

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VII LLC,
Petitioner,

v.

POZEN INC.,
Patent Owner.

IPR2015-01344
Patent 8,858,996

PETITION FOR *INTER PARTES* REVIEW

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<i>Iron Dome LLC v. Chinook Licensing DE LLC</i> , IPR2014-00674, Paper 9 (Sept. 10, 2004)	4

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35 U.S.C. § 102(b)	5, 48
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EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 8,858,996 (“the ’996 Patent”)
1002	File History of the ’996 Patent, U.S. Patent App. No. 14/244,471 (“the ’471 Application”)
1003	Declaration of Leon Shargel, Ph.D., R.Ph.
1004	U.S. Patent No. 5,204,118 (“Goldman”)
1005	“Remington’s Pharmaceutical Sciences,” Alfonso R. Gennaro, et al., Mack Publ’g Co., Seventeenth Edition, 1985 (“Remington”)
1006	U.S. Patent No. 5,698,225 (“Gimet”)
1007	U.S. Patent No. 5,714,504 (“Lindberg”)
1008	U.S. Patent App. Pub. No. US 2003/0069255 (“the ’255 Plachetka Publication”)
1009	U.S. Patent Prov. App. No. 60/294,588 (“the ’588 Application”)
1010	U.S. Patent App. No. 10/158,216 (“the ’216 Application”)
1011	U.S. Patent App. No. 11/129,320 (“the ’320 Application”)
1012	U.S. Patent No. 4,757,060
1013	“The Mechanism of Action of Aspirin,” J.R. Vane, et al., Pergamon (2003)
1014	G.B. Patent No. 1211134
1015	“Drug-Induced Peptic Ulcer Disease,” Valerie Vella, Journal of the Malta College of Pharmacy Practice (2005)

Exhibit No.	Description
1016	“Goodman & Gilman’s The Pharmacological Basis of Therapeutics,” Joel G. Hardman, et al., McGraw-Hill Publ’g Co., Ninth Edition (1996)
1017	“Upper Gastrointestinal (GI) pH in Young, Healthy Men and Women,” Jennifer B. Dressman, et al., Pharmaceutical Research, Vol. 7, No. 7, 756-761 (1990)
1018	“Effect of Orally Administered Prostaglandin E2 and its 15-Methyl Analogues on Gastric Secretion,” Karim, et al., British Med. Journal (Jan. 20, 1973)
1019	“Tagamet: The Discovery of Histamine H2-Receptor Antagonists,” SmithKlein Beecham Pharmas., Am. Chem. Soc. (Nov. 24, 1997)
1020	“Inhibition of Gastric ($H^+ + K^+$)-ATPase by the Substituted Benzimidazole Picoprazole,” B. Wallmark, et al., Biochimica et Biophysica Acta, Vol. 728, at 31-38 (1983)
1021	U.S. Patent No. 4,255,431
1022	Notice of Final Determination, In re: Patent Term Extension for U.S. Patent No. 6,143,771
1023	“Drug Discovery: Practices, Processes, and Perspectives,” Jie Jack Li, et al., John Wiley & Sons (Apr. 3, 2013)
1024	“Prevention of the Gastrointestinal Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs, Gregor J.E. Brown, et al., Drug Safety (6): 503-512 (December 21, 1999)
1025	U.S. Patent App. Pub. 2002/0045184 (“Chen”)
1026	“Management of NSAID-Related Gastrointestinal Mucosal Injury,” A.F. Barrison, et al., Inflammopharmacology 7(3), at 277-86 (1999)
1027	“Prevention of NSAID-Induced Gastroduodenal Ulcers,” A. Rostom, et al., Cochrane Database of Systematic Reviews (2000)

Exhibit No.	Description
1028	“Abolition by Omeprazole of Aspirin Induced Gastric Mucosal Injury in Man,” T K Daneshmend et al., Gut, Vol. 31, 514-517 (1990) (“Daneshmend”)
1029	U.S. Patent No. 6,319,519
1030	U.S. Patent No. 6,365,184 (“Depui”)
1031	VIMOVO® (Naproxen and Esomeprazole Magnesium) Tablets Horizon Pharma, http://www.horizonpharma.com/vimovo/ (last visited May 9, 2015)
1032	Horizon Pharma plc 2014 Irish Statutory Accounts,” Horizon Pharma Public Limited Company (Apr. 9, 2015)
1033	Shargel Walmart Receipts
1034	April 4, 2014 Patent Owner Responses to Invalidity Contentions
1035	Inhibit, http://www.merriam-webster.com/dictionary/inhibit (last visited Feb. 17, 2015)
1036	Organic Chemistry, Robert Thornton Morrison, Sixth Edition, 1992
1037	The Random House Dictionary of the English Language, Random House, First Printing, 1966
1038	The Oxford Encyclopedic English Dictionary, Joyce M. Hawkins, et al., 1991
1039	WO 98/54171
1040	U.S. Patent No. 6,262,085
1041	U.S. Patent Pub. No. 2001/0000468
1042	U.S. Patent No. 5,051,262
1043	U.S. Patent No. 5,314,697

Exhibit No.	Description
1044	“Effects of Misoprostol on Gastric Acid and Mucus Secretion in Man,” Donald E. Wilson, et al., Digestive Diseases and Sciences, Vol. 31, No. 2, Feb. 1986.
1045	“Measurement of Gastrointestinal pH Profiles in Normal Ambulant Human Subjects,” D. F. Evans, et al., Gut, Vol. 29, 1035-1041 (1988) (“Evans”)
1046	Prevent, http://www.merriam-webster.com/dictionary/prevent (last visited June 4, 2015)
1047	“Omeprazole,” Stephen P. Clissold, et al., Drugs, vol. 32 (1986) (“Clissold”)
1048	“Development of an Oral Formulation of Omeprazole,” Pilbrant and Cederberg, Scand. J. Gastroenterol., 20(Suppl. 108):113-120 (1985) (“Pilbrant”)
1049	“Effects of Single and Repeated Doses of Omeprazole in Gastric Acid and Pepsin Secretion in Man,” Howden et al., Gut, Vol. 25, 707-710 (1984) (“Howden”)
1050	“Omeprazole: A Study of Its Inhibition of Gastric pH and Oral Pharmacokinetics After Morning or Evening Dosage,” Prichard et al., Gastroenterol., 88:64-69 (1985) (“Prichard”)
1051	“The Effects of Oral Doses of Lansoprazole and Omeprazole on Gastric pH,” Tolman et al., J. Clin. Gastroenterol, 24(2):65-70 (1997) (“Tolman”)
1052	Citizen Petition, Horizon Pharma (February 4, 2014)

Exhibit No.	Description
1053	“Clinical Trial: Evaluation of Gastric Acid Suppression with Three Doses of Immediate-Release Esomeprazole in the Fixed-Dose Combination of PN 400 (Naproxen/Esomeprazole Magnesium) Compared with Naproxen 500 mg and Enteric-Coated Esomeprazole 20 mg: A Randomized, Open-Label, Phase I Study in Healthy Volunteers,” Miner et al., <i>Alim. Pharmacol. Ther.</i> , 32:414-424 (2010) (“Miner”)
1054	FDA Response to Horizon’s Citizen Petition (July 3, 2014)

I. Introduction

The Coalition for Affordable Drugs VII LLC (“CFAD” or “Petitioner”) respectfully requests *inter partes* review of claims 1-19 of U.S. Patent No. 8,858,996 (“the ’996 Patent”) (Ex. 1001) in accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.* The ’996 Patent is assigned to Pozen Inc.

II. Mandatory Notices Per 37 C.F.R. § 42.8

A. Real Party-In-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), CFAD certifies that Coalition For Affordable Drugs VII LLC; Hayman Credes Master Fund, L.P. (“Credes”); Hayman Orange Fund SPC – Portfolio A (“HOF”); Hayman Capital Master Fund, L.P. (“HCMF”); Hayman Capital Management, L.P. (“HCM”); Hayman Offshore Management, Inc. (“HOM”); Hayman Investments, L.L.C. (“HI”); nXn Partners, LLC (“nXnP”); IP Navigation Group, LLC (“IPNav”); J Kyle Bass; and Erich Spangenberg (collectively, “RPI”) are the real parties-in-interest. The RPI certify the following: CFAD is a wholly owned subsidiary of Credes. Credes is a limited partnership. HOF is a segregated portfolio company. HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HCM is the investment manager of HOF. HOM is the administrative general partner of Credes and HCMF. HI is the general partner of HCM. J Kyle Bass is the sole member of HI and sole shareholder of HOM. CFAD, Credes,

HOF, and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes, HOF, and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is the Manager and majority member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the Manager and majority member of IPNav. Other than HCM and J Kyle Bass in his capacity as the Chief Investment Officer of HCM and nXnP and Erich Spangenberg in his capacity as the Manager/CEO of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD, Credes, HOF, HCMF, HCM, HOM, HI, nXnP, or IPNav) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this petition. All of the costs associated with this petition are expected to be borne by HCM, CFAD, Credes, HOF, and/or HCMF.

B. Notice of Related Matters

Per 37 C.F.R. § 42.8(b)(2), CFAD is aware of the following judicial matters involving the '996 Patent: (1) *Horizon Pharma, Inc. v. Actavis Labs. FL, Inc.*, 3:15-cv-03322 (D.N.J.); (2) *Horizon Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, 3:15-cv-03324 (D.N.J.); (3) *Horizon Pharma, Inc. v. Lupin Ltd.*, 3:15-cv-03326 (D.N.J.); and (4) *Horizon Pharma, Inc., v. Mylan Pharmas., Inc.* 3:15-cv-03327

(D.N.J.). In addition, CFAD is aware of the following judicial and administrative matters involving patents related to the '996 Patent: (1) *AstraZeneca AB v. Dr. Reddy's Labs. Inc.*, 3:11-cv-02317 (D.N.J.); (2) *AstraZeneca AB v. Dr. Reddy's Labs., Inc.*, 3:13-cv-00091 (D.N.J.); (3) *AstraZeneca AB v. Watson Labs., Inc.-Florida*, 3:13-cv-03038 (D.N.J.); (4) *AstraZeneca AB v. Mylan Pharmas.*, 3:13-cv-04022 (D.N.J.); (5) *Dr. Reddy's Labs., Inc. v. Pozen Inc.*, IPR2015-00802 (P.T.A.B.); and *Coalition for Affordable Drugs VII LLC v. Pozen Inc.*, IPR2015-01241 (P.T.A.B.).

C. Lead and Back-Up Counsel and Service Information

Per 37 C.F.R. § 42.8(b)(3), CFAD designates counsel as follows:

Lead Counsel	Back-Up Counsel
Amy E. LaValle (Reg. No. 51,092) alavalle@conleyrose.com <u>Postal and Hand-Delivery Address:</u> Conley Rose, P.C. 5601 Granite Parkway, Suite 500 Plano, Texas 75024 (972) 731-2288 (phone) (972) 731-2289 (fax)	Jerry C. Harris, Jr. (Reg. No. 66,822) jcharris@conleyrose.com Rodney B. Carroll (Reg. No. 39,624) rcarroll@conleyrose.com <u>Postal and Hand-Delivery Address:</u> Conley Rose, P.C. 5601 Granite Parkway, Suite 500 Plano, Texas 75024 (972) 731-2288 (phone) (972) 731-2289 (fax)

Per 37 C.F.R. § 42.8(b)(4), CFAD may be served at the above addresses for Lead and Back-Up Counsel. CFAD consents to electronic service by e-mail. Per 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this Petition.

