



US009763876B2

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

(10) **Patent No.:** **US 9,763,876 B2**
(45) **Date of Patent:** ***Sep. 19, 2017**

(54) **ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS**

USPC 514/221
See application file for complete search history.

(71) Applicant: **Hale Biopharma Ventures, LLC**,
Encinitas, CA (US)

(56) **References Cited**

(72) Inventors: **Steve Cartt**, Union City, CA (US);
David Medeiros, South San Francisco, CA (US); **Garry Thomas Gwozdz**, Jim Thorpe, PA (US); **Andrew Loxley**, Philadelphia, PA (US); **Mark Mitchnick**, East Hampton, NY (US); **David Hale**, San Diego, CA (US); **Edward T. Maggio**, San Diego, CA (US)

U.S. PATENT DOCUMENTS

3,102,116	A	8/1963	Chase et al.
3,109,843	A	11/1963	Reeder et al.
3,136,815	A	6/1964	Reeder et al.
3,243,427	A	3/1966	Reeder et al.
3,296,249	A	1/1967	Bell
3,299,053	A	1/1967	Archer et al.
3,340,253	A	9/1967	Reeder et al.
3,371,085	A	2/1968	Reeder et al.
3,374,225	A	3/1968	Reeder et al.
3,547,828	A	12/1970	Mansfield et al.
3,567,710	A	3/1971	Fryer et al.
3,609,145	A	9/1971	Moffett
3,722,371	A	3/1973	Boyle
3,849,341	A	11/1974	Lambeiti
3,987,052	A	10/1976	Hester, Jr.
4,280,957	A	7/1981	Walsler et al.
4,397,951	A	8/1983	Taki et al.
4,608,278	A	8/1986	Frank et al.
4,748,158	A	5/1988	Biermann et al.
4,826,689	A	5/1989	Violanto et al.
4,868,289	A	9/1989	Magnusson et al.
4,921,838	A	5/1990	Catsimpoalas et al.
4,973,465	A	11/1990	Baurain et al.
4,997,454	A	3/1991	Violante et al.
5,091,188	A	2/1992	Haynes
5,100,591	A	3/1992	Leclef et al.
5,118,528	A	6/1992	Fessi et al.
5,145,684	A	9/1992	Liversidge et al.
5,182,258	A	1/1993	Chiou
5,188,837	A	2/1993	Domb
5,192,528	A	3/1993	Radhakrishnan et al.
5,236,707	A	8/1993	Stewart
5,268,461	A	12/1993	Shoji et al.
5,308,531	A	5/1994	Urfer et al.

(73) Assignee: **Hale Biopharma Ventures, LLC**,
Encinitas, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 17 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/527,613**

(22) Filed: **Oct. 29, 2014**

(65) **Prior Publication Data**

US 2015/0065491 A1 Mar. 5, 2015

Related U.S. Application Data

(63) Continuation of application No. 13/495,942, filed on Jun. 13, 2012, now Pat. No. 8,895,546, which is a continuation-in-part of application No. 12/413,439, filed on Mar. 27, 2009.

(60) Provisional application No. 61/040,558, filed on Mar. 28, 2008, provisional application No. 61/497,017, filed on Jun. 14, 2011, provisional application No. 61/570,110, filed on Dec. 13, 2011.

(51) **Int. Cl.**

A61K 9/00 (2006.01)
A61K 45/06 (2006.01)
A61K 31/355 (2006.01)
A61K 31/5513 (2006.01)
A61K 9/08 (2006.01)
A61K 47/10 (2017.01)
A61K 47/22 (2006.01)
A61K 47/26 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 9/0043** (2013.01); **A61K 9/008** (2013.01); **A61K 9/08** (2013.01); **A61K 31/355** (2013.01); **A61K 31/5513** (2013.01); **A61K 45/06** (2013.01); **A61K 47/10** (2013.01); **A61K 47/22** (2013.01); **A61K 47/26** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 9/0043**; **A61K 45/06**; **A61K 9/008**; **A61K 31/355**; **A61K 31/5513**; **A61K**

FOREIGN PATENT DOCUMENTS

CN	1303674	A	7/2001
EP	0396777	A1	11/1990

(Continued)

OTHER PUBLICATIONS

CA 2,723,470 Office Action dated Feb. 19, 2015.

(Continued)

Primary Examiner — Adam C Milligan

(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.

