharmaceuticals, for patenting in a medication formulation, and companies who “create” new excipients that are proprietary and may be helpful in one or more aspects of formulation design (chemistry, stability, microbiology, membrane permeation). Aegis, now merged into Neurelis, was such a company with their Intravail™ products (a line of alkyl glycosides). The Aegis business model was to license the technology to nasal companies to potentially help in formulation, but, in most cases, it was also a way to take a formulation using common excipients and not proprietary and convert to a formulation that was proprietary by virtue of the “new” excipient. My former company Intranasal Technology was one such client of Aegis in 2006. In my opinion, this process is logical to a POSA and is not an invention or a discovery.

99. The 505(b)(2) pathway for converting diazepam injection formulation or Diastat® formulation into a diazepam nasal spray is very logical and a reason why the “discovery” is not an invention. The scientific and regulatory basis is the following:

- The nasal spray developer must choose an already approved version of diazepam, either injection (IV or IM) or the rectal gel. Please recall the term Reference Listed Drug (“RLD”) discussed above.
- A key underpinning for FDA acceptance of 505(b)(2) applications, especially nasal for systemic administration, is that the blood level exposure from nasal delivery approximates that from a dose and route of administration previously approved. Blood level exposure includes both rate and extent of administration for the entire dosing period and also partial exposure assessment from time 0 to $t_{\max}$ as key factors. The comparison of exposure between nasal and the RLD is critical for **bridging** the safety and efficacy data from the approved innovator to the research nasal product. “Bioavailability” as loosely used in the ‘876 Patent and other Neurelis documents is not a driver.
- It is critical that the considerations for nasal product formulation design take into account the nature of, meaning rate and extent, not just “bioavailability”, as used by the ‘876 Patent and Neurelis.
- Therefore, a POSA knows to design a nasal product that fits the pharmacokinetic profile of an RLD.
- In this case, the pharmacokinetic profile of diazepam intramuscular injection, and diazepam rectal gel, are well known and good candidates.

- The most recently regulatory experience is with the approval of diazepam rectal gel (Diastat™), which, also carries a special label indication for administration at home by care givers, versus by physicians, nurses, EMS workers or ER workers. This is the unmet need and the applicable market niche. Therefore, it is logical that Neurelis conducted formulation designs to mimic and **bridge** to diazepam rectal gel as the RLD. It also explains their two approaches, one a suspension, and one a solution, as two options to accomplish the goal. One would only design a suspension if intending for oral absorption from swallowing the nasal residual whereby the particles may dissolve in the gut (thereby attempting to mimic the RLD, i.e., Diastat's™ PK/PD).

100. In conclusion, a POSA has very clear motivations that must satisfy two conditions: FDA acceptance of a safe and effective product and patent protection to garner investment and market monopoly. A POSA will not be successful if unable to satisfy these conditions. Yet, there is great expectation of being successful given what was known for off-label nasal administration of diazepam and other benzodiazepines and that diazepam solution chemistry was known and drives approaches for formulation already in the patent literature.

101. A POSA with nasal delivery design experience knows the general conditions that a formulation must consider:

- Solubility
- Physical and chemical stability in solution and container closure
- Microbiologic management (preserved or sterile product)
- Membrane Penetration (enhance residence time, increase permeation)

102. In my experience, both corporately and academically, a POSA would design a matrix of excipients as possible formulation candidates to address these various topics. A simple example table might look like something below:

Formulation	1	2	3	4
Solubility Options				
Stability Options				
Micro. Options				
Nasal Retention Time Options				
Permeation Enhancement				
Other special				

103. Within each “options” section would be a list of potential candidates that a POSA would know considering diazepam chemistry, excipients that are already approved in nasal products, or approved in other products, and “newer” products if accessible through licensing. The microbiology section is managed in one of two ways: terminal sterilization if product can withstand the heat cycle or aseptic

processing including an antimicrobial preservative or processing rendering the product sterile and labelled as such.

104. Under each of the headings above one could consider a number of non-exclusive options as outlined below.

- Solubility
 - Water
 - Alcohols
 - Glycols
 - Vegetable and Other Oils
 - Cyclodextrins
- Chemical Stability
 - Chelators
 - Buffers
- Retention
 - HPMC
- Microbiology
 - Alcohols
 - Parabens
 - Benzemethonium
 - Benzalkonium

- Permeation Surface Active Agents
- Others
 - Humectants
 - Taste or Odor Masking

105. A quick screening study for physical stability of option combinations is conducted. Those that can not or will not stay in solution, or change in color, pH or osmolality are discarded. Then the remaining options are made again and placed in accelerated stability testing (elevated temperature) for 30 days. Those candidates who fail physical stability are discarded as well as those that are not able to maintain the target concentration. The remaining candidates then have further study in combinations. This parallel approach can usually get good candidates in 4-6 months.

106. Further, in consideration of the formulation option approaches, I refer back to the 505(b)(2) pathway and the pharmacokinetics of diazepam rectal gel versus what pharmacokinetics were obtained when other nasal benzodiazepine formulations were administered to humans. Many formulations were true solutions using water and organic co-solvents or organic co-solvents. Typically, you would see a rapid rise of the blood levels and then a tailing off – no sustained action (See Nayzilam® midazolam nasal spray). Diazepam rectal gel has sustained levels due to relatively slow and less efficient absorption from the rectal vault as compared to

nasal. However, one **must design by intent** understanding the chemistry and clinical pharmacology of diazepam by all routes of administration. The Nayzilam® model does not fit to diazepam rectal gel.

107. Therefore, a POSA would know that enough diazepam has to enter the bloodstream during the first 10 minutes to abort or prevent recurrence of seizures. A POSA would know that the blood levels needed for success are much lower than the maximal levels achieved. *Id.* Within 20 minutes most of the nasal spray has been swept to the naso-pharynx and swallowed. See Chien, Ex. 1082, pp. 0011-0012. A POSA would also know that diazepam when administered orally as a tablet by intent has nearly complete absorption. A POSA would expect the swallowed diazepam solution and or particles entering the gastro-intestinal tract would also be nearly completely absorbed and providing a longer duration of exposure beyond that absorbed nasally and being successful to mirror diazepam rectal gel. This is not a surprising design or outcome.

108. The formulation approach that resulted in the '876 Patent's claimed formulations and hence the claims was obvious.

109. Neurelis argues that a POSA would not have been motivated to use a combination of organic solvents to increase the solubility of diazepam. Yet, the argument seems somewhat illogical since a POSA would know to maximize solubility for efficient dose loading in a nasal spray. The notion itself begs the

question. Moreover, standard textbooks (in my library) such as Remington's Pharmaceutical Sciences (1995 edition), explain the use of binary and ternary solutions in solubilizing medications. Remington's and The Merck Index (1996 edition) explains that low alcohols are miscible with each other and Vitamin E/tocopherols. The notion of using them together is quite old if present in these textbooks.

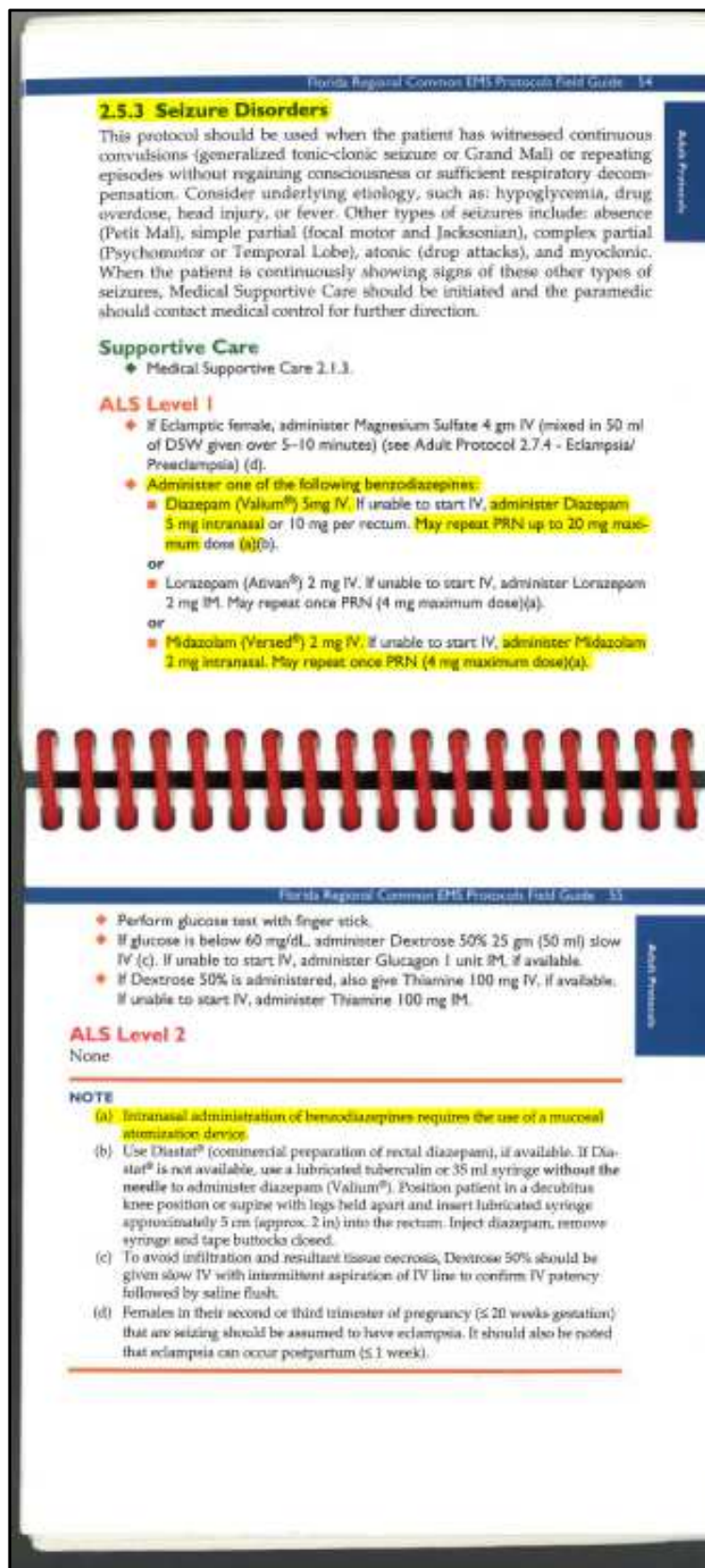
2. Background In The Intranasal Art

110. The prior art that informs the POSA includes a series of other patents leading up to the claimed invention and a significant body of literature, spanning over 20 years, regarding benzodiazepines and their role in emergency treatment of epileptic seizures. Transmembrane delivery, including nasal delivery, has been discussed and researched for over 30 years.

111. Prior to commercialization of alternative benzodiazepine delivery systems, and the dates of the patent in suit, physicians, pharmacists, and Emergency Medical Services (ambulances), and Emergency Rooms of hospitals, have administered FDA approved injection solutions of many medications, including benzodiazepines, with the assistance of the Mucosal Atomization Device (MAD™, Teleflex Inc. (<https://teleflex.com/usa/en/index.html>))), into the nasal cavity. This off-label approach has proven to be a viable and successful option in treating a

patient having seizures. Medical directors of such services have provided standing orders to other health care providers to deliver the injection as a nasal spray, as an option, when intramuscular or intravenous administration are not optimal for a given patient. Moreover, pharmacists have been directed by physicians to draw into syringes the concentrated form of midazolam injection, dispensed along with the MAD device, for use by parents and caregivers in the home setting. EMS in Florida were directed as early as 2005 to use diazepam IV solution together with the MAD device to treat seizures by administering diazepam intranasally. See next paragraph. All of this activity, and more, occurred prior to 2009 and is an obvious omission from the POR and Dr. Gizurason's declaration.

112. Florida Regional Common EMS Protocols Field Guide, Jones & Bartlett Publishers (2005) (Exhibit 1069), prescribed the use of diazepam IV solution to be used with MAD nasal sprayer for intranasal administration of diazepam to treat seizures. See pages 54-55 from EMS (Exhibit 1069, p. 0030) again copied below for convenience.



AQUESTIVE EXHIBIT 1150

Each mL of Valium™ (Diazepam) IV “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.” PDR, Exhibit 1042, p. 0010 (emphasis supplied).

113. Ativan™ (lorazepam) and Valium™ (diazepam) injection were first marketed in 1977 and 1963. The FDA approved indications are many and include the treatment of medical emergencies such as an epileptic seizure. Both medications are not very water-soluble and are thus dissolved in organic solvent(s). The molecular weight, water-solubility, octanol-water coefficient and partitioning due to lipophilic character were well understood. Other physical characteristics would be routinely considered by a POSA. A POSA would know to examine all available prior art that would assist in maximizing solubility to encompass a wide range of doses. Knowing the limitations of these medications, a POSA would use all available known matters that would increase the rate and extent of transmembrane delivery. One could alter the original molecule of interest to increase water solubility, make a salt or ester of the medication, can use formulation chemistry to manage stability and bioavailability, and can incorporate surface active agents that modify the permeability of nasal membranes.

114. A POSA would understand from looking at other FDA approved nasal sprays for guidance as to device/container closure choices, single/multiple spray capability, use of solvents and co-solvent systems, muco-adhesives, surface active agents, etc. Development and approval are easier if one can use materials and methods that FDA has already deemed safe and effective. In fact, FDA goes to great length to manage an inactive ingredient compendia for materials that are Generally Regarded as Safe (GRAS) including concentrations of excipients by route of administration. A POSA would look at this reference for transmembrane routes and their ingredients, including nasal delivery. The formulation materials in question are “old” in a technological sense and recognized as agents serving to increase solubility and enhance membrane permeation. A POSA would understand what these agents mean and how to use them. Moreover, a POSA would be inclined to make a matrix of various combinations of the ingredients in a simple screen using a parallel study of options, versus a serial study, and starting over when something does not turn out to work. A serial study approach is very inefficient.

115. The context of this approach is to create a nasal spray of a medicinal that has already been approved by the FDA for the treatment of seizure. Another way of saying it is reformulating an approved medication for a transmembrane, needle-free delivery approach, of which nasal is one option. A nasal delivery product with

a new chemical entity uses the traditional 505(b)1 development pathway to demonstrate safety and efficacy for registration. A generic drug development plan (505j) is not appropriate to reformulate a known active ingredient since by regulation it must be identical quantitatively and qualitatively to an already approved medication or a Reference Listed Drug (RLD).

116. The nasal delivery commercialization activity is mostly centered on a 505(b)(2) pathway in which a previously approved active ingredient is reformulated for another route of delivery. Major pharmaceutical companies use this approach as line extensions and to continue a franchise. Small companies tend to target already approved medications that are off-patent when, among other reasons, there may be perception of an unmet medical need suitable for a transmembrane approach. However, many small companies fail to commercialize, not for being unable to formulate and administer, but for reasons of business model and willingness of investors to sink significant capital into a product understanding that it may take 5-10 years to get FDA approval, if at all. And then of course, will the marketplace accept the price of such products and at what volume? The nasal products are expensive to manufacture, even at scale, and require a premium price to recover development, production, and ongoing operations costs and retail pharmacy distribution. The recently approved Nazylam™ (midazolam) nasal spray is illustrative.

<u>Product</u>	<u>Provider</u>	<u>Retail Price</u>
Diazepam 10 mg Injection	Walgreens Walmart CVS Kroger	\$29.98 (average)
Diastat Acudial 10 mg	Walgreens Walmart CVS Kroger	\$336.36 (average)
Nayzilam box (2 doses)	UCB	\$550.00

See Ex. 1081, pp. 0001 (\$29.98 average), 0003 (\$336.36 average), 0005 (\$550.00).

117. The development of Neurelis product followed the 505(b)(2) pathway. Like a generic drug, nasal delivery of the active ingredient must have a RLD that was already FDA approved. The advantage in the Hatch Waxman Act is that the FDA and the company can rely on certain previously obtained data to demonstrate safety and efficacy. For example, basic chemistry and toxicology studies do not have to be repeated. A way to look at it is through a gap analysis: You have the data necessary for approval, minus that which is known and accepted, and to identify

what one needs to do in the development plan. The general approach is what is necessary to gain the same label indication of your product as the RLD.

118. Therefore, Neurelis would have to consider which of the approved medications and delivery routes it wished to link to the new nasal spray. In this case, based on the dates of the matters at hand, there were 2 products (many generic injectables) and several approved routes of administration. The diazepam injection can be administered IV or IM. The Diastat™ gel is per rectum. There is only one RLD that follows their approach and that is linking to Diastat gel for the cluster seizure indication. Therefore, formulation development and pharmacokinetic and clinical testing have the Diastat™ blood level data as the exposure to copy.

119. The chart below shows the composition of DIASTAT® rectal diazepam product and the VALIUM® intravenous diazepam product.