III. Payment of Fees

The undersigned authorizes the Office to charge the fee required by 37 C.F.R. § 42.15(a) for this Petition to Deposit Account No. 50-1515.

IV. Requirements Per 37 C.F.R. § 42.104

A. Grounds for Standing

CFAD certifies that the '996 Patent is available for *inter partes* review and that CFAD is not barred or estopped from requesting *inter partes* review challenging claims 1-19 of the '996 Patent on the grounds identified in this Petition. Pursuant to 35 U.S.C. § 311(a), any person or entity, including CFAD, “who is not the owner of a patent may file with the Office a petition to institute an *inter partes* review of the patent.” *See Iron Dome LLC v. Chinook Licensing DE LLC*, IPR2014-00674, Paper 9 (Sept. 10, 2004) (allowing petition filed by third party with no relationship to any parties to lawsuits involving patent owner to proceed on the merits). Accordingly, CFAD has standing and is entitled to petition the PTAB for review of the '996 Patent.

B. Identification of Challenge and Precise Relief Requested

Ground 1: CFAD challenges claims 1-19 of the '996 Patent and seeks a ruling that those claims are unpatentable under 35 U.S.C. § 103(a) as obvious over Goldman (Ex. 1004) in view Remington (Ex. 1005) and in further view of Lindberg (Ex. 1007). Goldman, Remington, and Lindberg are available as prior art

under 35 U.S.C. § 102(b).

Ground 2: CFAD challenges claims 1-19 of the '996 Patent and seeks a ruling that those claims are unpatentable under 35 U.S.C. § 103(a) as obvious over Gimet (Ex. 1006) in view of Goldman (Ex. 1004) and in further view of Lindberg (Ex. 1007). Gimet, Goldman, and Lindberg are available as prior art under 35 U.S.C. § 102(b).

Ground 3: CFAD challenges claims 1-19 of the '996 Patent and seeks a ruling that those claims are unpatentable under 35 U.S.C. § 102(b) as anticipated by the Plachetka '255 Publication (Ex. 1008). As discussed in detail below in Section IX, the Plachetka '255 Publication is available as prior art under 35 U.S.C. § 102(b) because it published on April 10, 2003, more than one year prior to the earliest effective filing date of the '996 Patent.

C. Evidence Relied Upon to Support the Challenge

CFAD relies upon the publications cited herein in support of Grounds 1-3. CFAD also relies upon the Declaration of Leon Shargel, Ph.D., R.Ph. (Ex. 1003) and the documents cited therein. Filed herewith are an Exhibit List and copies of the references per 37 C.F.R. § 42.63(e) and 37 C.F.R. § 42.6(c).

D. The Grounds Are Not Redundant or Duplicative

The instant Petition is an original challenge to the '996 Patent, contains only three non-redundant grounds, and provides a detailed element-by-element analysis

that is supported by explanation and evidence, including expert testimony.

Grounds 1 and 2 are obviousness grounds based on different primary references, and Ground 3 is based on a single reference that is not included in Grounds 1 or 2.

As such, CFAD is entitled to have this challenge to the '996 Patent fully considered on the merits because the three unpatentability grounds presented in this Petition are not redundant, duplicative, or improper in any way.

V. Background

A. State of the Art

Non-steroidal anti-inflammatory drugs (NSAIDs) refer to a group of drugs that reduce pain, inflammation, and fever. (Ex. 1003, ¶ 30.) Aspirin is one type of NSAID. (*Id.*) Bayer first chemically synthesized aspirin in the 1890s and began selling aspirin in 1899. (*Id.*) Syntex Corporation disclosed its synthesis of the NSAID, naproxen, in 1968. (*Id.*) Since at least 1971, NSAIDs like aspirin and naproxen have been known to increase gastric acid production and, thus, increase the incidence of gastric ulcers. (*Id.*)

Acid inhibitors refer to a group of agents that reduce gastric acid secretion and gastric acidity. (Ex. 1003, ¶ 31.) Prostaglandins and proton pump inhibitors (PPIs) are types of acid inhibitors. (*Id.* at 32.) In 1996, misoprostol, a prostaglandin, was known to inhibit gastric acid secretion and was approved for the treatment of gastric ulcer disease induced by NSAIDs. (*Id.*) Omeprazole, a PPI,

and its inhibition of gastric action production, was discovered in the early 1980s.

(*Id.*) In 1987, a group led by Gunnel Sundén separated the PPI, esomeprazole, which is the enantiopure (S)-isomer of omeprazole, with improved purity and stability. (*Id.*; *see also* Ex. 1007, col. 3 ll. 48-55.)

Although NSAIDs provide certain therapeutic benefits, their tendency to increase the incidence of gastric ulcers may limit their use. (Ex. 1003, ¶ 34.) In order to avoid such limitations, NSAIDs have been used with acid inhibitors at least as early as 1986. (*Id.*) For decades before that time, doctors had recommended that patients take over-the-counter gastric acid neutralizers like Maalox[®] along with NSAIDs. (*Id.*) Moreover, acid inhibitors have been combined with NSAIDs in a single tablet (i.e., a combination therapy) at least as early as 1986. (Ex. 1003, ¶ 36.) For example, U.S. Patent No. 6,365,184 discloses a single tablet comprising both an NSAID and an acid inhibitor. (*Id.*)

Vimovo[®] is a combination therapy of naproxen and esomeprazole magnesium. (Ex. 1003, ¶ 39.) Vimovo's[®] ingredients, naproxen and esomeprazole magnesium, are available separately as generic drug products. (*Id.*) Pozen's affiliates, including Horizon Pharma USA ("Horizon") and AstraZeneca AB ("AstraZeneca"), currently market and sell Vimovo[®]. Horizon admits that the active pharmaceutical ingredients (APIs) in Vimovo[®] "have been on the market . . . for many years." (Horizon Pharma plc 2014 Irish Statutory Accounts (Ex. 1032) at

35.) For this reason, Horizon resorts to sales tactics to convince physicians to prescribe—and pharmacists to dispense—Vimovo®. (Ex. 1032 at 5.)

Horizon admits that sales of Vimovo® may suffer “[i]f we are unsuccessful in convincing physicians to complete prescriptions through our PME program or otherwise provide prescribing instructions *prohibiting the substitution of . . . generic naproxen and branded Nexium® (esomeprazole) as a substitute.*” (Ex. 1032, at 17 (emphasis added).) This is a common strategy when APIs are not themselves patent worthy. (Ex. 1003, ¶ 40.) Nonetheless, by virtue of obtaining the ’996 Patent, Pozen and its affiliates have succeeded, thus far, in extending a monopoly on a long-known combination that should be available to the public. (*Id.*)

The rewards for such an extension are considerable. Currently, Vimovo® can be purchased for \$26.46 per tablet. (Ex. 1003, ¶ 41.) In contrast, a similar dosage of the two APIs of Vimovo®—esomeprazole magnesium and naproxen—can be purchased without a prescription for under \$1.00 total. (*Id.*) In other words, for the same APIs, the public must pay 30-40 times more for Vimovo®.

B. Prosecution History of the ’996 Patent

The ’996 Patent was not substantively examined. The examiner did not make any rejections to the claims based on the prior art references that support the Grounds in this Petition. (Ex. 1002.) In fact, the application proceeded directly to

allowance without any office actions. (*Id.*) Although the references included in this petition, or similar disclosures thereof, are listed as “References Cited” on the face of the ’996 Patent, they are buried among hundreds of other cited references. (*Id.*)

C. Person of Ordinary Skill in the Art (POSA)

The field of the ’996 Patent is pharmacology. (Ex. 1003, ¶¶ 53.) A POSA in that field at the time of the alleged invention of the ’996 Patent, presumably June 1, 2001, would have been a pharmacist, medical doctor, or pharmaceutical scientist having a doctor of medicine degree, a doctor of pharmacy degree, or a Ph.D. degree, or equivalent training or degree, and at least two years of practical experience or clinical research in pharmaceutical formulations. (*Id.*)

Alternatively, a POSA at the time of the alleged invention would have been a pharmacologist or pharmacokineticist having a Ph.D. degree or equivalent training or degree and at least two years of practical experience or clinical research in pharmacology or pharmacokinetics. (*Id.*)

VI. Claim Construction

A. “inhibited/inhibits”

Claim 1 includes the term “inhibited” and claims 2 and 12 include the term “inhibits” to refer to the release of naproxen. (Ex. 1001, col. 21 ll. 34, 38; col. 22 l. 21.) Although the words “inhibit” and “inhibitor” appear frequently throughout the

specification of the '996 Patent, never once does the '996 Patent specification use either of these words to characterize the release of an NSAID. Instead, these words are used in the '996 Patent specification to describe the biochemical mechanism of action of acid inhibitors. (*See, e.g.*, Ex. 1001, col. 3 ll. 38-40 (“The term “acid inhibitor” refers to agents that inhibit gastric acid secretion and increase gastric pH.”).) This has nothing to do with the release of naproxen.

Because the '996 Patent specification neither uses “inhibit” in any way other than its plain and ordinary meaning, nor assigns it any different meaning to describe the release of an NSAID, its ordinary meaning should apply. Indeed, in litigation involving related patents, Pozen argued that plain and ordinary meaning should apply to the term “inhibit” and cited a dictionary definition to support its construction: “to prevent or slow down the activity or occurrence of (something).” (Ex. 1034 at 51; Ex. 1035 (www.merriamwebster.com/dictionary/inhibit).) Other dictionaries are consistent in defining “inhibit,” “inhibitor,” and “inhibition” to include “slow down,” “hinder,” or “prevent.” (Ex. 1036-1038). Thus, the broadest reasonable interpretation of “inhibit” in light of the specification of the '996 Patent is “to slow down, hinder, or prevent.” Accordingly, the broadest reasonable interpretation of “inhibited” is “slowed down, hindered, or prevented.” (Ex. 1003, ¶ 57.)

The meaning of “inhibit” is broader than the meaning of “prevent.”

“Prevent” means “to stop.” (Ex. 1046; Ex. 1003, ¶ 58.) Accordingly, the meaning of “inhibited” is broader than the meaning of “prevented.” “Prevented” means “stopped.” (*Id.*)

B. All Remaining Terms

Per 37 C.F.R. § 42.100(b), all remaining terms in claims 1-19 should “be given [their] broadest reasonable construction in light of the specification.”

VII. Ground 1: Goldman in view of Remington in further view of Lindberg Renders Obvious Claims 1-19

A. A POSA Would Have Combined Goldman, Remington, and Lindberg

A POSA faced with a common task such as manufacturing a combination therapy oral dosage form comprising known ingredients would have had a rationale (e.g., motivation) and a reasonable expectation of success in consulting one or more reputable publications providing conventional techniques and compositions to perform the task. (Ex. 1003, ¶ 88.) Goldman provides a POSA with a rationale, e.g., a specific teaching, suggestion and motivation, to look to conventional techniques for preparing medicament tablets as set forth in Remington and further incorporates by reference the disclosure of Remington. (Ex. 1005, col. 6 ll. 26-33; Ex. 1003, ¶ 65.)