(56)

References Cited

U.S. PATENT DOCUMENTS

5,317,010 A 5/1994 Pang et al.
 5,369,095 A 11/1994 Kee et al.
 5,457,100 A 10/1995 Daniel
 5,550,220 A 8/1996 Meyer et al.
 5,560,932 A 10/1996 Bagchi et al.
 5,639,733 A 6/1997 Koike et al.
 5,661,130 A 8/1997 Meezan et al.
 5,662,883 A 9/1997 Bagchi et al.
 5,665,331 A 9/1997 Bagchi et al.
 5,716,642 A 2/1998 Bagchi et al.
 5,738,845 A 4/1998 Imakawa
 5,780,062 A 7/1998 Frank et al.
 5,789,375 A 8/1998 Mukae et al.
 5,795,896 A 8/1998 Löfroth et al.
 5,814,607 A 9/1998 Patton
 5,817,634 A 10/1998 Meezan et al.
 5,831,089 A 11/1998 Huber
 5,861,510 A 1/1999 Piscopio et al.
 5,863,949 A 1/1999 Robinson et al.
 5,955,425 A 9/1999 Morley et al.
 5,981,719 A 11/1999 Woiszwillow et al.
 6,004,574 A 12/1999 Backstrom et al.
 6,090,925 A 7/2000 Woiszwillow et al.
 6,143,211 A 11/2000 Mathiowitz et al.
 6,165,484 A 12/2000 Raad et al.
 6,193,985 B1 2/2001 Sonne
 6,235,224 B1 5/2001 Mathiowitz et al.
 6,254,854 B1 7/2001 Edwards et al.
 6,268,053 B1 7/2001 Woiszwillow et al.
 6,316,029 B1 11/2001 Jain et al.
 6,316,410 B1 11/2001 Barbier et al.
 6,375,986 B1 4/2002 Ryde et al.
 6,395,300 B1 5/2002 Straub et al.
 6,428,814 B1 8/2002 Bosch et al.
 6,458,387 B1 10/2002 Scott et al.
 6,461,591 B1 10/2002 Keller et al.
 6,482,834 B2 11/2002 Spada et al.
 6,495,498 B2 12/2002 Niemiec et al.
 6,524,557 B1 2/2003 Backstrom et al.
 6,607,784 B2 8/2003 Kipp et al.
 6,610,271 B2 8/2003 Wermeling
 6,616,914 B2 9/2003 Ward et al.
 6,627,211 B1 9/2003 Choi et al.
 6,794,357 B1 9/2004 Backstrom et al.
 6,869,617 B2 3/2005 Kipp
 6,884,436 B2 4/2005 Kipp
 6,908,626 B2 6/2005 Cooper et al.
 6,932,962 B1 8/2005 Backstrom et al.
 6,991,785 B2 1/2006 Frey
 7,008,920 B2 3/2006 Kimura et al.
 7,037,528 B2 5/2006 Kipp
 7,132,112 B2 11/2006 Choi et al.
 7,434,579 B2 10/2008 Young et al.
 8,530,463 B2 9/2013 Cartt
 8,895,546 B2 11/2014 Cartt
 2001/0042932 A1 11/2001 Mathiowitz et al.
 2002/0110524 A1 8/2002 Cowan et al.
 2002/0127278 A1 9/2002 Kipp
 2002/0141971 A1 10/2002 Frey
 2002/0168402 A1 11/2002 Kipp
 2003/0017203 A1 1/2003 Crotts et al.
 2003/0031719 A1 2/2003 Kipp
 2003/0040497 A1 2/2003 Teng et al.
 2003/0087820 A1 5/2003 Young et al.
 2003/0100755 A1 5/2003 Sham et al.
 2003/0118547 A1 6/2003 Vandenberg
 2003/0118594 A1 6/2003 Nag et al.
 2003/0158206 A1 8/2003 Billotte et al.
 2003/0170206 A1 9/2003 Rasmussen et al.
 2003/0181411 A1 9/2003 Bosch et al.
 2004/0101482 A1 5/2004 Sanders
 2004/0115135 A1 6/2004 Quay
 2004/0126358 A1 7/2004 Warne et al.