Diastat® Rectal Diazepam and Valium® Diazepam Injection Formulas and MW

Product Ingredient	DIASTAT (diazepam rectal gel) Ex. 1042, p. 0002	VALIUM (diazepam injection) Ex. 1042, p. 0010
Diazepam	5 mg/ml	5 mg/ml
Propylene glycol	present (amount unknown)	40%
Ethyl alcohol	10%	10%
Hydroxypropyl methylcellulose	present (amount unknown)	--n/a--
Sodium benzoate	Present (amount unknown)	5%
Benzyl alcohol	1.5%	1.5%
Benzoic acid	Present (amount unknown)	Present (amount unknown)
water	Present (amount unknown)	--n/a--
Diazepam Molecular weight	284.74	284.74

120. Copying is a key scientific feature in human development studies that is necessary to be successful. The exposure (Cmax, Tmax, and AUC) of the new product will need to mimic the exposure of the RLD of choice. The premise is that safety and efficacy is linked to systemic blood exposure of the new product as compared to the RLD. One would only expect any new toxicity to be related to site of administration. So, blood level exposure becomes the target. A POSA would consider design of their product to mimic the RLD blood level exposure. **The over-riding consideration is that there is not a discovery – there are no**

unexpected results - you are designing and researching by intention - what you are doing is obvious to a POSA.

121. For illustration, I am providing pharmacokinetic data for what was known at and prior to the dates relevant in this case. All routes of administration are included.

<u>Product/Route</u>	<u>Dose (mg)</u>	<u>t_{max} (h)</u>	<u>C_{max} (ng/mL)</u>	<u>Bioavailability (%)</u>
Injection IV	10 mg	Instant	>400	100
Injection IM	10 mg	1.3	287	90
<u>Autoinjection IM</u>	10 mg	1.5	314	90
<u>Diastat Rectal</u>	<u>15 mg</u>	1.5	400	90
Tablet Oral	10 mg	1.3	317	100

Now, let's contrast these data with the data in Table 11-3 (provided below) of the '876 Patent below.

Product/ Route	Dose (mg)	T _{max} (h)	C _{max} (ng/mL)	Bioavailability (%)
Solution/ IN	10	1.5	272	96% ('876 Patent, Ex. 1001, 62:17-19, p. 0040).

TABLE 11-3						
Summary of Pharmacokinetic Parameters for Intranasal (10 mg) and IV (5 mg) Diazepam						
Parameter ^a	Diazepam Nasal Spray (10 mg/100 μ L)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
	n	Mean (SD) ^a	n	Mean (SD) ^a	n	Mean (SD) ^a
C_{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T_{max} (h) ^b	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC_{0-t} (h $\times$ ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
$AUC_{0-\infty}$ (h $\times$ ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λ_z (h ⁻¹)	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
$t_{1/2}$ (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)
^a Mean values are presented as arithmetic means.						
^b Median (min, max) reported for T_{max}						

‘876 Patent, Ex. 1001, p. 0040.

122. These data demonstrate that the solution product has data that approximate the data already from approved diazepam products. Of course, this is design by intent, and therefore not surprising at all as compared to the existing data.

123. The oral tablet data are instructive as to complete extent of exposure as compared to nasal. Diazepam nasal spray has two routes to be absorbed, in the nasal cavity, and then in the gut after swallowing (nasal+oral absorption).

Therefore, whatever drug is not absorbed in the nasal cavity is swallowed and will be taken into the bloodstream. The notion of nas-oral (“nasal oral absorption”) biopharmaceutics is known to a POSA in this field and also acknowledged by Dr. Gizurarson. Gizurarson Dec. ¶¶ 58, 59, 112, Exhibit 2012. The Glaxo product Imitrex™ (sumatriptan) nasal spray is held as an exemplar of such an outcome.

Glaxo is criticized for such a poor nasal spray formulation that did not get substantially or completely absorbed in the nose. In fact, one sees two peak blood level concentrations - one at 20 minutes representing nasal absorption and a second peak at 1.5 hours for oral peak absorption (as if you swallowed a tablet).

124. Dr. Gizurarson, Neurelis' expert, and Nayzilam™ (midazolam) patent inventor, opines on the need for rapid exposure for seizures and states also being aware of poor formulae with nas-oral characteristics. A fascinating element is that he licensed a midazolam nasal spray formula to UCB. Here, the inventor designed for rapid exposure and is what is more typical for nasal delivery. The data are:

- 5 mg midazolam dose intranasally
- T_{max} – **17.3 minutes**
- C_{max} – 54.7 ng/mL
- Bioavailability – **44%**

See Nayzilam Product Label and Instructions for Use, Exhibit 1072, p. 0015.

125. These data show that bioavailability itself is not a marker for what is necessary to successfully treat a patient with a seizure. One must reach a threshold concentration quickly; in this case the standard of care is to have seizures stop within 10 minutes. Given these facts, a relatively low midazolam exposure is obtained in the first 3-8 minutes. The data from Nayzilam™ mirror my own

published work with midazolam and is not surprising. See Wermeling, Figure 3, Exhibit 1151, p. 0005.

126. Given all that was known in prior art regarding formulation, administration technique and clinical pharmacology, and practices in medicine and pharmacy, I am completely confident a POSA could treat a patient with diazepam using a co-solvent system and permeation enhancers that have been disclosed prior to 2009 are also described in the '876 Patent at issue. The inventors designed by intention and dumbed down a nasal spray to make it "slower" than what is typical. The designs were done intentionally to match the Diastat® RLD and is not surprising at all.

VIII. GWOZDZ, MEEZAN'962 AND CARTT'784 MAKE ALL THE CLAIMS OF THE '876 PATENT OBVIOUS.

127. With the above background, a POSA would have found the combination of Gwozdz and Meezan'962 made claims 1-16 and 24-36 obvious and the combination of Gwozdz, Meezan'962 and Cartt'784 made claims 17-23 obvious. Moreover, a POSA would have been motivated to combine the teachings of these references with an expectation of successfully arriving at what is claimed in the '876 Patent, i.e., a method of successfully treating a patient.

128. In my opinion, the ‘876 Patent is obvious based on the plain language reading of the Gwozdz, Meezan’962 and Cartt’784 prior art. Moreover, a POSA would have been motivated to combine these references because they all relate to optimizing the intranasal administration of drugs. If need be, the teachings in these references could be readily modified by a POSA in predictable ways, without undue experimentation and with a reasonable expectation of success to obtain the claimed intranasal solutions and treat the patient.

A. Gwozdz (Exhibit 1014)

129. Gwozdz discloses all elements of the claims of the ‘876 Patent, with the exception of alkyl glycosides and some dosing regimens. In particular, Gwozdz makes the following general and specific disclosures:

- “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.”
Gwozdz, 4:13-17;
- “combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level.” Gwozdz, 7:14-16.

1. A POSA Would Have Used Gwozdz' Disclosure of Ternary Co-Solvent Systems Such as Tocopherol+Ethanol+Benzyl Alcohol, and Gwozdz' Disclosure is Not Limited to Administration to One Nostril

130. On pages 28-30 of its Response, Patent Owner concludes that Gwozdz does not allow for the use of the ternary co-solvent system, though it actually is disclosed in Gwozdz. Patent Owner argues that the ternary co-solvent system would, in fact, result in the diazepam precipitating out of solution. Patent Owner is wrong.

131. First, a POSA would have used Gwozdz' disclosure of ternary co-solvent systems such as tocopherol+ethanol+benzyl alcohol, because such systems offer the potential for better solubility.

132. Second, Gwozdz' disclosure is not limited to administration in one nostril, and use in more than one nostril would allow for a lower concentration of active in the solution being administered (thereby avoiding the potential for diazepam to precipitate out of the solution).

(a) A POSA Would Expect that a Ternary Co-Solvent System (Tocopherol+Ethanol+Benzyl Alcohol) Could Solubilize More Diazepam Than a Binary Co-Solvent System (Tocopherol+Ethanol)

133. Gwozdz expressly discloses tocopherol+ethanol (a binary solvent system) for dissolving diazepam. Gwozdz also discloses the use of tocopherol with a

combination of alcohols (including tocopherol+ethanol+benzyl alcohol – a ternary solvent system).

“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.”

Gwozdz, Ex. 1014, p. 0004, lines 13-17 (**emphasis added**).

“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**.”

Gwozdz, Ex. 1014, p. 0006, lines 16-19 (**emphasis added**).

134. A POSA would have expected that due to their properties, all three of these solvents would work well together as co-solvents in a ternary co-solvent system. For example: α -tocopherol is soluble in ethanol (95%); benzyl alcohol is miscible in all proportions with ethanol; benzyl alcohol is miscible in all proportions with fixed and volatile oils (e.g., tocopherols). See Handbook of Pharmaceutical

Excipients, Ex. 1031, p. 0007 (para. 17, “d-alpha tocopherol); p. 0010, Table III; Merck Index, Ex. 1076, pp. 0011, 0014.²

² I note that Patent Owner argues that a POSA would not have an expectation of success in adding benzyl alcohol to Gwozdz’ binary co-solvent system (tocopherol+ethanol) because of concerns that benzyl alcohol would accelerate the auto-oxidation of fats. POR, Paper 16, p. 33. Patent Owner is presumably referring to tocopherol as a fat. However, a POSA would not be concerned for several reasons, not the least of which is the absence of oxygen in these single-use emergency rescue products. Pointedly, the reference relied on by Patent Owner states that “[i]t can also accelerate the autoxidation of fats.” Ex. 1031, p. 0010. The reference does not provide any conditions necessary for such autoxidation to occur, nor does the reference indicate that tocopherols would autoxidize in the presence of benzyl alcohol. As Dr. Gizurarson testified, Exhibit 1031 (The Handbook of Pharmaceutical Excipients) does not identify tocopherols as a subject for autoxidation and that he himself merely considers the statement in The Handbook to be a general “warning signal.” Gizurarson Dep., Ex. 1149, 76:4-24. Therefore, given Gwozdz’ express direction to use tocopherol+ethanol+benzyl alcohol, a POSA would not have been dissuaded from using benzyl alcohol.

135. Patent Owner argues that any decrease in the percentage amount of tocopherol would result in the diazepam solution precipitating out, and therefore, argues that Gwozdz does not allow for the addition of benzyl alcohol (notwithstanding Gwozdz' express disclosure of tocopherol+two alcohols).

136. Patent Owner appears to be arguing that a POSA would not use a ternary system but would instead be limited to a binary system. Notwithstanding that, as noted above, Gwozdz expressly teaches and discloses the use of a ternary system (i.e., a tocopherol and two different alcohols, ethanol and benzyl alcohol).

137. However, in order to make its argument, Patent Owner ignores several important solubility considerations necessary to make the argument that the diazepam would precipitate out and would not be useful for intranasal administration.

138. First, Patent Owner ignores the fact that a ternary system has its own solubility properties and therefore it is wrong to extrapolate from a binary system to a ternary system.

139. A POSA would have recognized that the addition of benzyl alcohol to a tocopherol+ethanol co-solvent system – as suggested by Gwozdz – would result in a ternary co-solvent system with different solubility characteristics. Thus, a POSA would have been motivated – as taught by Gwozdz – to include benzyl alcohol in its solution for its potential benefits in solubilizing diazepam. A POSA following

Gwozdz' teachings would adjust the amounts of the three solvents to maximize solubility of the drug. This is Gwozdz' exact teaching, without any modification.

140. Patent Owner makes its argument regarding the solubility of a ternary co-solvent system (tocopherol+ethanol+benzyl alcohol) based on solubilities provided for a binary co-solvent system (tocopherol+ethanol) while disregarding the differences between the systems (and ignoring the potential benefits of a ternary co-solvent system). Patent Owner is not acknowledging that a POSA's first goal is to determine the solubility limits of diazepam in the ternary solvent system disclosed by Gwozdz – without being bound by any binary co-solvent system solubility numbers/values. In fact, Gwozdz specifically discloses the solubility limits in a binary system (p. 0007) and invites the POSA to experiment with a ternary system to determine the solubility limits in a ternary system.

141. Indeed, a POSA would have been very motivated to routinely experiment with a ternary system, which would inherently require that at least one of the two co-solvents in the binary system be reduced in order to make room for the third co-solvent (i.e., to create the ternary system). Combining and adjusting three solvents to maximize solubility of any water-insoluble drug (such as diazepam) is a simple, well-known, and routine technique that a POSA could (and would) easily do when directed (as by Gwozdz) to use three solvents (especially when the three solvents are specifically identified, as by Gwozdz).

142. Significantly, a POSA would expect that a ternary co-solvent system (tocopherol+ethanol+benzyl alcohol) could solubilize more diazepam than a binary co-solvent system (tocopherol+ethanol). In this regard, it is well-known to a POSA that a ternary co-solvent system will have different solubility properties than a binary co-solvent system. Moreover, a POSA would know to try a ternary co-solvent system if a binary co-solvent system wasn't satisfactory in a particular situation. Here, the POSA would know to try a ternary co-solvent system especially because Gwozdz expressly teaches that diazepam can be dissolved in a ternary co-solvent system of three solvents that are all miscible with each other (i.e., tocopherol+ethanol+benzyl alcohol). POSAs routinely conduct such experiments, which are not difficult to run.

(b) Gwozdz' Ternary Co-Solvent Diazepam Solution in a Reduced Concentration Can be Administered to Both Nostrils to Deliver the Same Amount of Diazepam and Avoid Possibility of Precipitating Out

143. Patent Owner also ignores the obvious fact that Gwozdz' intranasal solution could be administered in both nostrils. In the case of administration to both nostrils, the diazepam concentration used for each nostril could be reduced in half. Halving the concentration of diazepam would eliminate Patent Owner's concerns about precipitation, as there would be none.

144. Moreover, as disclosed in Cartt’784 (Ex. 1014, p. 0004, ¶ [0031], second column, lines 5-10), and as acknowledged by Patent Owner as an acceptable administration (see ‘876 Patent, Claim 22), a POSA would have known that intranasal solutions can be administered in one nostril; in both nostrils sequentially; or in one nostril, then the second nostril, and then the first nostril again (and, optionally, in the second nostril again), sequentially – in these cases, the concentration could be even further reduced.

145. In fact, Patent Owner’s own expert, Dr. Gizurarson, agrees that a POSA would reduce the concentration and apply a lower concentration to both nostrils in order to avoid salting out while still achieving the desired therapeutic effect.

Gizurarson Dep., Ex. 1149, 38:9-18.

2. The Combination of Ethanol and Benzyl Alcohol and Diazepam for Use in Treating Seizures in Humans was Well Known

146. A POSA would know that there are historic and commercial examples that combined benzyl alcohol with ethanol and diazepam, along with other solvents. In particular: i) the combination was known from commercial products Diastat™ and

Valium³ injection (which was used intranasally with the MAD device and known to work; *see* EMS, Ex. 1069, pp. 0029-0030, 0037-0039); and ii) benzyl alcohol and ethanol were known to be readily miscible. *See* Handbook of Pharmaceutical Excipients, Ex. 1031, p. 0010, Table III; Merck Index, Ex. 1076, p. 0011. Gwozdz also says to use tocopherol in combination with one or more alcohols, i.e., ethanol and benzyl alcohol: “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.” Ex. 1014, p. 0007, lines 3-8 (**emphasis** added). Dr. Gizurarson agreed that Gwozdz disclosed the combination of tocopherols and benzyl alcohol. Gizurarson Dep., Ex. 1149, 73:11-15. Moreover, a POSA would know that the combination of ethanol and benzyl alcohol were effective intranasally with diazepam (i.e., in the form of ValiumTM) as in Florida EMS manual. *See* EMS, Ex. 1069, pp. 0029-0030, 0037-0039. So starting from Gwozdz, the only thing missing is alkyl glycosides. In fact, Gwozdz does mention using penetration enhancers in injection formulations (Ex. 1014, p. 0010, line 14), which would mean a POSA could take injection formula from EMS

³ Diastat® and Valium® includes diazepam, ethanol, and benzyl alcohol. *See* PDR, Ex. 1042, pp. 0002 and 0010.

Florida manual (diazepam IV which has benzyl alcohol and ethanol) and add penetration enhancers.⁴ A POSA would then consider which penetration enhancers to use. In this system, we know that penetration enhancers soluble in an organic solvent would be appropriate. This would lead me to look in both the science and patent literature regarding penetration enhancers used – or that could be used – intranasally. One of the references I would consider would be Meezan’962 because it discusses the use of penetration enhancers for intranasal use. In particular, its penetration enhancers of choice are alkyl glycosides, and dodecyl maltoside in particular. Therefore, I would be motivated to add Meezan’s alkyl glycosides (e.g., dodecyl maltoside) to Gwozdz’ ternary co-solvent system (of tocopherol, ethanol, and benzyl alcohol) that was used to dissolve diazepam.