Goldman discloses the combined use of acid inhibitors with NSAIDs, including naproxen, to prevent the incidence of gastric ulcers and bleeding from

the use of such NSAIDs. A POSA also would have recognized that acid inhibitors are a well-known class of drugs that provide gastric acid inhibiting efficacy, and therefore the POSA would have had a rationale (e.g., motivation) and a reasonable expectation of success in substituting different acid inhibitor compounds into a given combination therapy formulation where the acid inhibitor compound contributes its individual therapeutic attributes (e.g., acid inhibition and gastric pH raising) to the combination. (Ex. 1003, ¶ 66.)

Further, the POSA tasked with evaluating and selecting acid inhibitors would have had a rationale (e.g., motivation) and a reasonable expectation of success in employing more recently obtained and therapeutically more effective compounds, such as PPIs, over previously known, less therapeutically effective compounds, such as prostaglandins and H₂ blockers. (Ex. 1003, ¶ 67.) Further, it would have been obvious to a POSA to select Lindberg's disclosed PPI esomeprazole and substitute it for Goldman's disclosed PPI omeprazole because Lindberg specifically teaches:

It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole . . . [a] more preferred embodiment of the present invention is directed to an optically pure crystalline

enantiomeric magnesium salt of omeprazole and method for the preparation thereof.

(Ex. 1007, col. 1 ll. 50-63; Ex. 1003, ¶ 68.) Moreover, a POSA would have also understood that “the optically pure salts are stable resisting racemization both in neutral pH and basic pH” and that “[t]his high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.” (Ex. 1007, col. 3 ll. 48-55; Ex. 1003, ¶ 69.)

B. Claim 1:

Goldman in view of Remington in further view of Lindberg discloses each limitation of claim 1.

1. A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:

Goldman discloses this limitation. (Ex. 1003, ¶ 71.) Specifically, Goldman discloses, in unit dosage form, “one tablet of [a] pharmaceutical composition in accordance with any of Examples 1-10.” (Ex. 1004, col. 8 ll. 4-7; Ex. 1003, ¶ 72.)

2. naproxen in an amount of 200-600 mg per unit dosage form; and

Goldman discloses this limitation. (Ex. 1003, ¶ 74.) Specifically, Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 75.)

3. esomeprazole in an amount of from 5 to 100 mg per unit dosage form,

Goldman in view of Remington in further view of Lindberg discloses this limitation. (Ex. 1003, ¶ 76.) Specifically, Goldman discloses compositions containing “proton pump inhibitor drugs including omeprazole.” (Ex. 1004, col. 5 ll. 9-31; Ex. 1003, ¶ 77.) Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll. 25-26.) A POSA would have understood this compound to be the PPI esomeprazole. (Ex. 1003, ¶ 79.) Lindberg further discloses that “oral . . . dosages will be in the range of 5 to 500 mg per day of active substance.” (Ex. 1007, col. 6 ll. 21-25.) As discussed above, a POSA tasked with evaluating and selecting compounds from the drug class (e.g., PPIs) would have had a rationale (e.g., motivation) and a reasonable expectation of success in replacing Goldman’s disclosed PPI omeprazole with Lindberg’s disclosed PPI esomeprazole because doing so would be a simple substitution of one known element for another to obtain improved pharmacokinetic, metabolic, and therapeutic properties as taught by Lindberg with predictable results. (Ex. 1007, col. 1 ll. 50-63; Ex. 1003, ¶ 81.)

4. wherein upon introduction of said unit dosage form into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium, and

Goldman in view of Remington in further view of Lindberg discloses this

limitation. (Ex. 1003, ¶ 82.) Specifically, Goldman discloses that the tablets can be prepared as described in Remington (Ex. 1005), which Goldman incorporates by reference. (Ex. 1004, col. 6 ll. 26-33; Ex. 1003, ¶ 86.) Goldman provides that “[v]arious conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed for example by Remington’s Pharmaceutical Sciences.” (Ex. 1004, col. 6 ll. 26-33; Ex. 1003, ¶ 87.) Remington discloses a unit dosage form “where unprotected drug [esomeprazole] coated over the enteric coat is released in the stomach, while the remainder [naproxen], being protected by the coating, is released further down the gastrointestinal tract.” (Ex. 1005, at 1637; Ex. 1003, ¶ 90.) Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll. 25-26.) A POSA would have understood this compound to be the PPI esomeprazole. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets. (Ex. 1007, col. 5 ll. 25-36; Ex. 1003, ¶ 85.) In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ an uncoated drug, and that, following administration, such formulations would release the drug upon contact with the surrounding medium (e.g., immediate release upon entering the stomach) regardless of pH. (Ex. 1003, ¶ 91.)

5. release of at least a portion of said naproxen is inhibited unless the pH of said medium is 3.5 or higher.

Goldman in view of Remington discloses this limitation. (Ex. 1003, ¶ 93.)

As discussed above, Goldman discloses that the tablets comprising known ingredients can be prepared as described in Remington (Ex. 1005), which Goldman incorporates by reference. (Ex. 1004, col. 6 ll. 26-33; Ex. 1003, ¶ 95.) Goldman discloses a composition containing “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 94.) Remington further discloses using enteric coatings to delay the release of drugs:

By definition, enteric coatings are those which remain intact in the stomach . . . to delay the release of drugs which . . . may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin . . .)

Thus, many modern enteric coatings are those [which] remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5.

(Ex. 1005, at 1637; Ex. 1003, ¶ 97.) Thus, Goldman in view of Remington teaches that the release of naproxen is inhibited unless the pH of said medium is 3.5 or higher. (Ex. 1005, at 1637; Ex. 1003, ¶ 99.)

C. Claim 2: The pharmaceutical composition of claim 1, wherein

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious. Goldman in view of Remington further discloses each limitation of claim 2.

1. said naproxen is present in a core layer,

Goldman in view of Remington discloses this limitation. (Ex. 1003, ¶ 102.)

Goldman discloses a composition containing “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 104.) Remington further discloses using enteric coatings to form a core layer. (Ex. 1005, at 1637; Ex. 1003, ¶ 106.)

2. wherein said core layer has a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher.

Goldman in view of Remington discloses this limitation. (Ex. 1003, ¶ 108.)

Remington discloses using enteric coatings to form a core layer to delay the release of drugs from said core, as discussed above. (Ex. 1005, at 1637; Ex. 1003, ¶ 110.)

Thus, Goldman in view of Remington teaches that the release of naproxen is inhibited unless the pH of said medium is 3.5 or higher. (Ex. 1005, at 1637; Ex. 1003, ¶ 111.)

D. Claim 3: The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer tablet comprising a core layer and one or more layers outside of said core layer.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious. Goldman in view of Remington further discloses this limitation of claim 3. (Ex. 1003, ¶ 113.) Specifically, Remington discloses a multilayered unit dosage form tablet, consisting of a core layer and an outer layer where the core layer is coated/protected and the outer layer is

unprotected/uncoated, and “where unprotected drug [esomeprazole] coated over the enteric coat is released in the stomach, while the remainder [naproxen], being protected by the coating, is released further down the gastrointestinal tract.” (Ex. 1005, at 1637; Ex. 1003, ¶ 115.)

E. Claim 4: The pharmaceutical composition of claim 3, wherein said core layer comprises naproxen.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 3 obvious. Goldman in view of Remington further discloses this limitation of claim 4. (Ex. 1003, ¶ 119.) Remington discloses using enteric coatings to form a core layer. (Ex. 1005, at 1637; Ex. 1003, ¶ 124.) Goldman discloses a composition containing “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 121.)

F. Claim 5: The pharmaceutical composition of claim 3, wherein at least one of said one more layers outside said core layer comprises esomeprazole.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 3 obvious. Goldman in view of Remington in further view of Lindberg further render obvious the one of said one more layers outside said core layer of claim 5. (Ex. 1003, ¶ 127.) Lindberg discloses uncoated dosage units of esomeprazole in the form of tablets. (Ex. 1007, col. 5 ll. 25-36; Ex. 1003, ¶ 130.)

G. Claim 6: The pharmaceutical composition of claim 3, wherein said one or more layers outside of said core layer do not contain naproxen.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 3 obvious. Goldman in view of Remington further discloses this limitation of claim 6. (Ex. 1003, ¶ 137.) Remington discloses using enteric coatings to form a core layer to delay the release of drugs from said core, as discussed above. (Ex. 1005, at 1637; Ex. 1003, ¶ 143.) Further, Remington discloses a multilayered unit dosage form “where unprotected drug [esomeprazole] coated over the enteric coat is released in the stomach, while the remainder [naproxen], being protected by the coating, is released further down the gastrointestinal tract.” (Ex. 1005, at 1637; Ex. 1003, ¶ 142.) A POSA would have understood that a typical purpose associated with enteric coatings is to delay release of a drug until after the drug has exited the stomach to prevent nausea or bleeding by irritating the gastric mucosa. For this reason, a POSA would have been motivated to keep all of the naproxen in the core layer and not in one or more layers outside of the core. (Ex. 1003, ¶ 146.)

H. Claim 7: The pharmaceutical composition of claim 1, further comprising at least one carrier.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious. Lindberg further discloses this limitation of claim 7. (Ex. 1003, ¶ 148.) Specifically, Lindberg discloses that “[t]he

pharmaceutical formulations contain . . . a pharmaceutically acceptable carrier.”

(Ex. 1007, col. 5 ll. 12-19; Ex. 1003, ¶ 149.)

I. Claim 8: The pharmaceutical composition of claim 1, further comprising at least one auxiliary agent chosen from the group consisting of lubricants, preservatives, disintegrants, stabilizers, wetting agents, emulsifiers, salts, buffers, coloring agents, flavoring agents, and aromatic substances.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious. Lindberg further discloses this limitation of claim 8. (Ex. 1003, ¶ 151.) Specifically, Lindberg discloses the pharmaceutical composition with auxiliary agents such as “lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.” (Ex. 1007, col. 5 ll. 25-35; Ex. 1003, ¶ 152.)

J. Claim 9: The pharmaceutical composition of claim 1, further comprising at least one ingredient to adjust pH.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious. Lindberg further discloses this limitation of claim 9. (Ex. 1003, ¶ 155.) Specifically, Lindberg discloses the pharmaceutical composition comprising at least one ingredient to adjust pH such as “stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like” (Ex. 1007, col. 5 ll. 25-35; Ex. 1003, ¶ 156.) A POSA would have understood that Lindberg’s alkaline compounds would have adjusted pH. (Ex. 1003, ¶ 157.)

K. Claim 10: A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 1.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious and further discloses each limitation of claim 10. (Ex. 1003, ¶ 159.) Specifically, Lindberg discloses that “[t]he compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions.” (Ex. 1007, col. 2 ll. 30-32; Ex. 1003, ¶ 161.)

L. Claim 11: The method of claim 10, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 10 obvious. Lindberg further discloses this limitation of claim 11. (Ex. 1003, ¶ 163.) Specifically, Lindberg discloses that “[t]he compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions” such as “rheumatoid arthritis.” (Ex. 1007, col. 2 ll. 30-34; Ex. 1003, ¶ 164.)

M. Claim 12:

Goldman in view of Remington in further view of Lindberg discloses each limitation of claim 12.