2004/0258663 A1 12/2004 Quay et al.
 2005/0130260 A1 6/2005 Linden et al.
 2005/0234101 A1 10/2005 Stenkamp et al.
 2006/0045869 A1 3/2006 Meezan et al.
 2006/0046962 A1 3/2006 Meezan et al.
 2006/0046969 A1 3/2006 Maggio
 2006/0106227 A1 5/2006 Reddy et al.
 2006/0147386 A1 7/2006 Wermeling
 2006/0198896 A1 9/2006 Liversidge et al.
 2007/0059254 A1 3/2007 Singh
 2007/0098805 A1 5/2007 Liversidge
 2007/0298010 A1 12/2007 Maggio
 2008/0200418 A1 8/2008 Maggio
 2008/0248123 A1 10/2008 Swanson et al.
 2008/0268032 A1 10/2008 Maggio
 2008/0279784 A1 11/2008 Cartt
 2008/0299079 A1 12/2008 Meezan et al.
 2009/0047347 A1 2/2009 Maggio
 2009/0130216 A1 5/2009 Cartt
 2009/0163447 A1 6/2009 Maggio
 2009/0258865 A1 10/2009 Cartt et al.
 2009/0297619 A1 12/2009 Swanson et al.
 2009/0304801 A1 12/2009 Liversidge et al.
 2010/0068209 A1 3/2010 Maggio
 2010/0203119 A1 8/2010 Leane et al.
 2010/0209485 A1 8/2010 Maggio
 2011/0172211 A1 7/2011 Baek et al.
 2011/0257096 A1 10/2011 Maggio
 2012/0196941 A1 8/2012 Maggio
 2013/0065886 A1 3/2013 Cartt
 2014/0128479 A1 5/2014 Maggio
 2014/0170220 A1 6/2014 Cartt

FOREIGN PATENT DOCUMENTS

EP 606046 7/1994
 EP 00780386 6/1997
 EP 0818442 1/1998
 EP 931788 7/1999
 EP 0945485 9/1999
 EP 1004578 5/2000
 EP 1208863 A2 5/2002
 EP 1417972 A1 5/2004
 JP 1-151528 6/1989
 JP 2003-505403 2/2003
 JP 2005-508939 4/2005
 JP 2007-510722 4/2007
 JP 2011516425 A 5/2011
 WO WO-90-05719 5/1990
 WO WO-91-19481 12/1991
 WO WO-94-05262 A1 3/1994
 WO WO-95-00151 A1 1/1995
 WO WO-95-31217 A1 11/1995
 WO WO-96-27583 9/1996
 WO WO-96-33172 10/1996
 WO WO-97-14407 A1 4/1997
 WO WO-98-03516 1/1998
 WO WO-98-07697 2/1998
 WO WO-98-30566 7/1998
 WO WO-98-33768 8/1998
 WO WO-98-34915 8/1998
 WO WO-98-34918 8/1998
 WO WO-99-07675 2/1999
 WO WO-99-29667 6/1999
 WO WO-99-52889 10/1999
 WO WO-99-52910 10/1999
 WO WO-00-01390 A1 1/2000
 WO WO-00-74681 12/2000
 WO WO-03004015 A1 1/2003
 WO WO-03-055464 7/2003
 WO WO-2005-018565 A2 3/2005
 WO WO-2005-044234 A2 5/2005
 WO WO-2005-089768 9/2005
 WO WO-2005-117830 A1 12/2005
 WO WO-2006-025882 A2 3/2006
 WO WO-2006-055603 5/2006
 WO WO-2006-075123 A1 7/2006

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	WO-2007-144081 A1	12/2007
WO	WO-2008-027395 A2	3/2008
WO	WO-2009-120933 A2	10/2009
WO	WO-2009121039 A2	10/2009

OTHER PUBLICATIONS

CN 201280039077.9 Office Action dated Dec. 26, 2014.

U.S. Appl. No. 60/148,464, filed Aug. 12, 1999, Noe

Ahsan et al., "Effects of the permeability enhancers, tetradecylmaltoside and dimethyl- β -cyclodextrin, on insulin movement across human bronchial epithelial cells", *European Journal of Pharmaceutical Sciences*, 2003; 20: 27-34.

Ahsan et al., "Sucrose cocoate, a component of cosmetic preparations enhances nasal and ocular peptide absorption", *Int J Pharm*, 2003; 251: 195-203.

Albert et al., "Pharmacokinetics of diphenhydramine in man", *J. Pharmacokinetic, Biopharm.*, 3(3):159-170 (1975).