147. Regarding amounts of tocopherol, Gwozdz teaches using about 30-99% w/w. Gwozdz, Ex. 1014, p. 0004, lines 17-19; p. 0007, lines 8-10. Gwozdz teaches using about 1-70% alcohol(s). Ex. 1014, p. 004, lines 20-21; p. 0007, lines

⁴ Moreover, notwithstanding Patent Owner’s comments to the contrary (see POR, Paper 16, pp. 35-36), a POSA would understand the benefits from using a penetration enhancer, even in situations of already-high bioavailability, as penetration enhancers would (among other things) be useful in adjusting the rate and amount of drug absorbed purely intranasally.

10-11. Ethanol is specifically mentioned as being present in amounts of 1-40% and 10-30%. Ex. 1014, p. 0007, lines 21-24. Based on Gwozdz teaching of using ternary co-solvent systems and based on the known miscibility of benzyl alcohol in both ethanol and tocopherol, a POSA would know to test percentages of benzyl alcohol in the ranges recited in the '876 Patent claims.

148. Regarding Meezan'962 – PTAB states:

“Petitioner does not explain why one of ordinary skill in the art would have reasonably expected the same increase in bioavailability identified for salmon calcitonin to apply to a benzodiazepine drug, much less a benzodiazepine drug that is combined with vitamin E, ethanol, and benzyl alcohol.” Decision, p. 30.

149. The PTAB has misapprehended the meaning of Meezan'962's teachings. It is not necessary that the increase in diazepam's bioavailability be the same as the increase in calcitonin's bioavailability – such an increase would, in fact, be impossible (calcitonin had much more room to improve). Rather, the question is whether a POSA would have expected a significant increase in diazepam's bioavailability through penetration enhancers, e.g., alkyl glycosides. Here, the POSA would have indeed expected a significant increase in bioavailability. This is because of how penetration enhancers, such as alkyl glycosides, generally function. In particular, it is well-known that larger molecules inherently have a more

difficult time crossing the membrane than do smaller molecules, and therefore, the improvement in transmembrane efficiency is inherent. If a penetration enhancer increases penetration for a large molecule, it will be expected to also increase penetration for a small molecule, simply because molecular size is the primary constraint of passing between epithelial cells. Regarding the co-solvent system used for calcitonin versus that used for diazepam – I would expect that a non-ionic surfactant that is soluble in organic solutions to function as a surfactant at a biological membrane.

150. Moreover, Meezan’962 specifically teaches that alkyl glycosides will also increase the bioavailability of small molecules. Also, I reiterate that Meezan’962 mentions small organic molecules, molecules below 1.5 kDaltons, etc.

Meezan’962, Ex. 1011, ¶ [0130], p. 0015. Diazepam fits these, having a molecular weight of 284.74. See PDR, Ex. 1042, p. 0010. Thus, Meezan’962 teaches the use of alkyl glycosides with benzodiazepines.

151. Meezan’962 also discloses using alkyl glycosides in non-aqueous systems.

See pp. 0010-0011, ¶ 74 (**emphasis added**):

“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**,....

152. Thus, a POSA would be motivated to increase the solubility of diazepam given its lower potency as compared to other benzodiazepines and in recognition of limited water solubility. A POSA knows that, given two nares per human (one spray per naris), that a lower concentration can be employed to avoid salting out of diazepam in solution. A POSA knows that combining organic solvents (e.g., in a ternary system) typically improves/increases the amount of medication dissolved. Alcohols and tocopherols were clearly taught in the prior art patent disclosures.

153. Patent Owner also states that the antimicrobial properties of ethanol and benzyl alcohol would be inactivated and/or reduced in the presence of an alkyl glycoside. POR, p. 31. Therefore – according to Patent Owner – a POSA would be “less likely to look to a nonionic surfactant to combine with a formulation that already included ethanol and benzyl alcohol.” *Id.* This is an irrelevant statement for several reasons.

154. First, I agree with Dr. Gizurarson that ethanol is not known to be used as an antibacterial in benzodiazepine formulations for intravenous, intramuscular, intranasal, or rectal administrations. Dr. Gizurarson testified in this regard that “I

am not aware of a formulation containing ethanol as an antibacterial.” Gizurarson Dep., Ex. 1149, 78:15-21.

155. Second, the formulation in the final package has to be aseptic; there are no bacteria to kill. Therefore, whether or not the antimicrobial properties are inactivated is irrelevant. Thus, the POSA would not be led away from considering nonionic surfactants.

156. Moreover, 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. Microbiologic management is either terminal sterilization or aseptic processing.

B. A POSA HAD THE MOTIVATION TO COMBINE THE TEACHINGS OF GWOZDZ, MEEZAN’962 AND CARTT’784

157. A POSA would have been motivated to combine the teachings of Gwozdz, Meezan’962, and Cartt’784 with an expectation of successfully arriving at what is claimed in the ‘876 Patent, i.e., a method of successfully treating a patient.

158. It is my understanding that Patent Owner argues that a POSA would not have been motivated to combine these references. Patent Owner is wrong.

159. I have already addressed several of Patent Owner's arguments that a POSA would not have been motivated to combine Gwozdz and Meezan'962, and Gwozdz, Meezan'962, and Cartt'784.

160. A few of Patent Owner's remaining arguments against a motivation to combine are discussed below.

1. Contrary to Patent Owner's argument, a POSA would not be deterred from applying Meezan'962's teaching of the use of alkyl glycosides in connection with non-aqueous solutions.

161. I understand that Patent Owner argues that a POSA would not combine the non-aqueous solutions of Gwozdz with the alkyl glycosides of Meezan'962 because Meezan'962 focuses on aqueous solutions and that Meezan'962 does not disclose benzodiazepines. See, e.g., POR, pp. 24-26. Patent Owner is wrong.

162. First, Meezan'962 expressly discloses that its "pharmaceutically acceptable carrier" can be aqueous or non-aqueous. Meezan'962, Ex. 1011, ¶ [0074], p. 0010.

163. Second, notwithstanding Dr. Gizurarson's statements in his declaration, Dr. Gizurarson testified that he was unaware of any documents to support the position that alkyl glycosides could not be used in non-aqueous solutions. Gizurarson Dep., Ex. 1149, 85:2-6.

164. Third, as discussed above, Meezan’962 expressly discloses the use of alkyl glycosides with small, organic molecules, such as benzodiazepines. Meezan’962, Ex. 1011, ¶ [0130], p. 0015.

165. Fourth, notwithstanding Dr. Gizurarson’s statements in his declaration, Dr. Gizurarson testified that he was unaware of any documents to support the position that alkyl glycosides could not be used with benzodiazepines. Gizurarson Dep., Ex. 1149, 94:9-18.

2. Contrary to Patent Owner’s argument, a POSA would not be deterred from applying the teachings of Cartt’784 to the disclosures of Gwozdz. Rather, the POSA would be motivated to combine the two references.

166. I understand that Dr. Peppas provided the following discussion regarding Cartt’784 and its disclosure of i) particulates in suspension, and ii) particulates dissolved in aqueous and non-aqueous solutions (and I agree with it in its entirety):

“247. Cartt’784 appears to prefer that its benzodiazepines be in particulate form. *See, e.g.*, Cartt’784, Abstract. However, the dosage form itself may be ‘a nasal spray or nasal drop, although presently preferred embodiments are nasal sprays...[which] may be liquid or solid nasal sprays.’ Cartt’784, [0138], Exhibit 1015, p. 0029. Moreover, Cartt’784 acknowledges that ‘[i]t is also possible for the drug to be fully soluble in the liquid.’ Cartt’784, [0139], Exhibit 1015, p. 0029. In particular, the dosage form may be in the form of liquid

droplets which ‘may be formed from solutions...’ Cartt’784, [0139], Exhibit 1015, p. 0029. Additionally, Cartt’784 notes that its formulation ‘may be contained within the reservoir [of a delivery device], optionally in a liquid solution...’ Cartt’784, [0141], Exhibit 1015, p. 0029.

248. The solution itself may be a combination of the drug in a ‘non-aqueous medium.’ Cartt’784, [0139], Exhibit 1015, p. 0029. Although not explicitly mentioned in Cartt’784, a tocopherol would be such a non-aqueous medium.

249. Moreover, Cartt’784 classifies both ethanol and benzyl alcohol as useful solvents. Cartt’784, [0182], Exhibit 1015, p. 0033.”

167. I note that ¶ [0144] of Cartt’784 discusses that many benzodiazepines, including diazepam – which are slightly soluble in water – would be difficult to dissolve in a volume of aqueous solvent suitable for intranasal administration, such as 50 µL to 100 µL per nostril. I further note that ¶ [0144] does not apply to non-aqueous solvents, such as referred to in ¶ [0139], nor does ¶ [0144] apply to all benzodiazepines (such as the water-soluble midazolam).

168. I also agree with Dr. Peppas – and as recognized by the Board – that:

“Petitioner, with supporting testimony from Dr. Peppas, further argues that one of ordinary skill in the art ‘would not be deterred from incorporating the teachings of Cartt ’784, even though it is not specifically directed to solutions (instead disclosing intranasal particulate formulations)’ and ‘would easily adapt’ these teachings ‘to

the Gwozdz/Meezan '962 combination.' *Id.* at 34–35 (citing Ex. 1041 ¶¶ 257–260).” Decision, p. 32.

169. I further agree with the Board that “Petitioner sufficiently explains why one of ordinary skill in the art would have looked to Cartt’784’s disclosure when seeking dosing regimens for the compositions disclosed in Gwozdz and Meezan’962.” Decision, p. 32.

170. To be clear, it is my opinion that a POSA would have looked to Cartt’784 for its disclosure of dosing regimens (including dosing amounts and volume amounts) for benzodiazepines (including diazepam). Moreover, it is my opinion that a POSA would have combined Cartt’784’s disclosure of intranasal benzodiazepine (diazepam) dosing regimens with Gwozdz’ disclosure of intranasal benzodiazepine (diazepam) in ternary solvent systems, and further with Meezan’962’s disclosure of alkyl glycosides (penetration enhancers).

IX. THE ‘558 PROVISIONAL APPLICATION’S (EXHIBIT 1008) INCORPORATION BY REFERENCE OF THE SIGMA CATALOGUE (EXHIBIT 2006) DOES NOT CONVEY TO A POSA EITHER A DIRECTED DISCLOSURE OF ALKYL GLYCOSIDES AS ABSORPTION ENHANCER OR EVEN THAT THE INVENTORS KNEW THAT ALKYL GLYCOSIDES WOULD NECESSARILY WORK AS SUCH.

171. Paragraphs [150]-[152] of the ‘558 provisional application, shown below, discuss a host of enhancers and expansively defines “enhancer” as “any material which acts to increase absorption across the mucosa and/or increases bioavailability.” ‘558, ¶ 150 (**emphasis added**).

chromoglycate, codeine phosphate, and isoproterenol hydrochloride or pharmaceutically acceptable salts or combinations thereof.

[149] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional inactive ingredient in the composition. By way of non-limiting example, minor amounts of ingredients such as stabilizers, coloring agents, pH adjusters, buffering agents, preservatives such as agents which may prevent degradation, wetting agents, and flavoring agents may also be present. Examples of coloring agents include β -carotene, Red No. 2 and Blue No. 1. Examples of preservatives include stearic acid, ascorbyl stearate and ascorbic acid. Examples of corrigents include menthol and citrus perfume.

[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.

[153] In some embodiments, the invention takes advantage of delivery of a drug incorporated into or onto a bioadhesive microsphere with an added pharmaceutical adjuvant applies to systems that contain active drug and mucolytic agent, peptidase inhibitors or non-drug polypeptide substrate singly or in combination. Suitably mucolytic agents are thiol-containing compounds such as N-acetylcysteine and derivatives thereof. Peptide inhibitors include actinonin, amastatin, bestatin, chloroacetyl-HOLeu-Ala-Gly-NH.sub.2, diproton A and B, ebelactone A and B, E-64, leupeptin, pepstatin A, phisphoramidon, H-Thr-(tBu)-Phe-Pro-OH, aprotinin,

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

173. This disclosure is an expansive hodgepodge listing of candidates without providing any direction to the POSA as to which candidate(s) to choose, other than the preferred lysophospholipids and the alternative acyl carnitines.

174. The ‘558 provisional goes on to list a host of non-preferred candidates and classes in ¶ [152], without any direction as to choosing one candidate over another.

175. ¶ [152] makes reference to the Sigma Catalogue, 1988, pp. 316-321 (Ex. 2006), which lists about 150 biological detergents; of these, only a very small percentage (i.e., only about a dozen) are alkyl glycosides. I note that in its

Response, Patent Owner states that a POSA would understand the ¶ [152] disclosure of biological detergents as being limited to non-ionic detergents. *See* POR, Paper 16, p. 11, fn 5.⁵ However, because of ¶ [152]’s listing of both ionic and non-ionic candidates (there are many charged, polar molecules listed in addition to non-ionic molecules to choose from)⁶, the ¶ [152] disclosure does not exclude other (not non-ionic) candidates. Therefore, in my opinion, the ‘588 Provisional application does not identify with any detailed particularity that the biological detergents in the Sigma catalogue should be non-ionic.

176. Moreover, given the overall discussion of enhancing agents in ¶¶ [150]-[152] of the ‘588 Provisional application, it is my opinion that the ‘588 Provisional

⁵ I note that ¶ [152] discloses “surface active agents (especially non-ionic materials).” I agree with Dr. Gizurarson that ¶ [152] associates non-ionic materials with “surface active agents,” and I further agree with Dr. Gizurarson that ¶ [152] does not associate non-ionic materials with “biological detergents.” Gizurarson Dep., Ex. 1149, 51:18-52:9 Moreover, even if a POSA were to consider this disclosure as applying to the biological detergents in the Sigma catalogue, that would only reduce the number of candidates in the SIGMA catalogue to about 100 (meaning, of 100 candidates only about a dozen were alkyl glycosides).

⁶ ¶¶ [150]-[151] also disclose candidates that are not non-ionic.

application does not identify with detailed particularity that it is incorporating the alkyl glycosides referred to in the Sigma catalogue. A POSA looking at the more than 100 non-ionic candidates listed in the Sigma catalogue would have no reason – and is given no direction – to select alkyl glycoside(s) over other candidates. Additionally, it would require the POSA to conduct undue experimentation to determine whether any of the alkyl glycosides are i) useful, and ii) better than any of the other biological detergent candidates. The ‘588 Provisional did not – and does not – provide a POSA with any direction or sufficient disclosure to select alkyl glycosides as claimed in the ‘876 Patent.

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

X. THERE ARE NO UNEXPECTED RESULTS OR CRITICALITY ASSOCIATED WITH ANY OF THE RECITED ALCOHOL RANGES OR AMOUNTS

178. The ‘876 Patent does not show criticality with respect to the amounts of ethanol and benzyl alcohol, as recited in the claims. Referring to the ‘876 Patent’s Figs. 1–3, Tables 4-1, 11-1, 11-2, and 11-3, the Board stated that “Petitioner’s assertion that Patent Owner never showed any unexpected results is not sufficiently supported by the evidence of record.” Paper 08, p. 19. I disagree because nowhere do Figs. 1–3, Tables 4-1, 11-1, 11-2, and 11-3 support or demonstrate any unexpected results or criticality.

179. Notwithstanding Patent Owner’s statements that the solution’s alcohol ranges provide unexpected results or criticality in the form of higher bioavailability than non-alcoholic suspensions, the ‘876 Patent does not demonstrate unexpected results or criticality with respect to the ranges/amounts of ethanol and benzyl alcohol, as recited in the claims. Institution Decision, Paper 08, pp. 18-19.

180. Furthermore, the Board relied on the ‘876 Patent’s Figs. 1–3, Tables 4-1, 11-1, 11-2, and 11-3 in stating that “Petitioner’s assertion that Patent Owner never showed any unexpected results is not sufficiently supported by the evidence of record.” Paper 08, p. 19. The “evidence” consists of:

- (a) Figs. 1–3 (graphical representations of the data upon which Table 11-3 is based);

- (b) Table 4-1 (alternate alcohol-free suspension formulations without any bioavailability data);
- (c) Table 11-1 (solution formulation referred to in Table 11-3);
- (d) Table 11-2 (suspension formulation referred to in Table 11-3); and
- (e) Table 11-3 (which is the PK data for solution and suspension formulations in Tables 11-1 and 11-2, respectively).

I disagree because, as I discuss below, nowhere does the Board’s “evidence” support or demonstrate any criticality or unexpected results.