1. A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:

Goldman discloses this limitation. (Ex. 1003, ¶ 166.) Specifically,

Goldman discloses, in unit dosage form, “one tablet of [a] pharmaceutical composition in accordance with any of Examples 1-10.” (Ex. 1004, col. 8 ll. 4-7; Ex. 1003, ¶ 167.)

2. a core layer comprising naproxen, wherein

Goldman in view of Remington discloses this limitation. (Ex. 1003, ¶ 168.) Specifically, Goldman discloses that the tablets can be prepared as described in Remington (Ex. 1005), which Goldman incorporates by reference. (Ex. 1004, col. 6 ll. 26-33; Ex. 1003, ¶ 169.) Goldman provides that “[v]arious conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed for example by Remington’s Pharmaceutical Sciences.” (Ex. 1004, col. 6 ll. 26-33; Ex. 1003, ¶ 170.) Goldman discloses a composition containing “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 173.) Remington further discloses using enteric coatings to form a core layer. (Ex. 1005, at 1637; Ex. 1003, ¶ 176.) Goldman provides a POSA with a rationale, e.g., a specific teaching, suggestion and motivation, to look to conventional techniques for preparing medicament tablets as set forth in Remington and further incorporates by reference the disclosure of Remington. (Ex. 1003, ¶ 172.)

3. said core layer has a coating that inhibits release of said naproxen from said core layer unless said dosage form is in a medium with a pH of 3.5 or higher; and

Goldman in view of Remington discloses this limitation. (Ex. 1003, ¶ 178.)

Remington discloses using enteric coatings to form a core layer and to delay the release of drugs from said core layer:

By definition, enteric coatings are those which remain intact in the stomach . . . to delay the release of drugs which . . . may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin . . .)

Thus, many modern enteric coatings are those [which] remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5.

(Ex. 1005, at 1637; Ex. 1003, ¶ 183.) Thus, Goldman in view of Remington teaches that the release of naproxen is inhibited unless the pH of said medium is 3.5 or higher. (Ex. 1005, at 1637; Ex. 1003, ¶ 184.)

4. a layer comprising esomeprazole, wherein

Goldman in view of Remington in further view of Lindberg discloses this limitation. (Ex. 1003, ¶ 184.) Specifically, Goldman discloses compositions containing “proton pump inhibitor drugs including omeprazole.” (Ex. 1004, col. 5 ll. 9-31; Ex. 1003, ¶ 186.) Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll.

25-26.) A POSA would have understood this compound to be the PPI esomeprazole. (Ex. 1003, ¶ 188.) Remington discloses a multilayered unit dosage form tablet, consisting of a core layer and an outer layer where the core layer is coated/protected and the outer layer is unprotected/uncoated, and “where unprotected drug [esomeprazole] coated over the enteric coat is released in the stomach, while the remainder [naproxen], being protected by the coating, is released further down the gastrointestinal tract.” (Ex. 1005, at 1637; Ex. 1003, ¶ 191.) As discussed above, a POSA tasked with evaluating and selecting compounds from the drug class (e.g., PPIs) would have had a rationale (e.g., motivation) and a reasonable expectation of success in replacing Goldman’s disclosed PPI omeprazole with Lindberg’s disclosed PPI esomeprazole into a layer as taught by Remington because doing so would be a simple substitution of one known element for another to obtain improved pharmacokinetic, metabolic, and therapeutic properties as taught by Lindberg with predictable results. (Ex. 1007, col. 1 ll. 50-63; Ex. 1003, ¶ 195.)

5. said layer has a non-enteric film coating that, upon ingestion by a patient, releases said esomeprazole into the stomach of said patient.

Goldman in view of Remington in further view of Lindberg discloses this limitation. (Ex. 1003, ¶ 196.) Remington discloses “[f]ilm-[c]oated [t]ablets” as “tablets which are covered with a thin layer or film of a water-soluble material”

with the “same general characteristics as sugar coating” (Ex. 1005, at 1604; Ex. 1003, ¶ 198.) Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll. 25-26.) A POSA would have understood this compound to be the PPI esomeprazole. (Ex. 1003, ¶ 202.) Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets. (Ex. 1007, col. 5 ll. 25-36; Ex. 1003, ¶ 203.) In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ a film coating, and that, following administration, such formulations would release the drug upon contact with the surrounding medium (e.g., immediate release upon entering the stomach). (Ex. 1003, ¶ 199.) A POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having a film-coated drug (e.g., esomeprazole) that releases into the stomach of said patient. (Ex. 1003, ¶ 200.)

N. Claim 13: The pharmaceutical composition of claim 12, wherein naproxen is present in said unit dosage form in an amount of 200-600 mg.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious. Goldman further discloses this limitation of claim 13. (Ex. 1003, ¶ 205.) Specifically, Goldman discloses a pharmaceutical composition containing “naproxen from 200 to 500 mg per dose.” (Ex. 1004, col.

5 ll. 9-19; Ex. 1003, ¶ 206.)

O. Claim 14: The pharmaceutical composition of claim 12, wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious. Lindberg further discloses this limitation of claim 14. (Ex. 1003, ¶ 208.) Specifically, Lindberg discloses esomeprazole with “oral . . . dosages . . . in the range of 5 to 500 mg per day of active substance.” (Ex. 1007, col. 6 ll. 21-25; Ex. 1003, ¶ 211.)

P. Claim 15: The pharmaceutical composition of claim 12, wherein

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious. Goldman in view of Lindberg further discloses each limitation of claim 15.

1. naproxen is present in said unit dosage form in an amount of between 200-600 mg and

Goldman discloses this limitation. (Ex. 1003, ¶ 214.) Specifically, Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 215.)

2. esomeprazole in an amount of from 5 to 100 mg per unit dosage form.

Lindberg discloses this limitation. (Ex. 1003, ¶ 216.) Specifically, Lindberg discloses esomeprazole with “oral . . . dosages . . . in the range of 5 to 500 mg per

day of active substance.” (Ex. 1007, col. 6 ll. 21-25; Ex. 1003, ¶ 219.)

Q. Claim 16: A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 12.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious and further discloses each limitation of claim 16. (Ex. 1003, ¶ 222.) Specifically, Lindberg discloses that “[t]he compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions.” (Ex. 1007, col. 2 ll. 30-32; Ex. 1003, ¶ 223.)

R. Claim 17: The method of claim 16, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 16 obvious. Lindberg further discloses this limitation of claim 17. (Ex. 1003, ¶ 225.) Specifically, Lindberg discloses that “[t]he compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions” such as “rheumatoid arthritis.” (Ex. 1007, col. 2 ll. 30-34; Ex. 1003, ¶ 226.)

S. Claim 18: A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 15.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 15 obvious and further discloses each limitation of claim

18. (Ex. 1003, ¶ 229.) Specifically, Lindberg discloses that “[t]he compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions.” (Ex. 1007, col. 2 ll. 30-32; Ex. 1003, ¶ 230.)

T. Claim 19: The method of claim 18, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 18 obvious. Lindberg further discloses this limitation of claim 19. (Ex. 1003, ¶ 232.) Specifically, Lindberg discloses that “[t]he compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions” such as “rheumatoid arthritis.” (Ex. 1007, col. 2 ll. 30-34; Ex. 1003, ¶ 233.)

VIII. Ground 2: Gimet in view of Goldman and Lindberg Renders Obvious Claims 1-19

A. A POSA Would Have Combined Gimet, Goldman, and Lindberg

A POSA would have known that Gimet’s disclosed prostaglandin, misoprostol, is an acid inhibitor. (Ex. 1003, ¶ 236.) As such, a POSA would have understood that Gimet discloses a combination therapy oral unit dosage form comprising an acid inhibitor (e.g., prostaglandin) in combination with an NSAID. (Ex. 1003, ¶ 236.) Similarly, a POSA would have understood that Goldman discloses a combination therapy oral unit dosage form comprising an acid inhibitor (e.g., PPIs) in combination with an NSAID (e.g., naproxen). (Ex. 1003, ¶ 237.)

The POSA would have known that NSAIDs are a well-known class of drugs which provide analgesic effects, and therefore the POSA would have had a rationale (e.g., motivation) and a reasonable expectation of success in substituting different NSAID compounds in a given combination therapy formulation where each drug contributes its individual therapeutic attributes to the combination. (Ex. 1003, ¶ 238.) Further, the POSA tasked with evaluating and selecting compounds from the drug class (e.g., NSAIDs) would have had a rationale (e.g., motivation) and a reasonable expectation of success in replacing Gimet's disclosed NSAIDs (e.g., piroxicam) with Goldman's disclosed NSAIDs (e.g., naproxen) because doing so would be a simple substitution of one known element for another to obtain predictable results. (Ex. 1003, ¶ 239.) Accordingly, it would have been obvious to a POSA to select naproxen from the listed NSAID/acid inhibitor combination therapies of Goldman as a simple substitution for piroxicam used in the NSAID/acid inhibitor combination therapies of Gimet.

A POSA also would have recognized that acid inhibitors are a well-known class of drugs that provide gastric acid inhibiting efficacy, and therefore the POSA would have had a rationale (e.g., motivation) and a reasonable expectation of success in substituting different acid inhibitor compounds into a given combination therapy formulation where the acid inhibitor compound contributes its individual therapeutic attributes (e.g., acid inhibition and gastric pH raising) to the

combination. (Ex. 1003, ¶ 241.)

Further, the POSA tasked with evaluating and selecting acid inhibitors would have had a rationale (e.g., motivation) and a reasonable expectation of success in employing more recently obtained and therapeutically more effective compounds, such as PPIs, over previously known, less therapeutically effective compounds, such as prostaglandins and H2 blockers. (Ex. 1003, ¶ 242.) Further, it would have been obvious to a POSA to select Lindberg's disclosed PPI esomeprazole and substitute it for Gimet's disclosed acid inhibitor (prostaglandin) because Goldman specifically teaches that "[p]roton pump inhibitors have been recently introduced as effective gastric acid inhibitors." (Ex. 1004, col. 1 ll. 25-27; Ex. 1003, ¶ 243.) It also would have been obvious to a POSA to select Lindberg's disclosed PPI esomeprazole and substitute it for Goldman's disclosed PPI omeprazole because Lindberg specifically teaches:

It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole . . . [a] more preferred embodiment of the present invention is directed to an optically pure crystalline enantiomeric magnesium salt of omeprazole and method for the preparation thereof.

(Ex. 1007, col. 1 ll. 50-63; Ex. 1003, ¶ 244.) Moreover, a POSA would have also

understood that “the optically pure salts are stable resisting racemization both in neutral pH and basic pH” and that “[t]his high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.” (Ex. 1007, col. 3 ll. 48-55; Ex. 1003, ¶ 245.)

B. Claim 1:

Gimet in view of Goldman and Lindberg discloses each limitation of claim

1.

1. A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:

Gimet discloses this limitation. (Ex. 1003, ¶ 248.) Specifically, Gimet discloses, in unit dosage form, “a pharmaceutical composition which is a core/mantle tablet.” (Ex. 1006, col. 3 ll. 8-14, Fig. 2; Ex. 1003, ¶ 249.)