Arnold et al., "Correlation of tetradecylmaltoside induced increases in nasal peptide drug delivery with morphological changes in nasal epithelial cells", *J. Pharm. Sci.* 93(9):2205-2213 (2004).

AU application 2009228093 First exam report dated Jul. 19, 2013.

Beam et al., "Blood, Brain, Cerebrospinal Fluid Concentrations of Several Antibiotics in Rabbits with Intact and Inflamed Meninges", *Antimicrobial Agents and Chemotherapy*, Dec. 1977, pp. 710-716.

Bhairi S.M., "A guide to the properties and uses of detergents in biological systems", *Calbiochem*, pp. 1-42 (2001).

Birkett et al., "Bioavailability and First Pass Clearance", *Australian Prescriber*, 1991, pp. 14-16, vol. 14.

Birkett et al., "How Drugs are Cleared by the Liver", *Australian Prescriber*, 1990, pp. 88-89, vol. 13, No. 4.

CA 2,723,470 Office action dated Jun. 7, 2012.

Castro et al., "Ecologically safe Alkyl glucoside-based gemini surfactants", *ARKIVOC*, xii:253-267 (2005).

Chavanpatil and Vavia, "Nasal drug delivery of sumatriptan succinate", *Pharmazie*, May 2005;60(5):347-349.

Chen et al., "Peptide Drug Permeation Enhancement by Select Classes of Lipids", presented at the 45th American Society of Cell Biology, S.F., CA, Dec. 10-14, 2005; 1 page total.

Chen-Quay et al., "Identification of tight junction modulating lipids", *J. Pharm. Sci.*, 98(2):606-619 (2009).

Chiou et al., "Improvement of Systemic Absorption of Insulin Through Eyes with Absorption Enhancers", *Journal of Pharmaceutical Sciences*, Oct. 1989, pp. 815-818, vol. 78, No. 10.

Chiou et al., "Systemic Delivery of Insulin Through Eyes to Lower the Glucose Concentration", *Journal of Ocular Pharmacology*, 1989, pp. 81-91, vol. 5, No. 1.

Chinese Patent Office from Application No. CN200980157305.0 dated Jan. 28, 2013.

Davis and Ilium, "Absorption enhancers for nasal drug delivery", *Clin. Pharmacokine.*, 2003;42(13):107-28.

De Vry and Schreiber, "Effects of selected serotonin 5-HT(1) and 5-HT(2) receptor agonists on feeding behavior: possible mechanisms of action", *Neurosci. Biobehav. Rev.*, 24(3):341-53 (2000). Definition downloaded Sep. 13, 2012 at the medical-dictionary.thefreedictionary.com/p/encephalin.

Definition of pilus, Merriam-Webster Medical Dictionary, <http://www.merriam-webster.com/medical/pilus>, accessed online on May 28, 2013.

Definition of villus, Merriam-Webster Medical Dictionary, <http://www.merriam-webster.com/medical/villus>, accessed online on May 28, 2013.

Drewe et al., "Enteral absorption of octreotide: absorption enhancement by polyoxyethylene-24-cholesterol ether", *Br. J. Pharmacol.*, 108(2):298-303 (1993).

Duquesnoy et al., "Comparative clinical pharmacokinetics of single

Edwards CM., "GLP-1: target for a new class of antidiabetic agents?", *J.R. Soc. Med.*, 97(6):270-274 (2004).

Eley and Triumalashetty, "In vitro assessment of Alkylglycosides as permeability enhancers", *AAPS PharmSciTech.*, 2(3): article 19, pp. 1-7 (2001).

EP application 09723906.5 Extended European search report dated Jun. 3, 2013.

EP08747813 Supplementary Search Report dated Jun. 2, 2010.

European Search Report (ESR) from EP 09 83 5809 dated Nov. 13, 2012.

Fix, "Oral controlled release technology for peptides: status and future prospects", *Pharmaceutical Research* Dec. 1996;13(12):1760-1764.

Fricker et al., "Permeation enhancement of octreotide by specific bile salts in rats and human subjects: in vitro, in vivo correlations", *Br. J. Pharmacol.*, 117(1):217-23 (1996).

Gordon et al., "Nasal Absorption of Insulin: Enhancement by Hydrophobic Bile Salts", *Proceedings of the National Academy of Sciences of the United States of America*, Nov. 1985, pp. 7419-7423, vol. 82.