181. For convenience, the table below has been generated from Tables 11-1 and 11-2 and from Claims 1, 8, and 15:

Formulation Comparisons Table		
U.S. Patent No. 9,763,876 Claim Limitation	'876 Patent Table 11-1 (Solution) (Col. 60, ll. 10-20)	'876 Patent Table 11-2 (Suspension) (Col. 61, ll. 1-10)
Claim 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 pharmaceutical composition comprising diazepam was prepared as a composition formulated as a solution to be delivered via a nasal delivery device...." (Col. 60, ll. 4-6.)	"The suspension formulation is set forth in Table 11-2...." (Col. 60, l. 66) <i>*contains WATER</i>
a benzodiazepine drug,	10% (w/v) Diazepam	100 mg/ml (10%) Diazepam
one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);	56.47% α -Tocopherol (vitamin E)	10 mg/ml (1.0%) Vitamin E TPGS
ethanol and	About 18.07% ethanol	
benzyl alcohol	10.50% Benzyl Alcohol	
in a combined amount from about 10% to about 70% (w/w); and	Combined amount is about 28.57% (see above)	
an alkyl glycoside.	0.25% Dodecyl maltoside	2.5 mg/ml (0.25%) Dodecyl maltoside
Claim 8		
Claim 15		
ethanol from 1 to 25% (w/v)	About 18.07% ethanol	
ethanol from 10 to 22.5% (w/v)		
benzyl alcohol from 1 to 25% (w/v).	10.50% Benzyl Alcohol	
benzyl alcohol from 7.5 to 12.5% (w/v).		
Additional Ingredients		
		78% Water (carrier) 10% Propylene glycol (dispersant) 0.5% Povidone (suspending agent) 0.2% Methylparaben (preservative) 0.05% Propylparaben (preservative)

182. As shown in the Formulation Comparison Table above, Tables 11-1 and 11-2⁷ are significantly different formulations with very limited similarities. The only similarities are that they contain diazepam and alkyl glycoside.

A. A POSA Would Have Known that Tocopherols Contribute to Increased Bioavailability.

183. It is also noteworthy that the solution contains a combination of alcohols and tocopherol; this combination is not present in the suspension. Gwozdz teaches that the combination of tocopherols and alcohol(s) increases bioavailability. Therefore, the bioavailability of the solution would be expected to be due (at least in part) to the presence of the combination of alcohol(s) and tocopherol in the solution (not just the range or amounts of alcohols, as the Board assumed). *See Gwozdz, Ex. 1014, p. 0007, lines 3-11.*

184. Therefore, based on at least Gwozdz, a POSA would have predicted and expected the resultant bioavailability of the Table 11-1 solution as compared to the Table 11-2 suspension (as shown in Table 11-3).

⁷ Tables 11-1 and 11-2 are the solution and suspension formulations referred to in Table 11-3.

B. A POSA Would Have Expected Solutions to Have Higher Bioavailabilities Than Suspensions

185. As discussed below, a POSA would recognize that neither unexpected results nor the criticality of alcohol(s) ranges/amounts can be supported by comparing a **solution with alcohol(s)** to a **suspension without any alcohol(s)**, as Patent Owner attempts to show in Table 11-3. This is an apples-and-oranges comparison.

186. It would have been obvious to a POSA that a solution would provide better bioavailability than a suspension. Therefore, a POSA would expect that the solution⁸ in Table 11-3 would inherently have better bioavailability than the suspension⁹ in Table 11-3.

187. A drug that is in solution does not go through another dissolution once it is applied to a mucosa. However, a drug that is in suspension *does* need to be dissolved prior to absorption (otherwise, it is akin to pushing a grain of sand through your skin). Therefore, a solution formulation, by definition, provides the best chance for absorption because the drug is already in solution.

⁸ That is, the solution formulation disclosed in Table 11-1.

⁹ That is, the suspension formulation disclosed Table 11-2.

C. Diazepam is 100% Bioavailable For Nasal and Oral Absorption

188. Table 11-3 relates only to diazepam solutions and suspension. The ‘876 Patent discloses that the diazepam solution demonstrates a 96% bioavailability (as compared to intravenous). See ‘876 Patent, 62:18, Ex. 1001, p. 0040. A POSA would not have looked at the bioavailability of the Table 11-3 solution as providing any information as to the bioavailability of the solution with other benzodiazepines. The reason is that both the nasally-administered solution and the nasally-administered suspension are actually nas-orally absorbed¹⁰, and therefore involve first pass metabolism effects. Diazepam is 100% bioavailable. See Ritschel Ex. 1077, pp. 0006; Goodman & Gillman, Ex. 1074, p. 0003; Valium® 2008 product label (>90%), Ex. 1080, p. 0001. However, other benzodiazepines do undergo first pass metabolism and therefore have less than 100% bioavailability. For example, midazolam has about 24-50% oral bioavailability; clonazepam has 75% oral bioavailability; and lorazepam has 85% oral bioavailability. See Knoester, Ex. 1043, p. 0005 (midazolam); Ritschel, Ex. 1077,

¹⁰ Dr. Gizurarson confirmed that the solution and suspension disclosed in Table 11-3 were nasally and orally absorbed. Gizurarson Dep., Ex. 1149, 123:12-125:3.

p. 0006 (clonazepam), p. 0007 (lorazepam). Therefore, the bioavailability data in Table 11-3 is solely limited to diazepam.

189. Therefore, the data from Table 11-3 cannot support any criticality or unexpected results for solutions claimed by the '876 Patent reciting benzodiazepines in general versus diazepam specifically.

190. Bioavailability is unique to the diazepam molecule, and with minor differences, will not greatly change when in solution regardless of the relative amounts of benzyl alcohol and ethanol used to dissolve the diazepam molecule into a solution. Therefore, regardless of the % of ethanol and benzyl alcohol within the ranges disclosed, and so long as the diazepam is fully dissolved, the bioavailability is relatively predictable.

191. I note that the last row of Table 2 in ¶ 78, above, *appears* to indicate that the bioavailability of nasally administered diazepam in PEG 300 is 42% - however, Table 2 does not actually make such an indication. Table 2 itself is reproduced from one of my papers (Exhibit 1151); I took the data for the last row of Table 2 from a paper by Lindhardt et al. (Ex. 1025) – the second author of which is Dr. Gizurarson. A closer review of the Lindhardt-Gizurarson paper reveals that its 42% value is not actually the bioavailability of its tested intranasal diazepam formulation.

192. Lindhardt-Gizurarson was a pharmacokinetic/pharmacodynamics study, so their study design was entirely different from a study intended to evaluate bioavailabilities. Therefore, instead of reporting a true bioavailability based on AUC(0- ∞), Lindhardt-Gizurarson only reported a partial AUC, i.e., an AUC that is generally calculated only until approximately the T_{max}; here, Lindhardt-Gizurarson calculated only AUC(0-60minutes). Due to diazepam's long half-life (which can be a full day or more; see PDR, Ex. 1042, p. 0002), a POSA would have understood that 60 minutes is nowhere near enough time for determining actual bioavailability for diazepam. In fact, Lindhardt's Figure 1 graph (Ex. 1025, p. 0003) indicates that the curve for the 7mg intranasal diazepam formulation was still *increasing* at 60 minutes (when the graph ended) – a POSA would understand this to mean that AUC was still increasing and that bioavailability could not be accurately calculated based on the partial AUC(0-60minutes). Others have also concluded that Linhardt-Gizurarson's bioavailability values are likely underestimated based on diazepam's long half. See Ivaturi, Exhibit 1028, first col., p. 0004.¹¹

¹¹ “Given that the half-life of DZP [diazepam] ranges from 24 to 48 h, [Lindhardt-Gizurarson's] bioavailability values are likely an under-estimate of the actual extent of absorption.”

193. I suspect that Patent Owner is also aware that 1 hour is not a long enough time period to calculate diazepam bioavailability, as evidenced by their '876 Patent's Figures 1-3 – instead of just 1 hour, Patent Owner's figures are pharmacokinetic graphs that extend out for 240 hours, 240 hours, and 24 hours, respectively. See '876 Patent, Ex. 1001, Figs. 1-3 (pp. 0005-0007), 8:53-9:3 (pp. 0013-0014), and 62:6-11 (p. 0040).

194. Another problem with relying on Lindhardt-Gizurarson's 42% value is that it apparently experienced some problems with precipitating out. See Ex. 1025, p. 0006, left column (discussing "precipitation in the nose"). If the diazepam did precipitate out and was swallowed, 60 minutes is not enough time to be absorbed ultimately into the bloodstream. To be clear, if the diazepam is swallowed, it *will* eventually be absorbed (i.e., yielding the expected ~100% bioavailability of diazepam) – however, such absorption will take more than 60 minutes due to several factors (e.g., half-life and the way in which diazepam is absorbed in the gastrointestinal tract). Therefore, any diazepam that was swallowed in Lindhardt-Gizurarson's study would not show up in their results (based on the short 60-minute test procedure), thereby resulting in the very low 42% value. To be clear, the Lindhardt-Gizurarson report of 42% bioavailability for an intranasal diazepam formulation is a mischaracterization and does not change the fact that diazepam is known to have a 100% bioavailability.

D. The Table 11-3 data for the solution is not evidence of any criticality associated with the recited claim ranges for ethanol and benzyl alcohol.

195. It is my understanding that Patent Owner claims that the bioavailability associated with the Table 11-1 diazepam solution was an unexpected result compared to the bioavailability of the Table 11-2 diazepam suspension, due (at least in part) to the presence of ethanol and benzyl alcohol in the specified (critical) amounts in the diazepam solution. The bioavailability data is disclosed in Table 11-3.

196. Even if a POSA would consider the comparison in bioavailability between the solution and suspension of Table 11-3 to be meaningful, which it is not (see discussion above), the data provided in Table 11-3 does **not** provide evidence of any criticality associated with the recited claim ranges for ethanol and benzyl alcohol.

197. Furthermore, only one bioavailability data point ($AUC_{0-\infty}$) is provided for the alleged higher bioavailability of the solution of Table 11-3, and then only for diazepam (not for any other benzodiazepine). The one data point is the $AUC_{0-\infty}$ for a diazepam solution having 10.5% benzyl alcohol and 18.07% ethanol (dehydrated).

198. It is my opinion that to determine the criticality of the ranges of ethanol and benzyl alcohol with respect to any claimed unexpected results requires a sufficient

number of tests both inside and outside the claimed ranges. Moreover, in order to establish criticality, a sufficient number of tests would have to establish that amounts inside the ranges demonstrate unexpected results, while also demonstrating that the amounts outside the ranges do not demonstrate unexpected results. **One test is not sufficient.**

199. Moreover, the sufficient number of tests would have to be scientifically valid. To be scientifically valid, the tests should further include examples wherein, e.g., the ethanol is within the claimed range but the benzyl alcohol is outside the claimed range (and vice versa). Also, in this case, the test should include comparisons of one solution with another solution. Obviously, and it is my opinion, the Table 11-3 comparison of a diazepam solution to a diazepam suspension does not qualify as a scientifically valid experiment to determine any unexpected results due to particular ranges of ethanol and benzyl alcohol. Otherwise, there is no way to determine whether the unexpected results (if any) are solely due to the ethanol amounts, solely due to the benzyl alcohol amounts, or solely due to the combination of ethanol and benzyl alcohol amounts. The '876 Patent did not disclose the necessary number of tests and associated experimental data to validate any claim of unexpected results.

200. Finally, the '876 Patent claims are not all limited to diazepam but many claims include all benzodiazepines. One cannot establish criticality of ethanol and

benzyl alcohol ranges for all benzodiazepines based solely on a single solution containing diazepam. A scientifically valid test for criticality of all benzodiazepines requires that a sufficient number of different types of benzodiazepines in solution should be tested – not just one diazepam solution (as is the case with the ‘876 Patent).

201. Certainly, neither I nor a POSA would consider the ‘876 Patent’s one data point based on one test for bioavailability to be sufficient to establish the criticality or any unexpected results associated with the ranges of ethanol and benzyl alcohol recited in the claims of the ‘876 Patent. **One test is not sufficient.**

202. Certainly, neither I nor a POSA would consider that a test of a single diazepam solution with a specific amount of ethanol and a specific amount of benzyl alcohol is sufficient to establish the criticality in the claimed ranges of amounts of ethanol and benzyl alcohol for any benzodiazepine in solution (not just diazepam). Moreover, neither I nor a POSA would consider that a test of a single diazepam solution with a specific amount of ethanol and a specific amount of benzyl alcohol is sufficient to establish the criticality in the claimed ranges of amounts of ethanol and benzyl alcohol for diazepam in solution. **One test is not sufficient.**

1. Nasally-Administered Diazepam's 100% Nas-Oral Bioavailability

203. Furthermore, considering diazepam's 100% bioavailability for nasal+peroral ("nas-oral") absorption, a POSA would expect near 100% bioavailability irrespective of the amounts of benzyl alcohol and ethanol in the solution.

Therefore, there are no critical amounts of either alcohol required in order to achieve a 100% nas-oral bioavailability for a diazepam solution.

204. The '876 Patent claims recite broad ranges of benzyl alcohol and ethanol for benzodiazepine solutions. A POSA would have no reason to expect that the bioavailability of the Table 11-3 diazepam solution with its nas-oral absorption would be applicable to other benzodiazepine solutions. As discussed, other benzodiazepines have much lower oral bioavailabilities: midazolam has about 24-50% oral bioavailability; clonazepam has 75% oral bioavailability; and lorazepam has 85% oral bioavailability. See Knoester, Ex. 1043, p. 0005 (midazolam); Ritschel, Ex. 1077, p. 0006 (clonazepam), p. 0007 (lorazepam).

205. For the above reason, a POSA would not have expected that the bioavailability of the Table 11-3 diazepam solution would be achieved by solutions of other benzodiazepines, even with the exact same amounts of alcohols (even with the exact same ternary co-solvent system).

**2. No Data Regarding Bioavailability of Solutions Having
Benzyl Alcohol and Ethanol Other Than in Table 11-3
(10.5% benzyl alcohol and 18.07% ethanol (dehydrated))**

206. The '876 Patent only tests the bioavailability of the diazepam solution provided in Table 11-3 (which has 10.5% benzyl alcohol and 18.07% ethanol (dehydrated)). Thus, it did not disclose any test for the bioavailability of diazepam solutions having any other amounts of benzyl alcohol and ethanol. Furthermore, it did not disclose any test for the bioavailability of any benzodiazepine solutions, other than diazepam, for any amounts of benzyl alcohol and ethanol. Therefore, the '876 Patent provides no data or support for the criticality of any particular ranges of benzyl alcohol and ethanol in combination, or in specific amounts (other than the exact amounts disclosed in Table 11-1, for which the bioavailability was disclosed in Table 11-3).

207. Therefore, the '876 Patent disclosure regarding bioavailability and amounts of alcohols (ethanol and benzyl alcohol) do not demonstrate any unexpected results or criticality.

**XI. A POSA WOULD INCLUDE BENZYL ALCOHOL IN AN
INTRANASAL SPRAY FOR ADDRESSING ACUTE LIFE
THREATENING HEALTH SITUATIONS, NOTWITHSTANDING
ANY IRRITATION THE BENZYL ALCOHOL MIGHT CAUSE**

208. In considering whether to include a nasal irritant (such as benzyl alcohol) in a life-saving nasal spray, a POSA would accept the potential for irritation in favor

of saving the life of the patient. The POSA would therefore use the best available solvents without regard to whether they may cause irritation. In fact, as discussed above, Florida EMS used diazepam intravenous solutions – which had benzyl alcohol – for nasal administrations in connection with seizures. See EMS, Ex. 1069, pp. 0029-0030, 0037-0039.

209. Dr. Gizurarson cites to one of my patents as unequivocally stating that the presence of benzyl alcohol in a particular IV composition for lorazepam made it unacceptable for intranasal administration. Gizurarson Dec. ¶¶ 90-92, Exhibit 2012.¹²

210. It is important to consider the full quote from my patent, which is provided below.

“A suitable liquid composition for use in a spray device for intranasal administration includes a solvent in which the desired concentration of

¹² Interestingly, Dr. Gizurarson testified that in his patent applications he himself has disclosed the use of benzyl alcohol for intranasal applications. Gizurarson Dep., Ex. 1149, 75:11-21. As will become important shortly, Dr. Gizurarson has disclosed that “in the case of acute health threatening indications, a relative high local irritation to the mucosa may be acceptable.” Gizurarson US Publication No. 2008/0275030, Ex. 1070, ¶ [0004], p. 0002.

lorazepam can be attained to provide the desired unit-dose in a total sprayed liquid volume that can be delivered by the device and accommodated and absorbed by the subject's nasal mucosa. Lorazepam is insoluble in water. A commercially available injectable composition approved by the FDA and sold by Wyeth Laboratories under the brand name Ativan®, includes 2 mg of lorazepam in 0.18 mL of polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as a preservative. This composition was not acceptable for intranasal spray administration because benzyl alcohol is irritating to the mucosa.”

US Patent No. 6,610,271, 6:25-39, Exhibit 2014.