2. naproxen in an amount of 200-600 mg per unit dosage form; and

Gimet in view of Goldman discloses this limitation. (Ex. 1003, ¶ 250.) Specifically, Gimet discloses that “[t]he tablet 16 includes an inner core 18 of an NSAID.” (Ex. 1006, col. 6 l. 25-28, Fig. 2; Ex. 1003, ¶ 251.) Gimet further discloses, “[i]f the inner core is piroxicam, the . . . therapeutically acceptable amount” is “10 to 20 mg.” (Ex. 1006, col. 4 l. 34-42.) Goldman also discloses a composition containing “piroxicam from 10 to 20 mg per dose” or “naproxen from 200 to 500 mg per dose.” (Ex. 1004, col. 5 ll. 9-19, 21-24; Ex. 1003, ¶ 252.) As

discussed above, a POSA tasked with evaluating and selecting compounds from the drug class (e.g., NSAIDs) would have had a rationale (e.g., motivation) and a reasonable expectation of success in replacing Gimet's disclosed NSAIDs (e.g., piroxicam) with Goldman's disclosed NSAIDs (e.g., naproxen) because doing so would be a simple substitution of one known element for another to obtain predictable results. Accordingly, it would have been obvious to a POSA to select naproxen from the listed NSAID/acid inhibitor combination therapies of Goldman as a simple substitution for piroxicam used in the NSAID/acid inhibitor combination therapies of Gimet.

3. esomeprazole in an amount of from 5 to 100 mg per unit dosage form,

Gimet in view of Lindberg discloses this limitation. (Ex. 1003, ¶ 255.) Specifically, Gimet discloses that “[s]urrounding the core is a mantle coating which consists of a prostaglandin.” (Ex. 1006, col. 3 ll. 8-14; Ex. 1003, ¶ 256.) Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll. 25-26.) A POSA would have understood this compound to be the PPI esomeprazole. (Ex. 1003, ¶ 256.) Lindberg further discloses that “oral . . . dosages will be in the range of 5 to 500 mg per day of active substance.” (Ex. 1007, col. 6 ll. 21-25.) As discussed above,

it would have been obvious to a POSA to select Lindberg's disclosed PPI esomeprazole and substitute it for Gimet's disclosed acid inhibitor (a prostaglandin) in an effective equivalent dosage range because PPIs are more effective as acid inhibitors. (Ex. 1003, ¶ 261.) As such, a POSA tasked with evaluating and selecting compounds from the drug class (e.g., acid inhibitors) would have had a rationale (e.g., motivation) and a reasonable expectation of success in replacing Gimet's disclosed acid inhibitor (prostaglandin) with Lindberg's disclosed PPI esomeprazole because doing so would be a simple substitution of one known element for another to obtain improved pharmacokinetic, metabolic, and therapeutic properties as taught by Lindberg with predictable results. (Ex. 1007, col. 1 ll. 50-63; Ex. 1003, ¶ 262.)

4. wherein upon introduction of said unit dosage form into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium, and

Gimet in view of Lindberg discloses this limitation. (Ex. 1003, ¶ 263.)

Specifically, Gimet discloses that “[s]urrounding the core is a mantle coating which consists of a prostaglandin.” (Ex. 1006, col. 3 ll. 8-14; Ex. 1003, ¶ 264.)

Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll. 25-26.) A POSA would have understood this compound to be the PPI esomeprazole. (Ex. 1003, ¶ 266.)

Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets. (Ex. 1007, col. 5 ll. 25-36; Ex. 1003, ¶ 267.) In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ an uncoated drug, and that, following administration, such formulations would release the drug upon contact with the surrounding medium (e.g., immediate release upon entering the stomach) regardless of pH. (Ex. 1003, ¶ 268.)

5. release of at least a portion of said naproxen is inhibited unless the pH of said medium is 3.5 or higher.

Gimet in view of Goldman discloses this limitation. (Ex. 1003, ¶ 270.) Specifically, Gimet discloses a tablet 16 that includes an NSAID inner core 18 surrounded by an enteric coating 20, the latter of which “aids in segregating the NSAID from the prostaglandin and in directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach.” (Ex. 1006, col. 6 ll. 24-36, Fig. 2; Ex. 1003, ¶ 271.) Goldman discloses a composition containing an NSAID “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 272.) A POSA would know that a typical patient would have a pH in the small intestine after exiting the stomach of greater than about 3.5. (Ex. 1003, ¶ 274.) Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a unit dosage form having a delayed release component, for example an enterically-coated drug (e.g., an NSAID such as naproxen) to inhibit the release of the drug from the

dosage form unless the pH of the surrounding medium (e.g., portions of the G.I. tract after exiting the stomach) is 3.5 or higher. (Ex. 1003, ¶ 276.)

C. Claim 2: The pharmaceutical composition of claim 1, wherein

As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious. Gimet in view of Goldman further discloses each limitation of claim 2. (Ex. 1003, ¶ 279.)

1. said naproxen is present in a core layer,

Gimet in view of Goldman discloses this limitation. (Ex. 1003, ¶ 280.) Specifically, Gimet discloses that “[t]he tablet 16 includes an inner core 18 of an NSAID.” (Ex. 1006, col. 6 ll. 25-28, Fig. 2; Ex. 1003, ¶ 281.) Goldman discloses a composition containing an NSAID “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 282.)

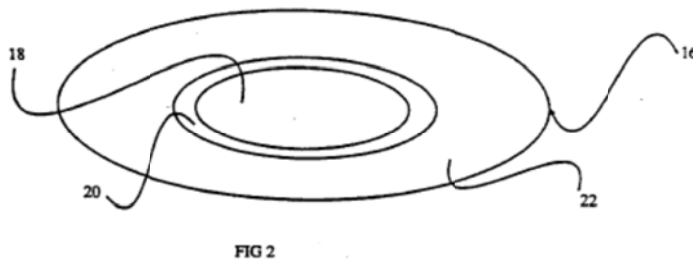
2. wherein said core layer has a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher.

Gimet in view of Goldman discloses this limitation. (Ex. 1003, ¶ 283.) Specifically, Gimet discloses a tablet 16 that includes an NSAID inner core 18 surrounded by an enteric coating 20, the latter of which “aids in segregating the NSAID from the prostaglandin [coating] and in directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach.” (Ex. 1006, col. 6 ll. 24-36, Fig. 2; Ex. 1003, ¶ 284.) Goldman discloses a composition containing an

NSAID “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 285.) A POSA would know that a typical patient would have a pH in the small intestine after exiting the stomach of greater than about 3.5. (Ex. 1003, ¶ 287.) Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a unit dosage form having a delayed release component, for example an enterically-coated drug (e.g., NSAID) to inhibit the release of the drug from the dosage form unless the pH of the surrounding medium (e.g., portions of the G.I. tract after exiting the stomach) is 3.5 or higher. (Ex. 1003, ¶ 289.)

D. Claim 3: The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer tablet comprising a core layer and one or more layers outside of said core layer.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious. Gimet further discloses this limitation of claim 3. (Ex. 1003, ¶ 291.) Specifically, Gimet discloses a multilayered “core [18]/mantle [22] tablet [16]”:



(Ex. 1006, col. 3 ll. 8-14, Fig. 2; Ex. 1003, ¶ 292.)

E. Claim 4: The pharmaceutical composition of claim 3, wherein said core layer comprises naproxen.

As discussed above, Gimet in view of Goldman and Lindberg renders claim

3 obvious. Gimet further discloses this limitation of claim 4. (Ex. 1003, ¶ 294.)

Specifically, Gimet discloses that “[t]he tablet 16 includes an inner core 18 of an NSAID.” (Ex. 1006, col. 6 ll. 25-28, Fig 2; Ex. 1003, ¶ 295.) Goldman discloses a composition containing an NSAID “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 296.)

F. Claim 5: The pharmaceutical composition of claim 3, wherein at least one of said one more layers outside said core layer comprises esomeprazole.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 3 obvious. Gimet in view of Lindberg further discloses this limitation of claim 5. (Ex. 1003, ¶ 298.) Specifically, Gimet discloses “a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID)” and that “[s]urrounding the core is a mantle coating which consists of a prostaglandin.” (Ex. 1006, col. 3 ll. 8-14, Fig. 1; Ex. 1003, ¶ 299.) Lindberg discloses uncoated dosage units of esomeprazole in the form of tablets (Ex. 1007, col. 5 ll. 25-36).

G. Claim 6: The pharmaceutical composition of claim 3, wherein said one or more layers outside of said core layer do not contain naproxen.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 3 obvious. Gimet further discloses this limitation of claim 6. (Ex. 1003, ¶ 305.) Specifically, Gimet discloses “a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID)” and that “[s]urrounding the core is

a mantle coating which consists of a prostaglandin.” (Ex. 1006, col. 3 ll. 8-14; Ex. 1003, ¶ 306.) Gimet further discloses that the composition of the mantle consists only of misoprostol, HPMC, crospovidone, colloidal silicon dioxide, hydrogenated castor oil, and microcrystalline cellulose, and does not disclose any NSAID in the mantle. (Ex. 1006, col. 7 ll. 25-44; Ex. 1003, ¶ 307.) Thus, based on the teachings of Gimet, a POSA would have understood that the mantle does not contain any NSAID such as naproxen. (Ex. 1003, ¶ 308.)

H. Claim 7: The pharmaceutical composition of claim 1, further comprising at least one carrier.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious. Gimet in view of Lindberg further discloses the at least one carrier of claim 7. (Ex. 1003, ¶ 310.) Specifically, Gimet discloses that the pharmaceutical composition includes “cornstarch.” (Ex. 1006, col. 7 ll. 25-44; Ex. 1003, ¶ 311.) A POSA would have understood that cornstarch is a carrier. Lindberg further discloses that “[t]he pharmaceutical formulations contain . . . a pharmaceutically acceptable carrier.” (Ex. 1007, col. 5 ll. 12-19; Ex. 1003, ¶ 313.)

I. Claim 8: The pharmaceutical composition of claim 1, further comprising at least one auxiliary agent chosen from the group consisting of lubricants, preservatives, disintegrants, stabilizers, wetting agents, emulsifiers, salts, buffers, coloring agents, flavoring agents, and aromatic substances.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious. Gimet in view of Lindberg further discloses at least one auxiliary agent

as per claim 8. (Ex. 1003, ¶ 315.) Specifically, Gimet discloses that various auxiliary agents “such as binders, bulking agents, lubricants, fillers and the like” can be combined with the pharmaceutical composition. (Ex. 1006, col. 4 ll. 28-33; Ex. 1003, ¶ 316.) Lindberg further discloses the pharmaceutical composition with auxiliary agents such as “lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.” (Ex. 1007, col. 5 ll. 25-35; Ex. 1003, ¶ 317.)

J. Claim 9: The pharmaceutical composition of claim 1, further comprising at least one ingredient to adjust pH.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious. Gimet in view of Lindberg further discloses this limitation of claim 9. (Ex. 1003, ¶ 320.) Specifically, Gimet discloses that the composition includes “sodium hydroxide.” (Ex. 1006, 8 ll. 18-45; Ex. 1003, ¶ 321.) Lindberg further discloses that the pharmaceutical formulations may be mixed with at least one ingredient to adjust pH, for example, “stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like” (Ex. 1007, col. 5 ll. 25-35; Ex. 1003, ¶ 322.) A POSA would have understood that Gimet’s sodium hydroxide and Lindberg’s alkaline compounds would have adjusted pH. (Ex. 1003, ¶ 323.)