Hathcox and Beuchat, "Inhibitory effects of sucrose fatty acid esters, Alone and in combination with ethylenediaminetetraacetic acid and other organic acids, on viability of *Escherichia coli* 0157:H7", *Food Microbiology*, vol. 13, Issue 3, 213-225 (1996).

Hovgaard et al., "Insulin Stabilization and GI Absorption", *Journal of Controlled Release*, Mar. 1992, pp. 99-108, vol. 19, Issue 1-3.

Hovgaard et al., "Stabilization of insulin by Alkylmaltosides. A. Spectroscopic evaluation", *International Journal of Pharmaceutics*, 132(1-2):107-113 (1996).

Hovgaard et al., "Stabilization of Insulin by Alkylmaltosides. B. Oral Absorption in Vivo in Rats", *International Journal of Pharmaceutics*, 1996, pp. 115-121, vol. 132.

Hussain et al., "Absorption enhancers in pulmonary protein delivery." *J Control Release*. Jan. 8, 2004;94(1):15-24.

International Search Report (ISR) from PCT/US2011/056735 dated Jun. 22, 2012.

JP2010-507633 Office Action dated Oct. 23, 2012.

JP2010-507633 Decision of refusal dated Jul. 9, 2013.

Katzung, B., "Basic and Clinical Pharmacology, 7th Edition", Appleton & Lange: Stamford, Connecticut, 1998, pp. 34-49.

Kissel et al., "Tolerability and absorption enhancement of intranasally administered octreotide by sodium taurodihydrofusidate in healthy subjects." *Pharm Res*. Jan. 1992;9(1):52-57.

Kite et al., "Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro." *J Clin Microbiol*. Jul. 2004;42(7):3073-3076.

Lacy, C, et al., "Drug Information Handbook, 7th Edition 1999-2000" Lexi-Comp, Inc., 1999, pp. 163-164.

Lahat et al., "Intranasal midazolam for childhood seizures", *The Lancet*, 1998; 352: 620.

Lehninger et al., "Principles of Biochemistry with an Extended Discussion of Oxygen-Binding Proteins", 1982, pp. 150-151, Worth Publishers, Inc.

Liu et al., "Interaction between chitosan and Alkyl P-D-glucopyranoside and its effect on their antimicrobial activity", *Carbohydrate Polymers*. 2004; 56: 243-250.

Maa and Prestrelski, "Biopharmaceutical powders: particle formation and formulation considerations", *Curr. Pharm. Biotechnol.*, 1(3):283-302 (2000).

Material Safety Data Sheet for Anatrace, Inc. product n-Dodecyl- β -d-Maltopyranoside, Anagrade, Dated: Jan. 25, 1994 and Revised: Jul. 15, 2004, http://media.affymetrix.com/estore/browse/level_three/category_and_products.jsp?category=35843&categoryIdClicked=35843&expand=true&parent=35900, access online on Dec. 13, 2012.

Mathew N.T., "Serotonin 1D (5-HT1D) agonists and other agents in acute migraine", *Neurol. Clin.*, 15(1):61-83 (1997).

Matsumura et al., "Surface activities, biodegradability and antimicrobial properties of n-alkyl glucosides, mannosides and

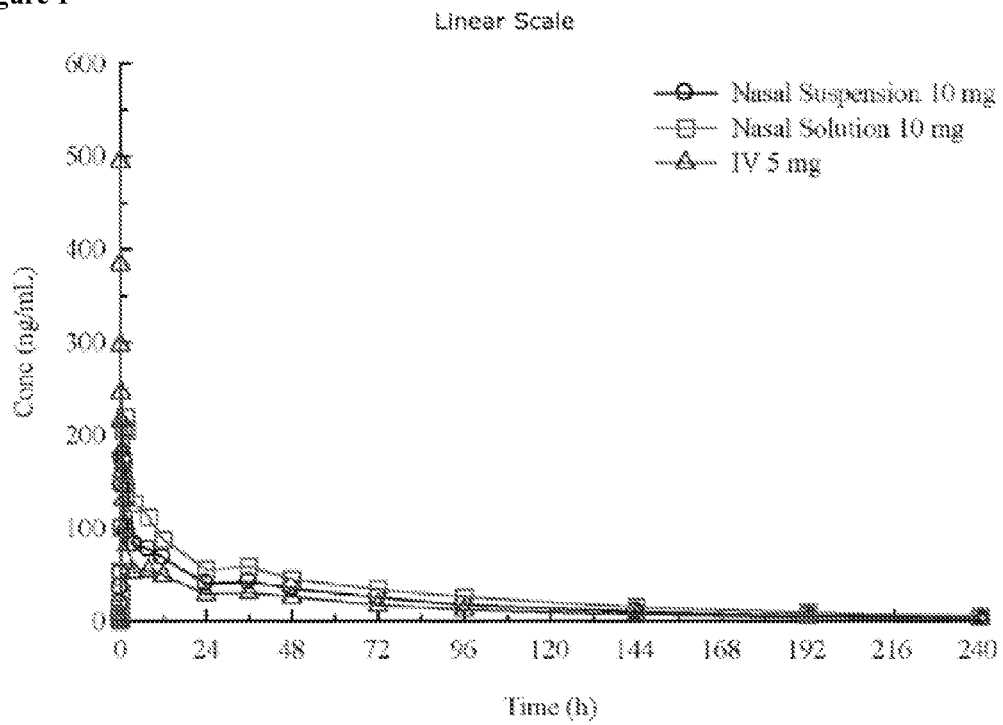
(56)