211. I agree that for most chronic administration uses, an excipient such as benzyl alcohol (which is irritating to the nasal mucosa), would be unacceptable. However, in cases of acute lifethreatening indications such as epileptic seizures, a relatively high local irritation to the mucosa is acceptable. My ‘271 patent quoted above was directed to the use of lorazepam as a sedative and to treat conditions of anxiety. These are not life-threatening situations. Nowhere in my ‘271 patent do I refer to, e.g., epileptic seizures or other life-threatening situations. Thus, my statement about benzyl alcohol as not being acceptable does not apply to intranasal use of lorazepam in such life-threatening situations. That is to say, the risk-benefit analysis in the face of acute health threats favors the use of organic solvents (such as benzyl alcohol) for what should be an infrequent use by a patient (such as in the case of epileptic seizures).

XII. CONCLUSION

212. Based on the foregoing it is my opinion that claims 1-16 and 24-36 of U.S. Patent No. 9,763,876 would have been obvious to a POSA in view of Gwozdz and Meezan'962, and that claims 17-23 would have been obvious to a POSA in view of Gwozdz, Meezan'962 and Cartt'784.

213. A POSA would have been motivated to combine these references because, as discussed above, they all relate to optimizing the intranasal administration of drugs. The teachings in these references could be readily modified by a POSA in predictable ways, without undue experimentation and with a reasonable expectation of success to obtain the claimed intranasal solutions and treat the patient.

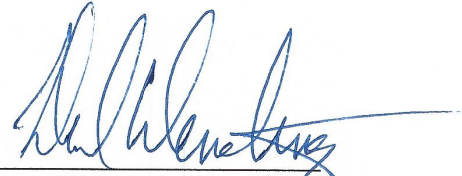
214. In particular, as discussed above, a POSA would have had a reasonable expectation of success in arriving at the '876 Patent's claimed invention by starting with Gwozdz' disclosure of intranasal benzodiazepine (diazepam) in ternary solvent systems, looking to Meezan'962's disclosure of alkyl glycosides (penetration enhancers) to increase the rate and amount of drug absorbed through the nasal mucosa, and looking to Cartt'784 for its disclosure of dosing regimens (including dosing amounts and volume amounts) for benzodiazepines (including diazepam). Moreover, arriving at the claimed invention would not have required undue experimentation.

IPR2019-00451

U.S. Patent No. 9,763,876

215. I declare under penalty of perjury that the foregoing is true and correct.

Executed on this the 27th day of January 2020.

A handwritten signature in blue ink, appearing to read "Daniel P. Wermeling", is written over a horizontal line.

Daniel P. Wermeling, Pharm.D.

APPENDIX A

AQUESTIVE EXHIBIT 1150



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DANIEL P. H. WERMELING, Ph.D.

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II. EDUCATION

Fellowship:
1985-87

Drug Product Evaluation Unit
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University of Kentucky
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Residency:
1983-85

University Hospital
Albert B. Chandler Medical Center
University of Kentucky
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Doctor of Pharmacy:
1977-83

College of Pharmacy
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III. PROFESSIONAL EXPERIENCE

Emeritus Professor, University of Kentucky. April 2018 - Present

Professor (with tenure – Special Title Series)
College of Pharmacy, University of Kentucky
2011 to 2018

CEO and Founder, AntiOp Inc., 2009 - Present

Associate Professor (with tenure – Special Title Series)
College of Pharmacy, University of Kentucky
1998 – 2011

Chief Scientist
Intranasal Therapeutics, Inc.
2004-2006

Senior Vice President and Chief Operating Officer
Intranasal Technology, Inc.
2002 – 2004 (unpaid leave of absence)

Scientific Director, Kentucky Center for Clinical Research & Investigator Services,
University of Kentucky Medical Center
1997 – 2000

Director, Investigational Drug Service
Department of Pharmacy
A B Chandler Medical Center
1990 – 2000

Associate Research Professor and Director
Drug Product Evaluation Unit
Center for Pharmaceutical Science and Technology
College of Pharmacy, University of Kentucky
1994 – 1998

Assistant Research Professor and Director
Drug Product Evaluation Unit
Center for Pharmaceutical Science and Technology
College of Pharmacy, University of Kentucky
1990 – 1994

Clinical Research Associate
Merrell Dow Research Institute
Cincinnati, Ohio
1988 – 1990

Coordinator - Bristol-Myers Industrial Clerkship
Investigational Drug Pharmacist
Assistant Director of Hospital Pharmacy

University of Kentucky Medical Center
1987 – 1988

Research Fellow – Drug Product Evaluation Unit, College of Pharmacy University of
Kentucky
1985 – 1987

Pharmacy Resident - University of Kentucky Medical Center
1983 – 1985

IV. ACADEMIC APPOINTMENTS

Emeritus Professor, University of Kentucky, 2018 - Present

Professor (with tenure – Special Title Series)
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2011 – 2018

Associate Professor (with tenure – Special Title Series)
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1998 – 2011

Associate Research Professor
Associate Member of the Graduate School Faculty
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University of Kentucky
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1994 – 1998

Assistant Research Professor
Associate Member Graduate School Faculty
Division of Pharmacy Practice & Science
College of Pharmacy
University of Kentucky
907 Rose Street
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1990 – 1994

V. HOSPITAL OR CLINICAL APPOINTMENTS

Assistant Director of Pharmacy – Obstetrics and Psychiatry
Investigational Drug Pharmacist
University Hospital
Albert B. Chandler Medical Center
Lexington, KY
1987 – 1988

Director, Investigational Drug Service
Department of Pharmacy
University Hospital
Albert B. Chandler Medical Center
Lexington, KY
1990 – 2000

VI. Consulting History

Scientific Consulting

NX Development Corporation – 2018 - Present

Alltech Inc. – 2011 – 2014
Alzheimer's Disease Early Stage Product Development

LiPoint Inc. 2008-2009
Nasal Drug Development

Celgene and Novartis – 2008 - 2009
Patent Analysis

Apotex Pharmaceuticals 2007-2008
Patent Analysis

The Round Table Group 2007-
Drug Development Consulting

Biovail Corporation 2006
Drug Delivery for Pain Management

Boston Life Sciences – 2005–6
Intrathecal Analgesia Delivery

Cydex Corporation – 2005
Nasal Formulation Approach

Intranasal Technology, Inc. 2004 - 2008
Nasal Drug Delivery

Purdue Pharma – 2003 – 2004
Oxycodone Pharmacokinetics & Pharmacodynamics

Intranasal Technology Inc.
1998 – 2001

Pain Care Incorporated
1994 – 1995

NIH Master Agreement for the Clinical Evaluation of
Investigational Anti-Epileptic Drugs - Co-Investigator
1993 – 1999

Health Economics Research
Propofol Pharmacoeconomic Evaluation
1992 – 1994

Hoffman LaRoche Pharmaceuticals
TAT Antagonist – Antiretroviral Pharmacokinetics
1992

Evaluation of Drug Interactions
Chapter 2 Anesthetic Drug Interactions
1988 – 1998

Litigation Consulting History

I have testified as an expert at trial or by deposition in the following matters:

- *GlaxoSmithKline Inc. v. Apotex Inc.*, No. T-1780-07 (Canada Fed. Ct.)
- *Estate of Vivian Caudill v. Sarah Belhausen*, No. 08-CI-00252 (Johnson Circuit Court, Kentucky)
- *Estate of Arthur C. McChesney, Jr. v. Saint Joseph Healthcare Inc.*, No. 08-CI-872 (Fayette Circuit Court, Kentucky)
- *Estate of Bonnie Cocanougher v. Saint Joseph Healthcare, Inc.*, No. 07-CI-2897 (Fayette Circuit Court, Kentucky)
- *Wyeth and Cordis Corp. v. Abbott Labs and Boston Scientific*, C.A. No. 3:08-CV-00230-JAP-TJB, District of New Jersey
- *Wyeth and Cordis Corp. v. Medtronic and Abbott*, C.A. No. 08-1021-JAP-TJB, District of New Jersey

VII. TEACHING ACTIVITY

Graduate Program Teaching

2007- 2009	CME 599/PS 760 Buccal and Nasal Drug Delivery, 2 contact hours
2004 - 2018	PPS 764 Drug Development Regulation and Clinical Research Methods, Primary Instructor, 3 credit course 26 of 43 contact hours. This is a required course for Clinical and Experimental Therapeutics Ph.D. program students.
2004	PHR 760-009 Introduction to Translational Research (Co-instructor), 2 credit course, 8 contact hours
2001	PHR 760 Introduction to Drug Development and Clinical Research – (Primary Instructor)
2001	NIH K-30 Elective Course in Clinical Research

Professional Program Courses

2015- 2018	PHR 914 – Clinical Reasoning. Course Designer and Instructor
2012- 2017	PPS 946 Introduction to Therapeutics– PY2 Course Director and Pain Management Module Leader
2012- 2017	PPS 895 – Independent Problems in Pharmacy Practice Emma Hatfield Amanda Robinson Abbey Bailey Elizabeth Riner Leann Hewlett
2008-11	PS 924 – The Drug Development Process – 3 contact hours
2006 - 2018	PPS 564 Introduction to FDA & the Drug Development Process – 2 credit hours elective – Primary Instructor
2006- 2012	PPS 946 - PY 2 Spring Semester Pain Management Module Leader – 23 contact hours
2004-05	PHR 956-7 Fall Semester, Pain Management Module Leader and Primary Lecturer PY 3 Therapeutics, 23 contact hours
1994-1999	Pharmacy Seminar (PHR 890)
1993-2002	Nervous Systems (PHR 851)
1992-2001	Pharmacy Practice Clerkship (PHR 866)
1991-1999	Advanced Institutional Practice Management (PHR 833)
1991-2001	Independent Problems in Clinical Pharmacy (PHR 895)
1988	Implications of Drug Therapy for Nurses (NUR 866)
1987-1988	Bristol-Myers Industrial Clerkship
1986-1988	Institutional Pharmacy Practice (PHR 880)
1986-1988	Applied Therapeutics I & II (PHR 866-868)
1986-1988	Clinical Orientation Clerkship (PHR 870)

Hospital Pharmacy Residency

Supervise 6-7 pharmacy residents per year (1 – 2 month rotations) who participate in a Clinical Drug Development Rotation. Residents obtain first hand experience in clinical research administration and conduct. 1990 – 1998

Post-Doctoral Fellow Training

Carinda Field, Pharm.D. (fellow)
1991 – 1993

Charles Xie, M.D., Ph.D. (fellow)
1996 – 1997

Graduate Students

Anna Hitron, Pharm.D., Masters Degree Candidate 2009-10, Committee Member

Ben Chamberlain, BS, mentor for NIH GCRC mentored student program. 2007-08

Committee Member for Jennifer King, Ph.D., Department of Gerontology
2004-2009

Committee Member for Jennifer Oh, Pharm.D., (thesis masters student and fellow) 2004-06

Mentor for Jodi L. Miller, Pharm.D., M.S. (non-thesis masters student and fellow)
2000 – 2002

Committee Member for Doug Hiser, D.D.S., M.S. (non-thesis masters student in College of Dentistry) 1998 – 1999

Mentor for Lance Piecoro, Pharm.D., M.S. P. H. (non-thesis masters student and fellow)
1995 – 1998

VIII. ADVISING ACTIVITY

2 new PYI students per year – 1990-1998

IX. ADMINISTRATIVE ACTIVITY AND UNIVERSITY, STATE AND NATIONAL SERVICE

University of Kentucky

University Senate Council - 2011
University Senator – 2008-2011
Senate Academic Program Committee 2008-2010

College of Pharmacy Committees

Conflict of Interest Committee 2017- 2018
College Accreditation Subcommittee Chair – 2014-15
Student Affairs Committee – 2013-15
Academic Performance Committee – 2012- 2018
Nominations Committee - 2011
Conflict of Interest Committee 2009-2018
Faith Pharmacy Student Advisory Committee 2009 – 2011
Curriculum Committee (Chair) 2009
PPS Department Graduate Education and Research Committee 2006 - 2009
Appointment, Promotion and Tenure 2005 - 2008
Practice Plan Committee 2005 – (chair 2009-10)-2009
Advisor to Associate Dean for Research on Clinical Research 2004-2009
College of Pharmacy Executive Committee, 2000 – 2001
Nominations Committee, 1999 –2001
College Practice Plan Committee, 1997 – 1999
PPS Division Practice Plan Expenditure Committee, 1997 – 1999
Clinical Pharmacology Oversight Committee, 1994 – 1999
Division Research/Computer Equipment Committee, 1993 – 1997
Co-Advisor Pre-pharmacy Club, 1994 – 1996
Co-Advisor Pre-pharmacy Club, 1994 – 1996
Residency and Seminar Committee, 1990 – 1991
Student Advisor Committee, 1984 – 1985
Curriculum Committee, 1983 – 1985

Hospital Committees

Corporate Compliance Committee 1999-2000
Research Subcommittee, 1999 – 2000
Integrated Clinical Information System, 1998 – 1999
Clinical Research Reengineering Task Force, 1995 – 1997
Health Enterprise Research Information Committee, 1997
Residency Research Committee, 1995 – 2000
Resident Advisor Committee, 1990 – 1991
Resident Advisor Committee, 1990 – 1991
Obstetric Service Task Force, 1987 – 1988
Resident Advisor Committee, 1985 – 1987
Pharmacy Computer Search Committee, 1985 – 1986

College of Medicine Committees

NIH Clinical Research Center Clinical Trials Scientific Review Committee – 2008-14
NIH Scientific Advisory Committee, Center for Clinical and Translational Research, University of Kentucky Medical Center, 2008-
NIH General Clinical Research Center Scientific Advisory Committee 2005 - 2008
NIH General Clinical Research Center/Advisory Committee, 1996 – 2001
NIH General Clinical Research Center/Drug Product Evaluation Unit Space Committee, 1993 – 2001

NIH General Clinical Research Center/Drug Product Evaluation Unit Operations Subcommittee, 1993 – 2001

University Committees

CCTS Drug Development Advisory Committee, Therapeutics Advisory Committee 2012- 2018
CCTS Data Safety and Monitoring Board 2010 - 15
Clinical and Translational Science Award (CTSA), Therapeutics Advisory Committee 2009-15
Clinical Research Task Force – 2004 - 2006
Institutional Bio-safety Committee – Ex-Officio, 1998 – 2000
KCCRIS Advisory Committee – Ex-Officio, 1997 – 2000
Research Process Planning Committee, 1997 – 2000
Medical Institutional Review Board – Ex-Officio Member, 1993 – 2000

Commonwealth of Kentucky

6th Congressional District Drug Abuse Task Force sponsored by US Congressman Andy Barr. 2015 - 2017

Kentucky Life Science Organization – State science and development leaders advising the Governor on life science economic development policy, 2004 - 2007

KLSO Executive Committee and Founding Board Member, 2004 - 2007

National Committees

American College of Clinical Pharmacy – Research Institute Fund Committee - 2010 - 2016

American College of Clinical Pharmacy – Credentials Committee – Fellowship Evaluation Subcommittee 2009 - 15

American College of Clinical Pharmacy – Blue Ribbon Task Force on Pharmacometrics. 2008-2009

American College of Clinical Pharmacy, Research Affairs Committee, Chair, Subcommittee on national pharmacy practice based research networks. 2007-08

National Institutes of Health, Gene and Drug Delivery Systems Study Section for SBIR/STTR Grants, July 10, 2006

National Institutes of Health, Gene and Drug Delivery Systems Study Section for SBIR/STTR Grants, November 28, 2005.