K. Claim 10: A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 1.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious and further discloses each limitation of claim 10. (Ex. 1003, ¶¶ 325-26.) Specifically, Gimet discloses “[a] method of treating inflammation.” (Ex. 1006, col. 12 ll. 41-44; Ex. 1003, ¶ 327.)

L. Claim 11: The method of claim 10, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 10 obvious. Gimet further discloses this limitation of claim 11. (Ex. 1003, ¶ 329.) Specifically, Gimet discloses that the composition may be used to treat “inflammatory conditions such as . . . osteoarthritis (OA) and rheumatoid arthritis (RA).” (Ex. 1006, col. 1 ll. 18-23; Ex. 1003, ¶ 330.)

M. Claim 12:

Gimet in view of Goldman and Lindberg discloses each limitation of claim 12.

1. A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:

Gimet discloses this limitation. (Ex. 1003, ¶ 332.) Specifically, Gimet discloses, in unit dosage form, “a pharmaceutical composition which is a core/mantle tablet.” (Ex. 1006, col. 3 ll. 8-14, Fig. 2; Ex. 1003, ¶ 333.)

2. a core layer comprising naproxen, wherein

Gimet in view of Goldman discloses this limitation. (Ex. 1003, ¶ 334.) Specifically, Gimet discloses that “[t]he tablet 16 includes an inner core 18 of an NSAID.” (Ex. 1006, col. 6 l. 25-28, Fig. 2; Ex. 1003, ¶ 335.) Gimet further discloses, “[i]f the inner core is piroxicam, the . . . therapeutically acceptable amount” is “10 to 20 mg.” (Ex. 1006, col. 4 l. 34-42.) Goldman also discloses a composition containing “piroxicam from 10 to 20 mg per dose” or “naproxen from 200 to 500 mg per dose.” (Ex. 1004, col. 5 ll. 9-19, 21-24; Ex. 1003, ¶ 336.) As discussed above, a POSA tasked with evaluating and selecting compounds from the drug class (e.g., NSAIDs) would have had a rationale (e.g., motivation) and a reasonable expectation of success in replacing Gimet’s disclosed NSAIDs (e.g., piroxicam) with Goldman’s disclosed NSAIDs (e.g., naproxen) because doing so would be a simple substitution of one known element for another to obtain predictable results. Accordingly, it would have been obvious to a POSA to select naproxen from the listed NSAID/acid inhibitor combination therapies of Goldman as a simple substitution for piroxicam used in the NSAID/acid inhibitor combination therapies of Gimet.

3. said core layer has a coating that inhibits release of said naproxen from said core layer unless said dosage form is in a medium with a pH of 3.5 or higher; and

Gimet in view of Goldman discloses this limitation. (Ex. 1003, ¶ 339.)

Specifically, Gimet discloses a tablet 16 that includes an NSAID inner core 18 surrounded by an enteric coating 20, the latter of which “aids in segregating the NSAID from the prostaglandin [coating] and in directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach.” (Ex. 1006, col. 6 ll. 24-36, Fig. 2; Ex. 1003, ¶ 340.) Goldman discloses a composition containing an NSAID “naproxen.” (Ex. 1004, col. 5 ll. 9-19; Ex. 1003, ¶ 341.) A POSA would know that a typical patient would have a pH in the small intestine after exiting the stomach of greater than about 3.5. (Ex. 1003, ¶ 343.) Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a unit dosage form having a delayed release component, for example an enterically-coated drug (e.g., an NSAID such as naproxen) to inhibit the release of the drug from the dosage form unless the pH of the surrounding medium (e.g., portions of the G.I. tract after exiting the stomach) is 3.5 or higher. (Ex. 1003, ¶ 345.)

4. a layer comprising esomeprazole, wherein

Gimet in view of Lindberg discloses this limitation. (Ex. 1003, ¶ 346.) Specifically, Gimet discloses that “[s]urrounding the core is a mantle coating which consists of a prostaglandin.” (Ex. 1006, col. 3 ll. 8-14; Ex. 1003, ¶ 347.) Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll. 25-26.) A POSA would have

understood this compound to be the PPI esomeprazole. (Ex. 1003, ¶ 350.) As discussed above, it would have been obvious to a POSA to select Lindberg's disclosed PPI esomeprazole and substitute it for Gimet's disclosed acid inhibitor (a prostaglandin) in an effective equivalent dosage range because PPIs are more effective as acid inhibitors. (Ex. 1003, ¶ 351.) As such, a POSA tasked with evaluating and selecting compounds from the drug class (e.g., acid inhibitors) would have had a rationale (e.g., motivation) and a reasonable expectation of success in replacing Gimet's disclosed acid inhibitor (prostaglandin) with Lindberg's disclosed PPI esomeprazole because doing so would be a simple substitution of one known element for another to obtain improved pharmacokinetic, metabolic, and therapeutic properties as taught by Lindberg with predictable results. (Ex. 1007, col. 1 ll. 50-63; Ex. 1003, ¶ 352.)

5. said layer has a non-enteric film coating that, upon ingestion by a patient, releases said esomeprazole into the stomach of said patient.

Gimet in view of Lindberg discloses this limitation. (Ex. 1003, ¶ 353.) Specifically, Gimet discloses that “[s]urrounding the core is a mantle coating which consists of a prostaglandin.” (Ex. 1006, col. 3 ll. 8-14; Ex. 1003, ¶ 354.) Gimet further discloses that the composition of the mantle includes “hydroxypropyl methylcellulose (HPMC).” (Ex. 1006, col. 7 ll. 25-44; Ex. 1003, ¶ 355.) A POSA would have understood HPMC to be a film coating. (*Id.*)

Lindberg discloses “the [m]agnesium salt of (–)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole” in the “form of dosage units.” (Ex. 1007, col. 8 ll. 15-22, col. 5 ll. 25-26.) A POSA would have understood this compound to be the PPI esomeprazole. (Ex. 1003, ¶ 357.)

Lindberg further discloses esomeprazole pellets “coated with a solution of hydroxypropyl methylcellulose.” (Ex. 1007, col. 13 ll. 3-5; Ex. 1003, ¶ 358.) In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ a film coating, and that, following administration, such formulations would release the drug upon contact with the surrounding medium (e.g., immediate release upon entering the stomach). (Ex. 1003, ¶ 359.) A POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having a film-coated drug (e.g., esomeprazole) that releases into the stomach of said patient. (Ex. 1003, ¶ 360.)

N. Claim 13: The pharmaceutical composition of claim 12, wherein naproxen is present in said unit dosage form in an amount of 200-600 mg.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious. Gimet in view of Goldman further discloses this limitation of claim 13. (Ex. 1003, ¶ 362.) Specifically, Gimet discloses that “[t]he tablet 16 includes an inner core 18 of an NSAID.” (Ex. 1006, col. 6 l. 25-28, Fig 2; Ex. 1003, ¶ 363.) Gimet further discloses, “[i]f the inner core is piroxicam, the . . . therapeutically

acceptable amount” is “10 to 20 mg.” (Ex. 1006, col. 4 l. 34-42.) Goldman also discloses a composition containing “piroxicam from 10 to 20 mg per dose” or “naproxen from 200 to 500 mg per dose.” (Ex. 1004, col. 5 ll. 9-19, 21-24; Ex. 1003, ¶ 364.)

O. Claim 14: The pharmaceutical composition of claim 12, wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious. Gimet in view of Lindberg further discloses this limitation of claim 14. (Ex. 1003, ¶ 366.) Specifically, Lindberg discloses esomeprazole with “oral . . . dosages . . . in the range of 5 to 500 mg per day of active substance.” (Ex. 1007, col. 6 ll. 21-25; Ex. 1003, ¶ 371.)

P. Claim 15: The pharmaceutical composition of claim 12, wherein

As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious. Gimet in view of Goldman and Lindberg further discloses each limitation of claim 15.

1. naproxen is present in said unit dosage form in an amount of between 200-600 mg and

Gimet in view of Goldman discloses this limitation. (Ex. 1003, ¶ 375.) Specifically, Gimet discloses that “[t]he tablet 16 includes an inner core 18 of an NSAID.” (Ex. 1006, col. 6 l. 25-28, Fig 2; Ex. 1003, ¶ 376.) Goldman discloses a composition containing an NSAID “naproxen from 200 to 500 mg per dose.” (Ex.

1004, col. 5 ll. 9-19; Ex. 1003, ¶ 377.)

2. esomeprazole in an amount of from 5 to 100 mg per unit dosage form.

Gimet in view of Lindberg further discloses this limitation. (Ex. 1003, ¶ 378.) Specifically, Lindberg discloses esomeprazole with “oral . . . dosages . . . in the range of 5 to 500 mg per day of active substance.” (Ex. 1007, col. 6 ll. 21-25; Ex. 1003, ¶ 383.)

Q. Claim 16: A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 12.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious and further discloses each limitation of claim 16. (Ex. 1003, ¶ 387.) Specifically, Gimet discloses “[a] method of treating inflammation.” (Ex. 1006, col. 12 ll. 41-44; Ex. 1003, ¶ 388.)

R. Claim 17: The method of claim 16, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 16 obvious. Gimet further discloses this limitation of claim 17. (Ex. 1003, ¶ 390.) Specifically, Gimet discloses that the composition may be used to treat “inflammatory conditions such as . . . osteoarthritis (OA) and rheumatoid arthritis (RA).” (Ex. 1006, col. 1 ll. 18-23; Ex. 1003, ¶ 391.)

S. Claim 18: A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 15.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 15 obvious and further discloses each limitation of claim 18. (Ex. 1003, ¶ 394.) Specifically, Gimet discloses “[a] method of treating inflammation.” (Ex. 1006, col. 12 ll. 41-44; Ex. 1003, ¶ 395.)

T. Claim 19: The method of claim 18, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

As discussed above, Gimet in view of Goldman and Lindberg renders claim 18 obvious. Gimet further discloses this limitation of claim 19. (Ex. 1003, ¶ 397.) Specifically, Gimet discloses that the composition may be used to treat “inflammatory conditions such as . . . osteoarthritis (OA) and rheumatoid arthritis (RA).” (Ex. 1006, col. 1 ll. 18-23; Ex. 1003, ¶ 398.)