References Cited

OTHER PUBLICATIONS

- Moses et al., "Insulin Administered Intranasally as an Insulin-Bite Salt Aerosol—Effectiveness and Reproducibility in Normal and Diabetic Subjects", *Diabetes*, Nov. 1983, pp. 1040-1047, vol. 32.
- Murakami et al., "Assessment of Enhancing Ability of Medium-Chain Alkyl Saccharides as New Absorption Enhancers in Rat Rectum", *International Journal of Pharmaceutics*, Feb. 1992, pp. 159-169, vol. 79, Issue 1-3].
- Ogiso et al., "Percutaneous Absorption of Elcatonin Chemical and Hypocalcemic Effect in Rat", *Chemical & Pharmaceutical Bulletin*, Feb. 1991, pp. 449-453, vol. 39, Issue 2, The Pharmaceutical Society of Japan, Tokyo, Japan.
- Olesen et al., "The Headaches", *Lippincott Williams & Wilkins*, p. 474 (2005).
- Paulsson and Edsman, "Controlled drug release from Gels using surfactant aggregates. II Vesicles formed from mixtures of amphiphilic drugs and oppositely charged surfactants", *Pharm, Res.*, 18(11):1586-1592 (2001).
- PCT/US08/62961 Search Report dated Jul. 25, 2008.
- PCT/US08/62961 International Preliminary Report on Patentability dated Nov. 10, 2009.
- PCT/US09/38696 Search Report dated Sep. 28, 2009.
- PCT/US09/38696 International Preliminary Report on Patentability dated Sep. 28, 2010.
- PCT/US2012/042311 Search Report dated Aug. 31, 2012.
- Phillips, A., "The challenge of gene therapy and DNA delivery", *J. Pharm Pharmacology* 53: 1169-1174, 2001.
- Pillion et al., "Synthetic long-chain Alkyl maltosides and Alkyl sucrose esters as enhancers of nasal insulin absorption", *J. Pharm. Sci.*, 91:1456-1462 (2002).
- Pillion et al., "Systemic Absorption of Insulin Delivered Topically to the Rat Eye", *Investigative Ophthalmology & Visual Science*, Nov. 1991, pp. 3021-3027, vol. 32, Issue 12.
- Pirollo et al., "Targeted Delivery of Small Interfering RNA: Approaching Effective Cancer Therapies", *Cancer Res.* 68(5): 1247-1250, 2008.
- Richards R.M., "Inactivation of resistant *Pseudomonas aeruginosa* by antibacterial combinations", *J. Pharm. Pharmacol.*, 23:136S-140S (1971).
- Salzman et al., "Intranasal Aerosolized Insulin", *The New England Journal of Medicine*, Apr. 25, 1985, pp. 1078-1084, vol. 312, Issue 17.
- Sanders et al., "Pharmacokinetics of ergotamine in healthy volunteers following oral and rectal dosing", *Eur. J. Clin. Pharmacol.*, 30(3):331-334 (1986).
- Shim and Kim, "Administration Route Dependent Bioavailability of Interferon- α and Effect of Bile Salts on the Nasal Absorption", *Drug Development and Industrial Pharmacy*, 19(10):1183-1199 (1993).
- Stevens and Guillet, "Use of Glucagon to Treat Neonatal Low-Output Congestive Heart Failure after Maternal Labetalol Therapy", *The Journal of Pediatrics*, Jul. 1995, pp. 151-153, vol. 127, Issue 1.
- Swarbrick et al., *Encyclopedia of Pharmaceutical Technology*, Informa Health Care, 2nd edition, vol. 1, p. 918 (2002).
- Tsuchido et al., "Lysis of *Bacillus subtilis* Cells by Glycerol and Sucrose Esters of Fatty Acids", *Applied and Environmental Microbiology*, vol. 53, No. 3, 505-508, 1987.