National Institutes of Health, Gene and Drug Delivery Systems Study Section Review Committee, November 17-18 2005

American College of Clinical Pharmacy, Task Force on Research in Special Populations, 2005-6

American College of Clinical Pharmacy, Research Committee, 1998 – 1999

American Society of Health-System Pharmacists, PALS Program, 1997 – 1999

American Society of Health-System Pharmacists, Council on Professional Affairs,
1996/97 & 1997/98 & 1998/99

University Health System Consortium Benchmarking Committee, 1997 – 1999

American Society of Health-System Pharmacists, Facilitator – Section of Clinical
Specialists – Investigational Drugs and Clinical Research, 1995 – 1997

American College of Clinical Pharmacy, Credentials Committee, 1995
Chair, 1996-1997, 1997 – 1998
Chairman, 1995 – 1996

American College of Clinical Pharmacy, Women's Health Care PRN
Chairman Elect, 1994 – 1995

American College of Clinical Pharmacy, Special Task Force on Women's Health
& Education Issues, 1991 – 1993
Vice Chairman, 1993 – 1994

American College of Clinical Pharmacy, Research Affairs Committee, 1991 –
1992, Vice Chairman, 1992 – 1993

American Society of Hospital Pharmacists Nominee for Position on FDA OTC
Drug Advisory Committee, October 1991

Liaison, University Health-System Consortium Clinical Research & Investigator Services,
1990 – 1999

ASHP Drug Therapy Research Awards Program Selection Panel, 1999 – 2000

X. SPECIAL ASSIGNMENTS

Senator – University of Kentucky 2008-2011, Senate Council 2011

University of Kentucky Human Gene Therapy Task Force, 1998 – 1999

Special Assistant to the Dean, 1999-2001

XI. HONORS

William T. Miles Award – May 2017

Thomas S. Foster Lecturer – September 2015

WR Martin Mentoring Senior Resident Research Award, Department of Psychiatry, University of Kentucky, 2009

Recipient, American College of Clinical Pharmacy Research Institute Award, 2007

Fellow, American College of Clinical Pharmacy (FCCP), October 2006

Kentucky Colonel, from Governor Ernie Fletcher, for research entrepreneurship in the Commonwealth of Kentucky, January 2006

Fellow, American Society of Health System Pharmacists (FASHP), June, 1998

Kentucky Society of Hospital Pharmacists
Research Pharmacist of the Year, 1988

XII. PROFESSIONAL ACTIVITY AND PUBLIC SERVICE

Organizations

American College of Clinical Pharmacology 2008-14
American College of Clinical Pharmacy 1990-
Kentucky Society of Hospital Pharmacy 1990 -
Phi Delta Chi (Pharmaceutical Fraternity) 1990-94
American Pharmaceutical Association 1990 - 2000
American Society of Health-System Pharmacists 1983-
Society of Research Administrators – 1990-97
American College of Research Professionals – 1994-97
Drug Information Association – 1994-97
American Association of Pharmaceutical Scientists 2000-2003

Journal Reviewer

Addiction 2018 x 2
Pharmacotherapy 2017
Pediatrics 2017
Addiction 2017
Pediatrics 2016
Expert Opinion in Drug Delivery 2016
Alcohol and Drug Dependence 2016
Addiction 2016
Journal of Clinical Pharmacology 2015
Pharmacotherapy 2015
Journal of Opioid Management 2015
Journal of Opioid Management 2014
Therapeutic Delivery 2014
Pediatrics 2014
Journal of Opioid Management 2013
Pharmacotherapy 2013
Currents in Pharmacy Teaching and Learning 2013

Annals of Internal Medicine 2012
 Journal of Opioid Management 2012
 Advanced Drug Delivery Reviews 2012
 Advanced Drug Delivery Reviews 2011
 Pharmacotherapy 2011
 Journal of Pharmacy and Pharmacology 2011
 Lancet 2010
 Expert Opinion in Drug Delivery 2010
 Journal of Clinical Pharmacology 2010 x2
 Journal of Clinical Anesthesia 2009
 European Journal of Pain 2009
 Journal of Drug Targeting 2009
 The Journal of Pain 2009 x 2
 Journal of Pain and Symptom Management 2009
 Pharmacotherapy 2009
 Journal of Clinical Pharmacology 2009 x 2
 Clinical Therapeutics 2009
 Epilepsy Research 2008
 BMC Pharmacology 2008
 Expert Opinion on Pharmacotherapy 2008 x2
 Journal of Pharmacy Practice and Research 2008
 Pharmacotherapy 2008
 Drug Benefit Trends 2007
 The Journal of Pain 2007
 Yonsei Medical Journals 2007
 Expert Opinion in Drug Discovery 2007
 Pharmacotherapy 2007
 Biopharmaceutics and Drug Disposition 2007
 Journal of Clinical Anesthesia 2006
 BMC Clinical Pharmacology 2006
 Pharmacotherapy – 2006
 Johns Hopkins Advanced Studies in Medicine 2006
 Journal of Pharmacy and Pharmacology 2006
 Drugs of Today 2006
 Drug Profiles 2006
 Journal of the American Board of Family Practice 2005 -
 The Annals of Pharmacotherapy – 1987-
 American Journal of Hospital Pharmacy 1987-
 Drug Intelligence and Clinical Pharmacy 1987- 1995
 The Journal of Pharmacy Technology 1990-91
 Journal of Pharmaceutical Sciences – 1990-91

Reviewer of Proposals

ACCP Women's Education Foundation – Foundation Awards Program Selection
 Panel 1997-2000
 ASHP Foundation Award – Innovative Clinical Pharmacy Research – 1997-2000

Reviewer of Abstracts

Judge: Best poster submission. ACCP Spring Meeting April 27, 2009.

For ACCP for publication in Journal of Pharmacology, Pharmacotherapy 1991-2001, 2004 – 2017

XIII. INVITED SPEAKING ENGAGEMENTS

International

- | | |
|------|--|
| 2013 | International Conference on Opioids. Expand Access to Naloxone for High Risk Patients. June 10, 2013, Boston, MA. |
| 2012 | International Nasal and Buccal Delivery, 2012. Intranasal Delivery of Pharmaceuticals for Systemic Drug Administration. April 22, 2012, London, UK |
| 2012 | FDA/CDC/NIDA Conference on Expanded Access to Naloxone. Intranasal Delivery of Naloxone for Treatment of Suspected Opioid Overdose. April 12, 2012. Bethesda, MD |
| 2010 | International Nasal Drug Delivery 2010. Intranasal Delivery of Opioid Antagonists. April 14 th , 2010. London, UK |
| 2008 | International Nasal Drug Delivery 2008. "Intranasal Delivery of Analgesic Compounds: Experience with Hydromorphone in Acute Trauma Pain. April 8 th , 2008, London, UK |
| 2008 | New Horizons in the Development of Antiepileptic Drugs: Non-traditional Approaches to Treat Epilepsy Conference. "Intranasal Delivery of Anti-epileptic Medications". March 7, 2008, Dublin, Ireland |
| 2007 | 10 th Annual Nasal Drug Delivery Conference. "Where is Nasal Delivery Research Headed? " February 8, 2007, London, UK. |
| 2006 | Biovail Pain Management Forum. "Drug Delivery Approaches Employed in Pain Management Pharmacotherapy." December 15, 2006. New York, NY. |
| 2005 | ATACCC 2005 Conference – Advanced Technology for Combat Casualty Care. "Needle-Free, Self-Administered Nasal Hydromorphone for the Rapid Treatment of Moderate to Severe Acute Pain." Sponsored by the Army and Navy Casualty Care Research Programs and the Air Force Surgeon General. Tampa, FL, August 16, 2005 |
| 2005 | Eighth Annual Anti-epileptic Drug Conference, "Intranasal Delivery of Benzodiazepines for the Treatment of Seizure". March 2005, Biscayne, FL |

- 2004 Practical Approaches to Nasal and Pulmonary Drug Delivery II, "Nasal Delivery of Analgesics for Acute and Break-Through Cancer Pain", Valois Nasal and Pulmonary Delivery Conference, Delray Beach, Florida
- 2003 Management Forum LTD – Sixth International Conference Exploring the Rapidly Developing Area of Nasal Drug Delivery, "Nasal Drug Delivery Opportunities in Pain Management Therapeutics", London, England
- 2002 Technology Catalysts – 19th Annual International Technology Transfer Forum, "Nasal Delivery of Medications for the Central Nervous System", Reston, Virginia
- 2002 Management Forum LTD – Fifth International Conference Exploring the Rapidly Developing Area of Nasal Drug Delivery, "Design of Products for Acute, Subacute, and Chronic CNS Medical Indications", London, England
- 2001 Strategic Research Institute – 6th International Drug Delivery Technologies and Deal Making Summit, "Nasal Drug Delivery: A Leading Edge Technology for Systemic Delivery", Princeton, New Jersey

National

- 2016 National Drug Abuse Summit. Drug Product Selection Considerations for New Naloxone Products. Atlanta GA Apr 2016
- 2014 Collaborative Perspectives on Addiction. Opioid Overdose: Intervention Efforts and Challenges. Atlanta, GA March 1, 2014.
- 2013 Feasibility and Due Diligence in Drug Development. National SBIR Meeting, October 25, 2013, Souix Falls, SD.
- 2009 University of Colorado College of Pharmacy. Leadership in Academic Departments of Clinical Pharmacy. Denver, CO May 21, 2009.
- 2007 Medical University of South Carolina. Nasal Drug Delivery of Medications for the Treatment of Alcoholism. January 5, 2007. Charleston, SC.
- 2006 National Institute of Alcohol Abuse and Alcoholism – Nasal Drug Delivery as an Interventional Approach to Alcohol Drug Therapy, NIH, June 20, 2006, Rockville, MD
- 2006 University of Chicago College of Medicine – "Nasal Drug Delivery – Pharmacotherapy Option and Research Tool". May 12, 2006, Chicago, IL
- 2005 American College of Clinical Pharmacy – Spring Research and Practice Meeting, Navigating Research: "Patient Safety, Privacy and Funding Issues", April 7, 2005 Myrtle Beach, SC.

2001 Institute for International Research – Inhalation Technology Conference, “Nasal Drug Delivery: A Leading Edge Technology for Systemic Delivery”, Boston, Massachusetts

2001 MedTech Insight, Investment in Innovation – A Preview of Early-Stage Medical Technology Companies, “Nasal Drug Delivery: A Leading Edge Technology Platform for Drug Delivery”, New York, New York

2000 American College of Clinical Pharmacy, “Pharmacokinetics (PK) of Intranasal Hydromorphone (HM) in Healthy Subjects”, Los Angeles, California

1999 Massachusetts Society of Health-System Pharmacists, “Managing Issues Related to Clinical Research”, Boston, Massachusetts

1999 Corporate Compliance and Clinical Research, University Health System Consortium, Chicago, Illinois

1998 Society of Research Administrators, “Addressing the Investment in Clinical Research”

1998 American Society of Health-System Pharmacists, “Is Your Pharmacy Ready for Gene Therapy?”

1997 American Society of Health System Pharmacists Annual Meeting, “Clinical Research: Regulatory Issues”

1996 Society of Research Administrators, “How to Prepare for a Successful FDA Audit for a Clinical Investigator or IRB”

1995 American Society of Health-System Pharmacists, “New NIH and FDA Guidelines Regarding Women’s Participation in Clinical Research”

1993 Auburn University, Annual Clinical Practice and Research Forum, “Development of a Clinical Research Unit”

1992 Burroughs Wellcome Company, Inc., “First Time in Man Drug Trials”

1991 American Society of Hospital Pharmacists, “Managing Grant Funds: The University Perspective”

1991 Applied Research Ethics National Association (ARENA), “Handling Equitable Selection”

1991 American College of Clinical Pharmacy, “Women’s Participation as Research Subjects”

1988 St. Louis Society of Hospital Pharmacists, “Pharmacy Considerations for Implementing a PCA Program in Your Hospital”

- 1987 American Society of Hospital Pharmacists, "Evaluation of the Travenol Infusor with Patient Control Module as a PCA Device for Treatment of Postoperative Pain"
- 1987 Georgia Society of Hospital Pharmacists, "Pharmacy Considerations for Implementing a PCA Program in Your Hospital"
- 1986 Intravenous Nurses Association of Northwest Florida, "Patient-Controlled Analgesia and the Cancer Patient"
- 1986 Indiana Society of Hospital Pharmacists, "Patient-Controlled Analgesia: Implementation of a Clinical Service Program"
- 1986 American Society of Hospital Pharmacists, "Patient-Controlled Analgesia: Implications for Patient Care and Pharmacy Services"
- 1986 Butorphanol Tartrate Symposium: Research Advances in Multiple Clinical Settings, "Patient-Controlled Analgesia for Postoperative Pain: Streamlining Drug Delivery for Pain Management"
- 1985 American Society of Hospital Pharmacists. "Patient-Controlled Analgesia: Parallel Development of the Research Tool and Clinical Service Program"
- 1985 Ohio Conference on Clinical Pharmacy and Clinical Pharmacology, "Patient Controlled Analgesia"
- 1984 Southeastern Residents Conference, "Pentobarbital Coma in Refractory Cerebral Edema"
- 1984 American Society of Hospital Pharmacists, "Osmolality of Injectable Drugs in Minibags: Predicted vs. Actual Value"

State

- 2016 Increasing Access to Naloxone in your Community. Continuous program given 1-2 times per month in the Commonwealth of KY. March 2016 -
- 2015 Factors to Consider When Starting A Pharmaceutical Company – a Regulatory Perspective. KSTC Regulatory Summit, Lexington, KY November 19, 2015
- 2014 Harm Reduction Involving Expanding Access to Opioid Antidote Naloxone. AHEC May 28, 2014. Morehead, KY.
- 2013 A Harm Reduction Strategy: Expand Access to the Opioid Antidote Naloxone. The Good, The Bad and The Ugly. UKMC CE Central and Department of Justice, Commonwealth of Kentucky. August 3, 2013.

2012 College of Pharmacy Continuing Education Series and Alumni Weekend October 19, 2012. Opioids and Risk Evaluation and Risk Mitigation Strategies (REMS): Collaborative Professional, Patient Education, and Patient Care Activities

2012 OVALS (Ohio Valley Life Science Associates) October 2, 2012. "Observations of Academic Pharmaceutical Start Up Companies".

2008 University of Kentucky College of Pharmacy Continuing Education Series, Fall Meeting, October 17, 2008. "Emerging Drug Delivery Systems for the Treatment of Pain."

2006 University of Kentucky College of Pharmacy Continuing Education Series, Fall Meeting, October 6, 2006. "Multi-modal, Mechanism Based Approaches to Treatment of Chronic Non-Malignant Pain".

2004 University of Kentucky, Health and Medical Care Delivery Systems – HSM 241, "Intranasal Technology, Inc.: A Leading Edge Specialty Pharmaceuticals Company", Lexington Kentucky

2003 University of Cincinnati, Biotechnology and Pharmaceutical Management Course, "Intranasal Technology, Inc.: A Leading Edge Specialty Pharmaceuticals Company", Cincinnati Ohio

2001 The Entrepreneurship Committee of the Greater Louisville Health Enterprises Network, Life Sciences Investor Forum "Intranasal Technology, Inc. A Leading Edge Drug Delivery Company", Louisville Kentucky

1996 Sanders-Brown Center on Aging, Conference for Pharmacists, "Considerations in Conducting Clinical Trials with Alzheimer's Disease Patients"

1986 Kentucky Pharmacists Association, "Patient-Controlled Analgesia: Implementation of a Clinical Service Program"

1985 Kentucky Pharmacists Association, "New Concepts in Pain Management"

1984 Intravenous Therapy and Nutrition Technology Update for 1984, University of Kentucky College of Pharmacy Continuing Education Program, "Preparing Drugs in the Pharmacy for Patient Administration – Concern for pH, Osmolality, and Drug Concentration"

Local

2016 Opioid Overdose Recognition and Training on Naloxone Administration. Trips to local agencies for in-service training and naloxone dispensing (Numerous) March 2016 - 2018

2015 Thomas S. Foster Lectureship. "Living The Dream". UK College of Pharmacy, September 25, 2015

2015 Video CE Lecture. Naloxone for Opioid Overdose Prevention. Department of Justice, Commonwealth of KY. September, 2015

2015 CCTS Clinical Research Update. Research and Commercialization of Naloxone Nasal Spray. November 10, 2015.

2015 Chrysalis House. Use of Naloxone At Home for Opioid Overdose Prevention. April 10, 2015, Lexington, KY

2014 Naloxone for Community Opioid Overdose Prevention: Radio Interview WUKY March 26, 2014

2014 Pharmacists Role in Expanding Access to Naloxone. Bluegrass Pharmacists Association. March 25, 2014

2008 "The Drug Approval Process". Transylvania University, Lexington, KY Pre-professional Degree Student Forum, May 12, 2008

2007 "Drug Development in the United States". NIH GCRC Mentored Student Lecture Series, July 23, 2007.

2007 "Nasal Drug Delivery for Treatment of Alcoholism". NIH General Clinical Research Center lecture, March 12, 2007.

2006 "Translational Research in Nasal Drug Delivery". Center for Drug and Alcohol Translational Research, University of Kentucky, March 6, 2006

2001 "Making New Drugs in the Bluegrass: Public-Private Partnership" Fasig-Tipton, Lexington Kentucky, Sponsored by the Lexington Rotary Club

2001 Start Up @ 5, Sawyers Downtown, Lexington Kentucky, Sponsored by Kentucky Science and Technology Corporation

2000 "Evolution of Faculty Research into a New Economy Business" Hyatt Regency, Lexington, Kentucky, Sponsored by UK Board of Trustees

1996 Channel 36-TV interview with Sandy Gray, "Making Sense of Medications Today"

1994 Department of Psychiatry Grand Rounds

1994 Investigational Drugs for Treatment of Sepsis at the University of Kentucky Medical Center, Radisson Hotel, Lexington, Kentucky, September 12, 1994

1993 "Drug Development Opportunities: Psychiatric Drug Evaluation"

XIV. PATENTS ISSUED

Intranasal Naloxone Compositions and Methods of Using Same.

AntiOp Patent 9,289,425

Date of Patent: March 22, 2016

Issued To; AntiOp

Intranasal Naloxone Compositions and Methods of Using Same.