IX. Ground 3: The Plachetka ’255 Publication Anticipates Claims 1-19

A. The Earliest Effective Filing Date of the ’996 Patent is May 16, 2005 Due to a Break in Priority

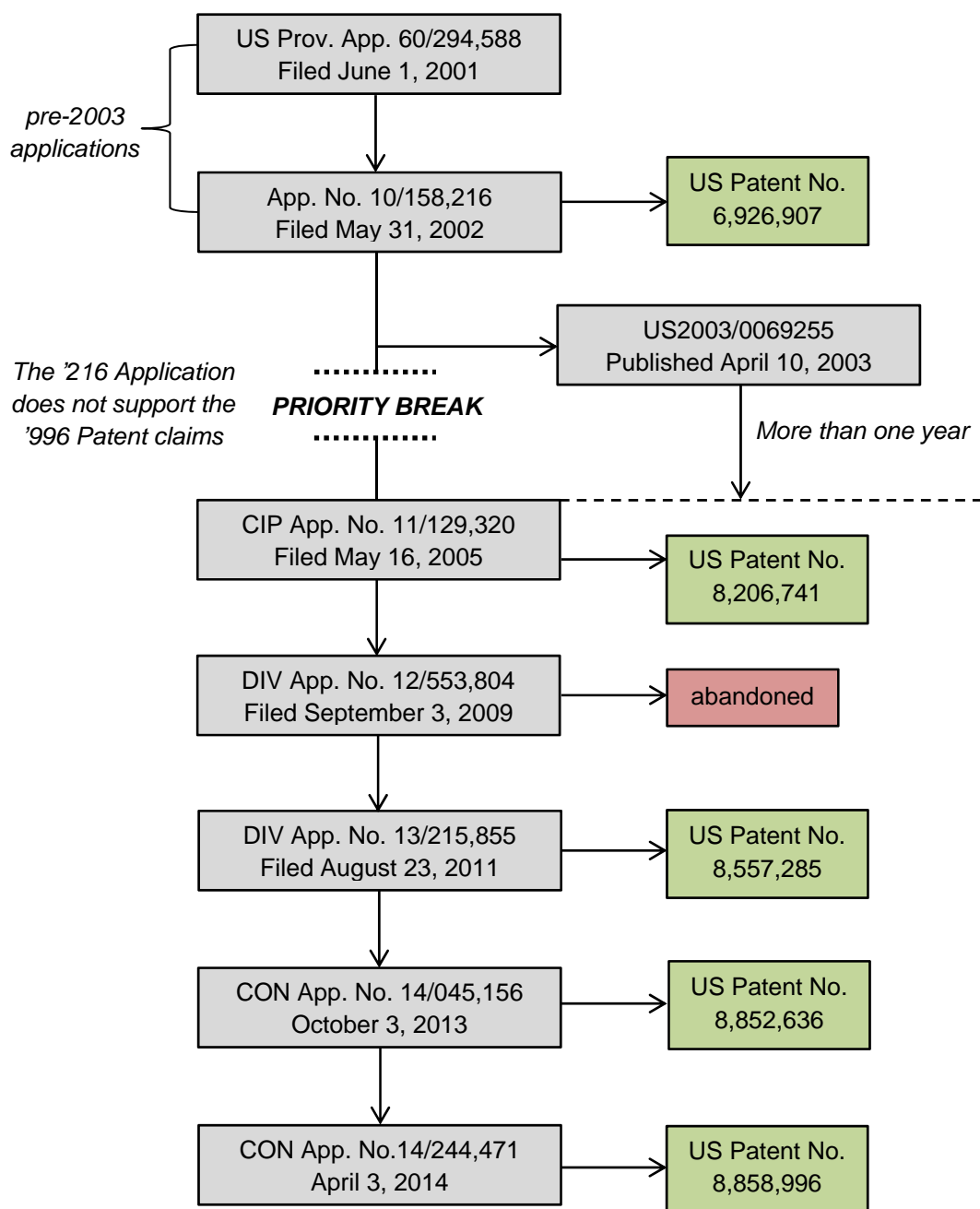
The ’996 Patent issued on October 14, 2014 from U.S. Patent App. No. 14/244,471 (“the ’471 Application”) (Ex. 1002). The ’471 Application, filed on April 3, 2014, is a sixth-generation descendent of U.S. Patent Prov. App. No. 60/294,588 (“the ’588 Application”) (Ex. 1009), filed on June 1, 2001. The ’996 Patent claims priority to the ’588 Application and to the first-generation

descendent of the '588 Application, U.S. Patent App. No. 10/158,216 (“the '216 Application”) (Ex. 1010), filed on May 31, 2002 (collectively, “the pre-2003 applications”). Despite the claim of priority, the '996 Patent claims are not supported by the pre-2003 applications because the claims are broader than the disclosures of the pre-2003 applications.

The '216 Application published as the Plachetka '255 Publication (Ex. 1008) on April 10, 2003, more than two years before the filing of any application to which the '996 Patent may claim priority. The next application in the chain, U.S. Patent App. No. 11/129,320 (“the '320 Application”) (Ex. 1011), filed on May 16, 2005, is the earliest application that supports the '996 Patent claims. As such, the effective filing date of the claims of the '996 Patent is no earlier than May 16, 2005, and the Plachetka '255 Publication is prior art to the '996 Patent under 35 U.S.C. § 102(b).

The following flow chart shows the application chain that preceded the '996 Patent and the priority break:

**Application Chain Leading to
U.S. Patent No. 8,858,996**



Under the broadest reasonable construction standard, the '996 Patent claims are broad enough to encompass naproxen/esomeprazole pharmaceutical compositions that:

- release at least a portion of the naproxen immediately at any pH;
- “inhibit” or slow down the release of all of the naproxen at a pH below 3.5 until the pH reaches 3.5 or higher; and
- do not have a “coordinated release” or sequential release of the esomeprazole and the naproxen.

The break in the priority arises because neither of the two pre-2003 applications has a written description to support a naproxen/esomeprazole pharmaceutical composition with any of these features. Indeed, these features are contrary to much of what the pre-2003 applications do support. The pre-2003 applications disclose NSAID/acid inhibitor pharmaceutical compositions that:

- release none of the NSAID immediately;
- “prevent” or stop the release of all of the NSAID until reaching a pH of 3.5 or higher; and
- have a “coordinated release” or sequential release of the acid inhibitor and the NSAID.

The pre-2003 applications describe pharmaceutical compositions that “prevent” or stop the release of all of the NSAID by surrounding the NSAID with

an enteric coating. The '996 Patent claims are broader because they require only a portion of the NSAID (naproxen) to be subject to an “inhibited” release. As such, the '996 Patent claims are broad enough to cover pharmaceutical compositions wherein at least some of the naproxen is released immediately at any pH.

Moreover, the '996 Patent claims all recite a coating that “inhibits” or slows down the release of at least a portion the naproxen at a pH below 3.5 unless the pH reaches 3.5 or higher, rather than “preventing” or stopping the release until the pH is 3.5 or higher. As discussed above in Section VI(A), the meaning of “inhibit” is broader than the meaning of “prevent.” “Inhibit” means “to slow down, hinder, or prevent.” “Prevent” means “to stop.” Because “inhibit” means either to slow down or to stop, the '996 Patent claims read on a coating that merely decreases the release rate of the naproxen, instead of stopping the release of naproxen, until the pH of the medium is 3.5 or higher.

Finally, contrary to the disclosure in the pre-2003 applications, none of the claims of the '996 Patent recite a “coordinated release” or sequential release of the esomeprazole and the naproxen as an element. The '996 Patent claims are broad enough to cover pharmaceutical compositions that release at least a portion of esomeprazole and naproxen simultaneously.

Because all of the claims of the '996 Patent exceed the scope of the disclosure in the pre-2003 applications, they cannot rely on the pre-2003

applications for priority. Although the Plachetka '255 Publication does not support claims 1-19 of the '996 Patent, it anticipates all of the claims as discussed below.

See Chester v. Miller, 906 F.2d 1574, 1576-77 (Fed. Cir. 1990) (holding that a patent may be § 102(b) prior art as to broader claims of a subsequent application while not containing a sufficient disclosure with respect to the anticipated broader claims).

B. The Plachetka '255 Publication Discloses Each Limitation of Claims 1-19

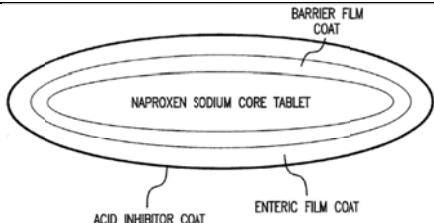
<p>U.S. Pat. No. 8,858,996 Filed: April 3, 2014 Earliest Priority: May 16, 2005</p>	<p>Ground 3 (§ 102(b)) U.S. Patent App. Pub. No. US 2003/0069255 ("Plachetka '255 Publication") Published: April 10, 2003 Claims 1-19</p>
<p>1. A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:</p>	<div data-bbox="734 1062 1162 1285" data-label="Image"> <p>The diagram shows a cross-section of a tablet with four concentric layers. The outermost layer is labeled 'BARRIER FILM COAT'. Inside that is the 'NAPROXEN SODIUM CORE TABLET'. The next layer inward is labeled 'ACID INHIBITOR COAT', and the innermost layer is labeled 'ENTERIC FILM COAT'.</p> </div> <p>FIG.1</p> <p>In its first aspect, the invention is directed to a pharmaceutical composition in unit dosage form suitable for oral administration to a patient . . . The term “unit dosage form” as used herein refers to a single entity for drug administration. For example, a single tablet or capsule combining both an acid inhibitor and an NSAID would be a unit dosage form. <i>See ¶¶ [0011]-[0013]; see also Claims 1 and 12, and Fig. 1.</i></p>
<p>naproxen in an amount of 200-600 mg per unit dosage form; and</p>	<p>The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. . . . The most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount of</p>

	<u>between 200 mg and 600 mg.</u> <i>See ¶ [0012]; see also Claim 11.</i>
esomeprazole in an amount of from 5 to 100 mg per unit dosage form,	For example, the proton pump inhibitor omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 20 mg per unit dosage form being preferred. Other typical amounts are: <u>esomeprazole, 5-100 mg, with about 40 mg per unit dosage form being preferred</u> <i>See ¶ [0041]; see also Claim 5.</i>
wherein upon introduction of said unit dosage form into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium, and	<u>The outermost layer contains an “acid inhibitor” in an effective amount which is released from the dosage form immediately after administration to the patient.</u> <i>See ¶ [0051]; see also ¶¶ [0011], [0048]; Fig. 1 and Claim 5.</i> <u>The term “acid inhibitor” refers to agents that inhibit gastric acid secretion and increase gastric pH.</u> <u>other agents that may be effectively used include</u> proton pump inhibitors such as omeprazole, <u>esomeprazole</u> , pantoprazole, lansoprazole or rabeprazole. <i>See ¶ [0011].</i>
release of at least a portion of said naproxen is inhibited unless the pH of said medium is 3.5 or higher.	<u>The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5.</u> The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an unprotected stomach . . . The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released. <i>See ¶ [0050]; see also ¶¶ [0012]-[0015] and Claims 1, 12, and 18.</i>
2. The pharmaceutical composition of claim 1, wherein	As shown above, the Plachetka '255 Publication anticipates claim 1. <i>See supra.</i>
said naproxen is present in a core layer,	FIG. 1 is a schematic diagram of a four layer tablet dosage form. <u>There is a naproxen core layer</u> surrounded by a barrier layer. <i>See ¶ [0017]; see also ¶¶ [0012]-[0015] and Claims 9 and 12-14.</i>
wherein said core layer has a coating that inhibits its release from said unit dosage form	<u>The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5.</u> The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an