- Türker et al., "Nasal route and drug delivery systems", *Pharm. World Sci.*, 26(3):137-42 (2004).
- Turton et al., "A role for glucagon-like peptide-1 in the central regulation of feeding", *Nature*, 1996; 379:69-72.
- U.S. Appl. No. 12/116,842 Office action mailed May 25, 2011.
- U.S. Appl. No. 12/116,842 Office action mailed Apr. 2, 2013.
- U.S. Appl. No. 12/116,842 Office action mailed Nov. 15, 2011.
- U.S. Appl. No. 12/116,842 Office action mailed Dec. 17, 2013.
- U.S. Appl. No. 12/266,529 Office action mailed Jul. 10, 2012.
- U.S. Appl. No. 12/266,529 Office action mailed Nov. 16, 2011.
- U.S. Appl. No. 12/413,439 Office action mailed Mar. 18, 2011.
- U.S. Appl. No. 12/413,439 Office action mailed Nov. 21, 2011.
- U.S. Appl. No. 12/413,439 Office action mailed Jun. 19, 2014.
- U.S. Appl. No. 13/495,942 Office Action mailed Oct. 1, 2013.
- Vidal et al., "Making sense of antisense", *European Journal of Cancer*, 41:2812-2818, 2005.
- Watanabe et al., "Antibacterial Carbohydrate Monoesters Suppressing Cell Growth of *Streptococcus mutans* in the Presence of Sucrose", *Current Microbiology*, Sep. 2000, pp. 210-213, vol. 41, No. 3.
- Weber and Benning, "Metabolism of orally administered Alkyl beta-glycosides in the mouse", *J. Nutr.*, 114:247-254 (1984).
- Webpage for Anatrax products of Affymetrix, http://www.affymetrix.com/estore/browse/level_three_category_and_products.jsp?category=35843&categoryIdClicked=35843&expand=true&parent=35900, accessed online on Dec. 13, 2012.
- Wermeling et al., "Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers," *Anesthesia & Analgesia* 103(2):344-349 (2006).
- Yamamoto et al., "The Ocular Route for Systemic Insulin Delivery in the Albino Rabbit", *The Journal of Pharmacology and Experimental Therapeutics*, Apr. 1989, pp. 249-255, vol. 249; No. 1.
- Yu Xinrui et al., "Triptan Medicament and Migraine", *World Pharmacy (Synthetic Drug and Biochemical Drug Formulation Fascicule)*, 22(2):91-92 (2001).
- Canadian Patent Application No. 2756690 Examiner's Report dated Oct. 20, 2015.
- Chinese Patent Application No. 201280039077.9 Office Action dated Nov. 21, 2016.
- Chinese Patent Application No. 201280039077.9 Second Office Action dated Aug. 11, 2015.
- Chinese Patent Application No. 201280039077.9 Third Office Action dated Mar. 17, 2016.
- European Patent Application No. 12801372.9 Extended EP Search Report dated Mar. 26, 2015.
- European Patent Application No. 12801372.9 Communication dated Jul. 5, 2016.
- Japanese Patent Application No. 2014-515967 Office Action dated Mar. 30, 2016.
- Japanese Patent Application No. 2014-515967 Office Action dated Nov. 28, 2016.
- Newman. Aerosol deposition consideration in inhalation therapy. *Chest* 152S-160S (1985).
- U.S. Appl. No. 12/413,439 Office Action dated Jul. 14, 2016.
- U.S. Appl. No. 12/413,439 Office Action dated Oct. 5, 2015.
- U.S. Appl. No. 14/948,081 Office Action dated Oct. 31, 2016.
- U.S. Appl. No. 12/116,842 Office Action mailed Jul. 8, 2015.
- U.S. Appl. No. 14/021,988 Office Action mailed May 22, 2015.

Figure 1



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.