AntiOp Patent 9,192, 570

Date of Patent: November 24, 2015

Issued To; AntiOp

"Intranasal Opioid Compositions"

Patent no. US 8,198,291 B 2

Date of Patent: June 12, 2012

Issued to: Daniel Wermeling and Assigned to University of Kentucky

"System and Method for Intranasal Administration of Lorazepam"

Patent No.: US 6,610,271

Date of Patent: August 26, 2003

Issued to: Daniel Wermeling

"Programmable Multi-Dose Intranasal Drug Delivery Device"

Patent No.: US 6,948,492

Date of Patent: September 27, 2005

Issued to: Daniel Wermeling and co-inventors

"Programmable Multi-Dose Intranasal Drug Delivery Device"

Notice of Allowance March 9, 2009

US Patent Application No.: 11/204,611

Patent No. 7,559,321

Date of Patent: July 14, 2009

Issued to: Daniel Wermeling and co-inventors

Patents Submitted / Pending as Primary Inventor

Pharmaceutical Compositions Comprising an Opioid Receptor Antagonist and Methods for Using Same.

US2007/0212307

Intranasal Delivery of Antipsychotic Drugs

WO 2006/023497A2

US20060039869A1

Composition & Methods for Intranasal Delivery of Tricyclic Cannabinoids

US-2007-0060639-A1

PCT/US2006/034562

"System and Method for Intranasal Administration of Opioids"

Pub. No.: US 20030077300 A1

Pub. Date: April 24, 2003

"Intranasal Benzodiazepine Compositions "

Pub. No. US 20040176359

"Intranasal Opioid Compositions"

Pub No. US 20040115133

XV. INDs NDAs SUBMITTED TO THE FDA

INDs

Cimetidine Injection 1991 (SKB contract)

DSPC Liposome 1994 (The Liposome Company contract)

Ondansetron Nasal Spray 1996 (GSK contract)

Hydromorphone Nasal Spray 1998 (Intranasal Technology Inc. contract)

Butorphanol Nasal Spray 1998 (Intranasal Technology Inc. contract)

Lorazepam Nasal Spray 1999 (Intranasal Technology Inc. contract)

Midazolam Nasal Spray 1999 (Intranasal Technology Inc. contract)

Haloperidol Nasal Spray 2000 (Intranasal Technology Inc. contract)

Naloxone Nasal Spray 2012 (AntiOp Inc., f/k/a Alcomed Inc.)

NDAs

Naloxone Nasal Spray # 205678

XVII. PEER REVIEWED RESEARCH AND CREATIVE PRODUCTIVITY

Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Daniel Wermeling. Therapeutic Advances and Drug Safety. 2015, 6(1) 20-31.

Prescribe Naloxone to Reduce Opioid Mortality. Daniel Wermeling, Catherine Martin. Journal of American Academy of Child and Adolescent Psychiatry. Jan 2015 Page 256.

Intranasal Administration of Naloxone Injection for the Treatment of Opioid Overdose. Amanda Robinson, **Daniel Wermeling** American Journal of Health System Pharmacy. 2014 71: December 15 2014

Naloxone for Opioid Overdose Prevention: Pharmacists Role in Community Based Practice Settings. Abby Bailey, **Daniel Wermeling.** Annals of Pharmacotherapy 2014, 48 (5) 601-606.

Survey of Naloxone Legal Status in Opioid Overdose Prevention. Lee Ann Hewlett, **Daniel Wermeling.** J Opioid Mgmt. 2013 Sep-Oct 9(5) 369-377.

A Response to the Opioid Overdose Epidemic: Naloxone Nasal Spray. Daniel Wermeling. Drug Delivery and Translational Research, 2014, Volume 3, Issue 1, 63-74.

Comparison of the Behavioral and Cardiovascular Effects of Intranasal Dextroamphetamine. Joshua A. Lile, Shanna Babalonis, Cleeve Emurian, Catherine A. Martin, **Daniel P. Wermeling** and Thomas H. Kelly. Journal of Clinical Pharmacology, 2011, 51 Jun; 888-898.

Opioid Harm Reduction Strategies: Focus on Expanded Access to Intranasal Naloxone. Wermeling, DP. Pharmacotherapy 2010; 30 (7).

A Multicenter, Open-Label, Dose-Ranging Trial of Intranasal Hydromorphone for Managing Acute Pain from Traumatic Injury. Wermeling, DP, Clinch TC, Rudy AC, Dreitlein D, Sumer S, LaCouture P. The Journal of Pain 2010 11 (1) 24-31.

Intranasal Delivery of Antiepileptic Medications for the Treatment of Seizures. Wermeling DP. Neurotherapeutics 2009 Apr; 6: (2) 352-358.

A Pharmacokinetic and Pharmacodynamic Study, in Healthy Volunteers, of a Rapidly Absorbed Intranasal Midazolam Formulation. Wermeling, DP, Record KE, Archer SM, Rudy AC. Epilepsy Research 2009 83: 124-132.

Clinical Research in Special Populations: ACCP White Paper. Cheang KI, Ott C, Garnber S, Cambell H, Hansen L, Ma Q, Nazeri E, Gunning K, **Wermeling DP.** Pharmacotherapy 2008 28 (9) 1203-1206.

A Pharmacokinetic Profile of Intranasal Hydromorphone in Emergency Room Trauma Patients. Lacotoure P, Dreitlein D, Suner S, Hefti F, Clinch T, Pike D, **Wermeling, D.** The Journal of Pain 2008 9 (4) suppl (2) 36-41.

A Pilot Pharmacokinetic Study of Nasally Delivered Haloperidol Compared to Intravenous and Intramuscular Administration. Wermeling D, Ashford W, Archer S, Rudy A, Miller J. Pharmacotherapy 2008; 28: 875-882.

Microneedles Permit Transdermal Delivery of a Skin-Impermeable Medication to Humans. Wermeling DP, Banks SA, Hudson DA, Gill HS, Prausnitz M, Stinchcomb AS. Proceedings of the National Academy of Sciences 2008, Feb 12, 108: (6) 2058-63.

Intranasal Absorption of Delta 9 tetrahydrocannabinol and WIN 55,212-2mesylate in rats. Valiveti S, Agu RU, Hammell DC, Paudel KS, Earles DC, **Wermeling DP.** Stinchcomb AS. Eur J Pharm Biopharm 2006, Aug 23.

Pharmacokinetics and Pharmacodynamics of a New Intranasal Midazolam Formulation in Healthy Volunteers. Wermeling DP, Record K, Kelly TH, Archer SM, Clinch T, Rudy AC. *Anesthesia and Analgesia* 103 (2) August 2006

Ziconotide Infusion for Severe Chronic Pain: A Case Series of Patients with Neuropathic Pain. Wermeling DP, Berger JR., *Pharmacotherapy* 2006; 26 (3), 395-402.

Pharmacokinetics, Bioequivalence and Dose Reproducibility of Intranasal Butorphanol After Administration with Two Different Nasal Spray Pumps. Wermeling DP, Miller JL, Archer SM, Rayens MK, Rudy AC., *Journal of Clinical Pharmacology* August 2005; 45 (8): 969-73.

A Review of Ziconotide, an N-Type Calcium Channel Antagonist, Delivered by Intrathecal Administration for the Treatment of Chronic Pain. Wermeling, DP. *Pharmacotherapy* 2005; 25 (8) 1084-94.

A Randomized, Double-Blind, Parallel-Group Study Comparing the Analgesic Effects of Intranasal Butorphanol Tartrate to Placebo, Using a Unit Dose Nasal Spray Device, in the Dental Impaction Pain Model. Wermeling, DP, Grant GM, Lee A, Alexander N, Rudy AC. *Clinical Therapeutics* 2005; 27 (4): 430-440.

Bioavailability of Intranasal Butorphanol Administered from a Single-dose Sprayer. Davis GA, Rudy A, Archer SM, Wermeling, DP. *American Journal of Health System Pharmacy* 2005 62 (1): 48-53

A Multiple Dose Phase 1 Study of Intranasal Hydromorphone Hydrochloride in Healthy Volunteers. Rudy AC, Coda BA Archer SM, Wermeling DP. *Anesth Analg* 2004 99 (5): 1379-86.

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Grant Activity

Funded Grants

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NIH NIDA. Grant Number: 2R42DA030001-04. May 1 2013 – April 30 2016. \$2.97 M Total.
University of Kentucky Sub-Award of \$ 300,000 per year for 3 years.
Role: Principal Investigator

Kentucky Science and Technology Corporation (KSTC). Matching Award to Phase 2 of
NIDA 2 R 42DA030001-01 – April, 1 2012. \$ 500,000
Role: Principal Investigator

Kentucky Science and Technology Corporation (KSTC). Matching Award to Phase 1 of
NIDA 1 R 42DA030001-01 – Feb, 1 2011. \$ 150,000
Role: Principal Investigator

NIH NIDA 1R42DA030001-01 – “Intranasal Naloxone: An Opioid Overdose Antidote”.
\$1,451,714 in total/2 years. UK Contract Portion \$ 430,055. 2010-2012.
Role: Principal Investigator

Clinical and Translational Science Award (CTSA), Therapeutics Advisory Committee
2009-2011, 5% effort.

ACCP Frontiers Award – “fMRI Imaged Neuroactivation and Craving in Alcoholics is
Modulated by Ondansetron”. American College of Clinical Pharmacy, \$ 30,000, August
2007. Role: Principal Investigator.

NIH MO1RR02602 – Priority Score 150 – Alcohol Related fMRI Imaged Neuroactivation
and Craving: Part A Imaging Validation; Part B Medication Administration. October
2007, Role: Principal Investigator.

NIH – R41HD055009-01, A Device Containing Immobilized Chelator to Remove
Aluminum in TPN Solutions. October 2007, 2.5% effort, Role: Subinvestigator

NIH 1R41AA016500-01, Priority Score 161, Nasal Delivery of Naltrexone for the
Treatment of Alcoholism: Role: Principal Investigator 10% effort. National Institute on
Alcoholism and Alcohol Abuse, \$ 100,000, June 2006.

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Evaluate Effects on Human Cognition, Mood and Brain Function. NCRR 2.5% effort.
Role: Subinvestigator.

The Effects of Intranasal Corticotropin Releasing Hormone on Cortical and Subcortical
Information Processing. PI Royce Lee, M.D. \$ 1000 per year for 2 years. Role – Co-
Investigator on grant from Brain Foundation and subcontract from University of Illinois
Chicago. April 2006.

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Co-investigator \$ 3000/yr. NARSAD Foundation and University of Illinois subcontract.
April 2006

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\$379,970 1999

A Double Blind, Randomized, Placebo-Controlled, Parallel Study to Investigate the Safety, Tolerability and Pharmacokinetics of Multiple Oral Doses of GW572016 in Healthy Volunteers, Glaxo EFG10002 (Co-Principal Investigator)
\$671,627 2000

ITI Infrastructure, Project #4 (DPEU). Inhalation Technology, Inc. (Principal Investigator)
\$2,177,587 2000-1

A Single-Dose, Open-Label, Three Way Crossover, Randomized, Pilot Bioavailability Study of Lorazepam Comparing Intranasal Administration to Intravenous and Intramuscular Administration in Healthy Human Volunteers, Inhalation Technology, Inc. (Principal Investigator)
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\$160,896 1998

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\$55,633 1999

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\$74,374 1998

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\$81,236 2000

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\$142,173

Open-Label Extension Study of Continuous Subcutaneous Infusion of Sufentanil Citrate for the Treatment of Chronic Pain. Pacific Research Assoc. (Principal Investigator), 1999
\$99,918

Application to FDA for Notice of Suitability. Inhalation Technology, Inc. (Principal Investigator), 1999
\$49,832

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\$56,283

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\$914,201

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A Single Blind, Open-Label, Three-Way Crossover Pilot Bioavailability Study of Hydromorphone HCL Comparing IN to IV and IM Administration in Healthy Human Volunteers. Inhalation Technology, Inc. (Principal Investigator), 1998
\$56,283

Open-Label Dose-Filtration Study of Continuous Infusion of Sufentanil Citrate for the Treatment of Chronic Pain. Durect Corp. (Principal Investigator), 1998
\$38,054

A Phase II Pilot Study of Ziconotide (SNX-111) Administered by Bolus Epidural Injection in Patients with Chronic Pain. Neurex/Elan Pharmaceuticals (Principal Investigator), 1998
\$116,713

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\$50,000

Alza E-Trans (Fentanyl) Protocol C-94-057. Paraxel (Principal Investigator), 1998
\$17,800

A Prospective, Randomized Single-Blind Crossover Comparison Study of the Safety and Efficacy of Apothecon-Warfarin and DuPont-Warfarin in the Treatment of Patients with Atrial Fibrillation. Apothecon/UHC (Sub-Investigator), 1998
\$75,045.47

Single-Site, Phase II, Open-Labeled, Rising Dose, Feasibility, Safety & Efficacy Study of SNX-111 Administered Intrathecally in Bolus Doses for Chronic Pain. Neurex (Principal Investigator), 1998
\$136,754

An Open-Label, Long-Term Safety and Tolerability Study of Ziconotide® Administered Intrathecally to Patients with Chronic, Severe Pain. Elan Pharmaceuticals (Principal Investigator), 1998
\$117,200

Multidisciplinary Clinical Research Training Program. National Institutes of Health (Sub-Investigator)
\$1,080,000 (5 yr. budget – approx. \$216,000 each year) submitted

A Four-Way Crossover, Dose Study of Flunisolide Administered Through Intravenous Injection, Oral Solution, and Oral Inhalation System (AEROBID) With and Without the Spacer (AEROCHAMBER) in Normal Healthy Male or Female Volunteers. Forest Laboratories (Principal Investigator), 1997
\$148,000

A Double-Blind, Parallel Group, Placebo-Controlled Study of Intravenous Kytril (Granisetron Hydrochloride) in the Treatment of Post-Operative Nausea and Vomiting in Patients Undergoing Elective Surgery with General Anesthesia. Smith-Kline Laboratories (Principal Investigator), 1996-1997
\$20,000

A Multicenter, Phase II, Placebo-Controlled Pilot Study of SNX-111 Administered Intrathecally to Patients with Acute Postoperative Pain. Neurex (Co-Principal Investigator)
\$36,000

The Effects of Renal Dysfunction on the Pharmacokinetics and Pharmacodynamics of Suramin in Cancer Patients. Parke-Davis Laboratories (Co-Principal Investigator)
\$19,000

Investigation of the Influence of Topical Application of Glycolic Acid on the Percutaneous Penetration of Model Penetrants Through Human Skin in Vivo. Hilltop Research (Co-Principal Investigator)
\$27,120

A Double-Blind, Placebo Controlled Trial of Metrifonate in Patients with Probable Alzheimer's Disease. Bayer, Inc. (Principal Investigator)
\$152,400

An Open Label Extension Trial of Metrifonate in Patients with Probable Alzheimer's Disease. Bayer, Inc. (Co-Investigator)
\$98,400

A Phase I/II Open Label, Rising Dose, Safety and Feasibility Study of SNX-111 Administered Intrathecally to Patients With Intractable Chronic Pain. Neurex (Co-Principal Investigator)
\$33,500

A Trial of Recombinant Methionyl Human Brain Derived Neurotrophic Factor Given By Daily SQ Injection to Patients With Amyotrophic Lateral Sclerosis. Amgen (Co-Investigator)
\$318,500

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Finding, Safety and Tolerability Trial of R-IGF-1 in Patients With Acute Kidney Failure. Chiron (Co-Investigator)
\$117,400

Double-Blind, Randomized, Placebo-Controlled, Parallel Group Trial of the Efficacy and Safety of Enlimomab Compared to Placebo Administered Within 6 Hours of Onset of Stroke Symptoms for Treatment of Acute Ischemic Stroke. Boehringer-Ingelheim (Co-Investigator)
\$109,200

Cervene Modification of Outcome in Patients with Acute Ischemic Stroke: a Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Dose Comparison Study by 24 Hour Infusion. Baker-Norton Pharmaceuticals (Co-Investigator)
\$86,400

A controlled pilot study of 1,25(OH)D-3 (calcitriol) in the treatment of Alzheimer's Disease. NIH Program Project Grant - Specific Aim 2 (Co-Investigator)
Salary savings, 7.5% FTE (approx. \$9,000/yr)

A Double-Blind, Placebo-Controlled Trial of Anti-Tumor Necrosis Factor in Patients with Severe Sepsis. Bayer (Co-Investigator)
\$158,000

A Multi-Center, Pharmacokinetic and Pharmacodynamic Study of Dofetilide in Subjects With Stable Atrial Fibrillation (AF) and Reduced Left Ventricular Ejection Fraction, Pfizer (Co-Investigator)
\$128,931

A Double-Blind, Randomized, Placebo-Controlled, Dose-Response, Study of Inhaled Nitric Oxide 9OHM-11771) in the Treatment of Acute Respiratory Distress Syndrome (ARDS) Ohmeda (Co-Investigator)
\$175,240