unless said dosage form is in a medium with a pH of 3.5 or higher.	unprotected stomach . . . The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released. <i>See ¶ [0050]; see also ¶¶ [0012]-[0015] and Claims 1, 12, and 18.</i>
3.The pharmaceutical composition of claim 1, wherein	As shown above, the Plachetka '255 Publication anticipates claim 1. <i>See supra.</i>
said unit dosage form is a multilayer tablet comprising a core layer and one or more layers outside of said core layer.	FIG. 1 is a schematic diagram of a four layer tablet dosage form. <u>There is a naproxen core layer</u> surrounded by a barrier layer . . . <u>Finally, there is an outer layer that releases an acid inhibitor</u> <i>See ¶ [0017]; see also ¶¶ [0012]-[0015] and Claims 1, 12, 13, and 14.</i>
4.The pharmaceutical composition of claim 3, wherein	As shown above, the Plachetka '255 Publication anticipates claim 3. <i>See supra.</i>
said core layer comprises naproxen.	FIG. 1 is a schematic diagram of a four layer tablet dosage form. <u>There is a naproxen core layer</u> surrounded by a barrier layer. <i>See ¶ [0017]; see also ¶¶ [0012]-[0015] and Claims 1, 9, 12, 13, and 14.</i>
5.The pharmaceutical composition of claim 3, wherein	As shown above, the Plachetka '255 Publication anticipates claim 3. <i>See supra.</i>
at least one of said one more layers outside said core layer comprises esomeprazole.	<u>The outermost layer contains an “acid inhibitor” in an effective amount which is released from the dosage form immediately after administration to the patient.</u> <i>See ¶ [0051]; see also ¶¶ [0011], [0048]; Fig. 1 and Claim 5.</i> <u>The term “acid inhibitor” refers to agents that inhibit gastric acid secretion and increase gastric pH. . . . other agents that may be effectively used include</u> proton pump inhibitors such as omeprazole, <u>esomeprazole</u> , pantoprazole, lansoprazole or rabeprazole. <i>See ¶ [0011].</i>
6.The pharmaceutical composition of claim	As shown above, the Plachetka '255 Publication anticipates claim 3. <i>See supra.</i>

3, wherein	
said one or more layers outside of said core layer do not contain naproxen.	<p>A schematic diagram of a four layer tablet dosage form is shown in FIG. 1. <u>The first layer contains naproxen</u> <u>The second layer is a barrier layer</u> which protects the first layer containing naproxen . . . the core naproxen sodium tablet is coated with coating ingredients such as Opaspray[®]K-1-4210A or Opadry[®]YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used. <u>The function of the third layer is to prevent the release of naproxen</u> sodium until the dosage form reaches an environment where the pH is above about 4 or 5. . . .Methacrylic acid copolymers are used as the enteric coating ingredient, triethyl citrate and dibutyl phthalate are plasticisers, and ammonium hydroxide is used to adjust the pH of the dispersion . . .<u>The outermost layer contains an “acid inhibitor”</u>. . . The acid inhibitor in the present example is a proton pump inhibitor or, preferably the H2 blocker famotidine. . . A typical film coating formulation contains Opadry Clear[®]YS-1-7006 . . . Other ingredients may include: plasticisers such as triethyl citrate, dibutyl phthalate, and polyethylene glycol; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the [acid inhibitor]. <i>See ¶¶ [0048]-[0051]; see also ¶¶ [0064]-[0067]; and [0073]-[0076].</i></p>
7.The pharmaceutical composition of claim 1, further comprising	As shown above, the Plachetka '255 Publication anticipates claim 1. <i>See supra.</i>
at least one carrier.	<p><u>The pharmaceutical compositions of the invention include</u> tablets, dragees, liquids and capsules and can be made in accordance with methods that are standard in the art . . . Drugs and drug combinations will typically be prepared in admixture with conventional excipients. <u>Suitable carriers</u> include, but are not limited to: water; salt solutions; alcohols; gum arabic; vegetable oils; benzyl</p>

	alcohols; polyethylene glycols; gelatin; carbohydrates such as lactose, amylose or starch; magnesium stearate; talc; silicic acid; paraffin; perfume oil; fatty acid esters; hydroxymethylcellulose; polyvinylpyrrolidone; etc. <i>See ¶ [0043].</i>
8. The pharmaceutical composition of claim 1, further comprising	As shown above, the Plachetka '255 Publication anticipates claim 1. <i>See supra.</i>
at least one auxiliary agent chosen from the group consisting of lubricants, preservatives, disintegrants, stabilizers, wetting agents, emulsifiers, salts, buffers, coloring agents, flavoring agents, and aromatic substances.	<u>The pharmaceutical preparations can be</u> sterilized and, if desired, <u>mixed with auxiliary agents</u> such as: <u>lubricants, preservatives, disintegrants; stabilizers; wetting agents; emulsifiers; salts; buffers; coloring agents; flavoring agents; or aromatic substances.</u> <i>See ¶ [0043].</i>
9. The pharmaceutical composition of claim 1, further comprising	As shown above, the Plachetka '255 Publication anticipates claim 1. <i>See supra.</i>
at least one ingredient to adjust pH.	A pharmaceutically acceptable enteric coating surrounds the naproxen core . . . It contains methacrylic acid copolymers which prevent the release of naproxen in the unprotected stomach. <u>Also included [is] . . . sodium hydroxide which is used to adjust the pH of the dispersion.</u> <i>See ¶ [0053]; see also ¶ [0067].</i> Omeprazole granules contain an <u>alkalizing excipient such as sodium bicarbonate.</u> <i>See ¶ [0083].</i>
10. A method of treating a patient for pain or inflammation, comprising	The invention includes <u>methods of treating a patient for pain, inflammation</u> and/or other conditions by administering the pharmaceutical compositions described above. <i>See ¶ [0014]; see also Claim 22.</i>

administering to said patient the pharmaceutical composition of claim 1.	<i>See</i> claim 1, <i>supra</i> .
11. The method of claim 10, wherein	As shown above, the Plachetka '255 Publication anticipates claim 10. <i>See supra</i> .
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with <u>osteoarthritis or rheumatoid arthritis</u> . <i>See ¶ [0014]; see also</i> Claim 23.
12. A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:	 <p style="text-align: center;">FIG. 1</p> <p>In its first aspect, the invention is directed to <u>a pharmaceutical composition</u> in <u>unit dosage form</u> suitable for oral administration to a patient . . . The term “unit dosage form” as used herein refers to a single entity for drug administration. For example, a single <u>tablet</u> or capsule combining both an acid inhibitor and an NSAID would be a unit dosage form. <i>See ¶¶ [0011]-[0013]; see also</i> Claims 1 and 12, and Fig. 1.</p>
a core layer comprising naproxen, wherein	FIG. 1 is a schematic diagram of a four layer tablet dosage form. <u>There is a naproxen core layer</u> surrounded by a barrier layer. <i>See ¶ [0017]; see also ¶¶ [0012]-[0015] and</i> Claims 9 and 12-14.
said core layer has a coating that inhibits release of said naproxen from said core layer unless said dosage form is in a medium with a pH of 3.5 or higher; and	<u>The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5.</u> The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an unprotected stomach . . . The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released. <i>See ¶ [0050]; see also ¶¶ [0012]-[0015] and</i> Claims 1, 12, and 18.

a layer comprising esomeprazole, wherein	<p><u>The outermost layer contains an “acid inhibitor” in an effective amount which is released from the dosage form immediately after administration to the patient.</u> See ¶ [0051]; <i>see also</i> ¶¶ [0011], [0048]; Fig. 1 and Claim 5.</p> <p><u>The term “acid inhibitor” refers to agents that inhibit gastric acid secretion and increase gastric pH. . . . other agents that may be effectively used include</u> proton pump inhibitors such as omeprazole, <u>esomeprazole</u>, pantoprazole, lansoprazole or rabeprazole. See ¶ [0011].</p>
said layer has a non-enteric film coating that, upon ingestion by a patient, releases said esomeprazole into the stomach of said patient.	A typical film coating formulation contains Opadry Clear [®] YS-1-7006 which helps in the formation of <u>the film and in uniformly distributing [the acid inhibitor] within the fourth layer . . . The film coating is thin and rapidly releases [acid inhibitor] for absorption.</u> See ¶ [0051].
13. The pharmaceutical composition of claim 12, wherein	As shown above, the Plachetka '255 Publication anticipates claim 12. <i>See supra.</i>
naproxen is present in said unit dosage form in an amount of 200-600 mg.	The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. . . . <u>The most preferred NSAID is naproxen</u> in an amount of between 50 mg and 1500 mg, and more preferably, <u>in an amount of between 200 mg and 600 mg.</u> See ¶ [0012]; <i>see also</i> Claim 11.
14. The pharmaceutical composition of claim 12, wherein	As shown above, the Plachetka '255 Publication anticipates claim 12. <i>See supra.</i>
esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.	For example, the proton pump inhibitor omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 20 mg per unit dosage form being preferred. Other typical amounts are: <u>esomeprazole, 5-100 mg, with about 40 mg per unit dosage form being preferred</u> See ¶ [0041]; <i>see also</i> Claim 5.
15. The	As shown above, the Plachetka '255 Publication anticipates

pharmaceutical composition of claim 12, wherein	claim 12. <i>See supra.</i>
naproxen is present in said unit dosage form in an amount of between 200-600 mg and	The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. . . . <u>The most preferred NSAID is naproxen</u> in an amount of between 50 mg and 1500 mg, and more preferably, <u>in an amount of between 200 mg and 600 mg.</u> <i>See ¶ [0012]; see also Claim 11.</i>
esomeprazole in an amount of from 5 to 100 mg per unit dosage form.	For example, the proton pump inhibitor omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 20 mg per unit dosage form being preferred. Other typical amounts are: <u>esomeprazole, 5-100 mg, with about 40 mg per unit dosage form being preferred</u> <i>See ¶ [0041]; see also Claim 5.</i>
16. A method of treating a patient for pain or inflammation, comprising	The invention includes <u>methods of treating a patient for pain, inflammation</u> and/or other conditions by administering the pharmaceutical compositions described above. <i>See ¶ [0014]; see also Claim 22.</i>
administering to said patient the pharmaceutical composition of claim 12.	<i>See claim 12, supra.</i>
17. The method of claim 16, wherein	As shown above, the Plachetka '255 Publication anticipates claim 16. <i>See supra.</i>
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with <u>osteoarthritis or rheumatoid arthritis</u> . <i>See ¶ [0014]; see also Claim 23.</i>
18. A method of treating a patient for pain or inflammation, comprising	The invention includes <u>methods of treating a patient for pain, inflammation</u> and/or other conditions by administering the pharmaceutical compositions described above. <i>See ¶ [0014]; see also Claim 22.</i>
administering to said	<i>See claim 15, supra.</i>

patient the pharmaceutical composition of claim 15.	
19. The method of claim 18, wherein	As shown above, the Plachetka '255 Publication anticipates claim 18. <i>See supra.</i>
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with <u>osteoarthritis or rheumatoid arthritis</u> . <i>See ¶ [0014]; see also Claim 23.</i>

X. Any Secondary Considerations of Nonobviousness Would Fail

CFAD is unaware of any evidence of secondary considerations of nonobviousness in this case. (Ex. 1003, ¶ 26.)

XI. Conclusion

CFAD respectfully requests that the Board institute an *Inter Partes* Review of claims 1-19 on the grounds set forth above.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on June 5, 2015 a copy of the foregoing PETITION FOR *INTER PARTES* REVIEW was provided via FedEx, overnight delivery, to the Patent Owner by serving the correspondence address of record for the '996 Patent:

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