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Intravenous Ondansetron for the Treatment of Postoperative Emesis in Pediatric Patients Undergoing Outpatient Surgery -Glaxo (Co-Investigator)
\$30,000

An Open-Label Study of the Pharmacokinetics of Venlafaxine in Extensive and Poor Metabolizers of Dextromethorphan-Phase I Phenotype Study Wyeth-Ayerst (Co-Investigator)
\$144,888

A Double-Blind Comparison of Sertindole and Haldol^R: An Assessment of the Chronic Safety, Efficacy, Quality of Life and Relapse in Stable Schizophrenic Patients (M93-132) Outpatient-Abbott Labs (Co-Investigator)
\$174,019

A Double-Blind, Placebo-Controlled, Dose-Response Comparison of the Safety and Efficacy of Three Doses of Sertindole and Three Doses of Haldol^R in Schizophrenic Patients (M93-113) Inpatient Abbott Labs (Co-Investigator)
\$106,192

Tricyclic Versus Serotonin Specific Reuptake Inhibitor Anti-Depressant in Low Back Pain, Pain Care Inc. (Co-Investigator)
\$12,243

A Trial of Recombinant Methionyl Human Brain-Derived Neurotrophic Factor (f-tHuBDNF) Given By Daily Subcutaneous Injection to Patients with Amyotrophic Lateral Sclerosis (ALS) Amgen (Co-Investigator)
\$136,500

Phase I Pilot Study Evaluating the Effect of Study-State CP- 99219 On the Pharmacokinetics of Theophylline in Healthy Male Subjects Pfizer (Co-Investigator)
\$77,113

A Randomized, Double-Blind, Multi-Center Trial Comparing 7 Days of Oral Therapy With CP-99219 (100 mg or 200 mg daily) or Ciprofloxacin Hydrochloride (500 mg daily) for the Treatment of Uncomplicated Urinary Tract Infections Pfizer (Principal Investigator)
\$35,973

Erythromycin Citrate: Bioequivalency Study-Baxter Healthcare Corporation (Principal Investigator)
\$110,664

Randomized, Placebo-Controlled Trial of E5 Antiendotoxin Monoclonal Antibody in Patients With Severe Sepsis Pfizer (Co-Investigator)
\$55,000

A Placebo-Controlled Study to Determine the Effects of 500mg, 1000mg and 2000mg Citicoline in Ischemic Stroke Patients Parexel (Co-Investigator) \$83,460

The Safety and Efficacy of Tiagabine HCL Monotherapy in the Treatment for Partial Seizures: High Dose Versus Low Dose Abbott (Co-Investigator)
\$90,809

A Double-Blind, Placebo-Controlled, Dose Finding Study to Evaluate the Safety and Efficacy of Three Different Doses of Metrifonate (BAY A 9826) in Patients with Probable Alzheimer's Disease Miles (Co-Investigator)
\$221,000

Prospective, Double-Blind, Placebo-Controlled, Randomized, Multi-Center, North American Study of the Safety and Efficacy of Murine Monoclonal Antibody to Tumor Necrosis Factor (TNFMAb) for the Treatment of Patients With Septic Shock Miles (Co-Investigator)
\$162,073

A Randomized, Double-Blind, Placebo-Controlled Study of Intravenous Ondansetron Versus Droperidol For the Prevention of Post-Operative Nausea and Vomiting In Outpatient Surgery. Glaxo (Principal Investigator)
\$75,000

A Phase III Study of r-metHuG-CSF in the Treatment of Severe Community Acquired Pneumonia (CAP) Amgen (Co-Investigator)
\$78,750

A Randomized, Double-Blind, Placebo-Controlled Trial Testing the Efficacy of Tirilazad Mesylate in Patients With Acute Ischemic Stroke (RANTTAS) (The Upjohn Company) NIH (Co-Investigator)
\$75,000

A Double-Blind, Randomized, Multi-Center Study of the Safety and Recovery Profiles of Tracrium, Norcuron, and Pavulon in Intensive Care Patients Who Require Neuromuscular Blocking Agents to Facilitate Mechanical Ventilation. Burroughs Wellcome (Co-Investigator)
\$46,803

Phase I Safety and Tolerance Study of IP-AD-32 in Patients with Refractory Cancer Confined to the Peritoneal Cavity. Theradex (Co-Investigator)
\$24,155

A Double-Blind, Placebo-Controlled, Randomized, Single-Center Study of the Safety, Tolerability, and Pharmacokinetics of Metrifonate. Miles (Co-Principal Investigator)
\$352,898

A Phase II/III Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Safety and Efficacy Study of Recombinant Human Ciliary Neurotrophic Factor. Regeneron (Co-Investigator)
\$107,100

Open-Label, Multiple-Dose, Pharmacokinetic/Pharmacodynamic Study of Dirithromycin and Oral Contraceptives (On - 7/7/7/28). Lilly Research Laboratories (Principal Investigator)
\$111,460

A Double-Blind, Placebo-Controlled, Study to Determine Whether Procrit Can Reduce Peri-Operative Transfusion Requirements In Subjects Undergoing Major Orthopedic Surgery. R. W. Johnson Research Institute (Co-Investigator)
\$89,031

A Study to Evaluate the Safety and Efficacy of Human r-IL1ra in Increasing Survival in Patients With Severe Sepsis. Synergen (Co-Investigator)
\$68,250

Induction and Maintenance of General Anesthesia: An Economic Evaluation of Propofol and Thiopental/Isoflurane in Patients Undergoing Elective Intra-Abdominal Surgery. Health Economics Research (Principal Investigator)
\$181,480

A Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Potential Efficacy of Initiating IV Administration of CGS-19755 to Serious Head Trauma Patients Prior to Surgery. Ciba-Geigy (Co-Investigator)
\$98,000

A Multi-Center Phase I Evaluation of AD-32 Administered by Intravesical Instillation in Patients with Superficial Transitional Cell Carcinoma of the Urinary Bladder. Anthra Pharmaceuticals (Co-Investigator)
\$18,192

The Safety of Intravenous Valproate Abbott Laboratories (Co-Investigator)
\$7,182

The Effects of Subcutaneous r-HuEPO in Patients with Chronic Lymphocytic Leukemia R.W. Johnson Pharmaceuticals Research Institute (Co-Investigator) \$30,000

An Open Study to Determine the Safety and Efficacy of Procrit Sterile Solution in Correcting Anemia in Renal Transplant Patients with Chronic Graft Dysfunction, R.W. Johnson Pharmaceuticals Research Institute (Co-Investigator)
\$36,070

A One Year Multi-Center Double Blind Comparison of the Effects of Once Daily Dosing with Three Dose Levels of SKF 105657 or Placebo in the Treatment of Symptomatic Benign Prostatic Hyperplasia with Six Month Untreated Follow-Up SmithKline Beecham (Co-Investigator)
\$111,082

Dose Tolerance of DSPC Liposome in Healthy Volunteers The Liposome Company
(Principal Investigator)
\$162,389

A Controlled Trial of Intravenous Plus Oral RS-87476 in Acute Non-Hemorrhagic
Cerebral Infarction Syntex Research (Co-Investigator) \$30,000

Investigation of Intravenous Infusion Monitoring System: Site Check IMED Corporation
(Co-Investigator)
\$14,592

A Study to Evaluate the Safety and Efficacy of Human Recombinant Interleukin-1
Receptor Antagonist (IL-1RA) in the Treatment of Sepsis Syndrome Synergen, Inc. (Co-
Investigator)
\$153,000

A Double-Blind Comparison of the Efficacy of a Two-Dose Regimen of Oral Granisetron
(1 mg twice, 2 mg once) in Preventing Active Nausea and Emesis in Patients Receiving
Moderate Emetogenic Chemotherapy SmithKline Beecham (Co-Investigator)
\$61,920

Kinetics of Edatrexate and Its Metabolites after Single 40 and 80 mg/m² Intravenous
Doses in Cancer Patients with Varying Degrees of Renal Insufficiency Ciba-Geigy (Co-
Investigator)
\$97,750

Measurement of Muscle Strength and Abilities to Perform Activities of Daily Living in
Patients with Amyotrophic Sclerosis Regeneron Pharmaceuticals (Co-Investigator)
\$20,000

A Relative Bioavailability Study of RO 24-7429 (TAT Antagonist) Tablets (With and
Without Food) vs. Oral Solution (Fasting) in Normal Volunteers Hoffman-LaRoche
(Principal Investigator)
\$72,487

Acute Dose Tolerance and Pharmacokinetics of Oral 1045U85/HCL in Healthy Male
Volunteers Burroughs Wellcome (Co-Investigator) \$237,754

Evaluation of Gastric pH Control in Head Trauma Patients by Continuous IV Infusion of
Cimetidine SmithKline Beecham - (Co-Investigator)
\$23,161

Evaluation of Streptokinase Infusion Kit for the Emergency Room Delivery of
Thrombolytic Therapy Baxter Healthcare Corporation - (Co-Investigator)
\$48,000

Investigation of Intravenous Infusion Monitoring System: Gemini IMED Corporation -
(Co-Investigator)
\$18,958 Part A, \$12,500 Part B

Transurethral Resection of Prostatic Tissue Using an Endoscopic Ultrasonic Surgical Aspirator System Valleylab, Inc. (Co-Investigator)
\$204,286

Pharmacokinetic Analysis of Lidocaine Administered by the Baxter Infusor Baxter Healthcare Corporation (Co-Investigator)
\$26,059

MK 787/791 vs. Ampicillin Plus Clindamycin plus Gentamicin in the Treatment of Serious Gynecological and Lower Abdominal Infections in Female Patients Merck Sharp & Dohme Research Laboratories (Co-Investigator)
\$112,500

IRB Equitable Selection Survey ARENA (Co-Investigator)
\$800

Single Oral Dose Pharmacokinetic and Pharmacodynamic Comparison of S-Atenolol and Racemic Atenolol (Termorin) in Healthy Adults Sepracor, Inc. (Co-Investigator)
\$75,000

Pivotal Study of Human MAB-T88 in Patients with Gram-Negative Sepsis. Cetus Corporation (Co-Investigator)
\$70,000

A Study to Assess the Effects of Chronic Oral Carvedilol on the Steady-State Pharmacokinetics of Oral Digoxin in Patients with Mild to Moderate Hypertension. SmithKline Beecham Pharmaceuticals (Principal Investigator)
\$83,000

Double-Blind, Placebo-Controlled Study of the Effect of Ceftizoxime Sodium in the Management of Patients with Preterm, Premature Rupture of Membranes. Fujisawa Pharmaceutical Company (Co-Investigator)
\$77,000

A Randomized Multi-Center Study of a Single Dose Oral Fluconazole Tablet Compared with Seven Days of Miconazole Vaginal Cream in the Treatment of Acute Candidal Vaginitis in Women 18-65 Years of Age. Pfizer Pharmaceuticals (Principal Investigator)
\$35,000

A Randomized Multi-Center Study of a Single Dose Oral Fluconazole Tablet Compared with Seven Days of Clotrimazole Vaginal Tablets in the Treatment of Acute Candidal Vaginitis in Women 18-65 Years of Age. Pfizer Pharmaceuticals (Principal Investigator)
\$70,000

A Phase II Dose Finding Placebo Controlled Study of YM617 in Patients with Signs and Symptoms of Benign Prostatic Hyperplasia. Yamanouchi Pharmaceuticals (Co-Investigator)
\$95,000

A Phase II Open-Label, Randomized Controlled Study of rhIGF-1 in Patients with Severe Head Injury. Genentech (Co-Investigator)
\$199,000

The Comparison of Sulbactam/Ampicillin (Unasyn) and Ampicillin/Gentamicin in the Treatment of Chorioamnionitis. Pfizer (Co-Investigator)
\$116,000

Double-Blind, Placebo-Controlled Pilot Study Evaluating Safety and Tolerability of Two Intravenous Bolus Doses of CGS-19755 in the Treatment of Patients with Acute Stroke. Ciba-Geigy (Co-Investigator)
\$84,000

A Placebo Controlled, Double Blind, Crossover, Dose/Response Study of Oral Torsemide in Patients with Ascites Due to Cirrhosis. Boehringer Mannheim Pharmaceuticals (Principal Investigator)
\$59,200

Acute Dose Tolerance, Pharmacokinetics, and Pharmacodynamics of Oral 349U85 in Healthy Male Volunteers. Burroughs Wellcome (Co-Investigator)
\$270,000

Comparative Clinical Efficacy of Two Tablet Strengths of Deflazacort in the Treatment of Steroid Dependent Asthma. Merrell Dow Pharmaceutical (Co-Investigator)
\$52,278

Long Term Safety and Efficacy Study of Deflazacort in Patients with Chronic Steroid Dependent Asthma. Merrell Dow Pharmaceutical (Co-Investigator)
\$21,356

Comparative Safety and Efficacy of Clarithromycin and Suprax in the Treatment of Lower Respiratory Tract Infections. Abbott Laboratories (Co-Investigator)
\$24,000

Unasyn - Pharmacy Surveillance Project. Pfizer Pharmaceuticals (Co-Investigator)
\$275,000

A Double-Blind, Placebo Controlled Study to Determine the Safety of r-HuEPO and Whether r-HuEPO can Reduce the Postoperative Transfusion Requirements in Subjects Undergoing Orthopedic Surgery. R.W. Johnson Foundation (Co-Investigator)
\$79,000

Assessment of Time to Study State After Multiple Dose Nefazodone in Extensive and Poor Metabolizers of Dextromethorphan. Bristol-Myers (Co-Investigator)
\$150,000

Infusion Device for Lidocaine Administration. Baxter Laboratories (Co-Investigator)
\$70,000

Evaluation of the Travenol Infusor/Patient Control Module for the Treatment of Postoperative Pain Travenol Laboratories (Co-Investigator)
\$25,000

Evaluation of Stadol with the Travenol Infusor and Patient Control Module for Patient-controlled Analgesia. Bristol-Myers (Co-Investigator)
\$12,500

An Evaluation of the Bioavailability of BW825C and Pseudoephedrine from 825C/Pseudoephedrine Combination Capsules and Syrup in Normal Male Volunteers. Burroughs Wellcome Company (Co-Investigator)
\$52,108

A Randomized Comparative Trial of Morphine Administered by Patient-Controlled Analgesia vs. Intramuscular Injection for the Treatment of Pain in Postoperative Patients. Bard Medsystems (Principal Investigator)
\$8,000

Multi-Institutional Study of Patient-Controlled Analgesia. Travenol Laboratories (Principal Investigator)
\$100,050

A Comparative Study Of CGS-15849 vs. Its Components and Placebo on Intraocular Pressure in Normal Subjects. Ciba-Geigy (Co-Investigator)
\$65,678

A Multiple Dose Placebo Double-Masked Comparative Tolerability Study of Diclofenac Sodium vs. Placebo in Normal Subjects. Ciba-Geigy (Co-Investigator)
\$84,114

Other Creative Activity

National

"Advent IV Medication Delivery Systems Implementation Guide." A reference manual for pharmacists preparing small volume parenteral using a gravity-feed syringe system. Sponsored by Quest Medical.

"Patient-Controlled Analgesia Device Inservice." A VHS tape describing methods for pharmacy preparation, nurse monitoring and patient utilization of a novel PCA device. Sponsored by Baxter.

"Electronic Research Administration Binder." An asserted copyright computer program for research administration. 1998

Intranasal Therapeutics Inc.

Address: Intranasal Therapeutics, Inc.
Coldstream Research Campus
1513 Bull Lea Boulevard
Lexington KY 40511-1200
www.intranasal.com

- Co-founder and consultant for a university-based start-up specialty pharmaceutical and drug delivery company – 1996 - 1999
- Senior Vice President and Chief Operating Officer – 1999-2004
- Chief Scientist 2004 - 06
- Technology based on University of Kentucky research in nasal transmembrane delivery of pharmaceuticals to the systemic circulation
- From 1996-2003 ITI funded over \$6 million into University of Kentucky research programs. The research funding supported major programs at UK and led to scholarly productivity by faculty
- Patents have been submitted and issued to UK from this research
- ITI has licensed the technology from UK and is partnering with larger pharmaceutical companies for finance and marketing support
- ITI has moved initial operations in the University incubator facility to the UK Coldstream Research campus where a research and development and manufacturing plant has been constructed
- ITI was the first private company to receive equity and debt financing from the Commonwealth of Kentucky Economic Development Cabinet. Total investment was \$3.5 million
- In July 2006 ITI closed a \$ 39 million venture capital financing for clinical and basic research and physical plant expansion

AntiOp Inc. (f/k/a Alcomed Inc.)

3732 Wembley Lane
Lexington, KY 40515

- Founder, President and Chief Executive Officer
- Incorporated in Kentucky as a University of Kentucky spin-off May 2009
- Focused on developing nasal delivery technology for treatment of opioid overdose
- Virtual pharmaceutical company
- Completed NDA and Submission
- Assets sold to Indivior (f/k/a Reckitt Benckiser Pharmaceuticals)