

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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COALITION FOR AFFORDABLE DRUGS VII LLC,  
Petitioner,

v.

POZEN INC.,  
Patent Owner.

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IPR2015-01344  
Patent 8,858,996

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**DECLARATION OF LEON SHARGEL, PH.D., R.PH.**

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I, Leon Shargel, Ph.D., R.Ph., declare and state as follows:

**I. Introduction and Bases for Opinions**

1. My name is Leon Shargel, and I reside in Raleigh, North Carolina. I have been retained by Conley Rose, P.C. on behalf of the Coalition for Affordable Drugs VII LLC (“CFAD or Petitioner”) and understand that I am submitting this declaration in connection with the above-referenced *inter partes* review (IPR) proceeding.

2. Specifically, I have been requested to evaluate claims 1-19 of U.S. Patent No. 8,858,996 (“the ’996 Patent”) (Ex. 1001). As detailed in this declaration, it is my opinion that claims 1-19 are anticipated or rendered obvious by prior art references that predate the ’996 Patent. If requested by the parties to this proceeding or the Patent Trial and Appeal Board (“Board”), I will testify about my opinions expressed herein.

3. I reserve the right to modify or supplement my opinions, as well as the bases for my opinions, based on the nature and content of the documentation, data, proof, and other evidence that other experts may present or based on any additional discovery or other information provided to me or found by me in this matter.

**A. Qualifications**

4. I have over 45 years of educational and work experience in the fields of pharmaceuticals, pharmacology, and pharmacokinetics. Along with the

experience listed in my *curriculum vitae* (CV), attached hereto as Appendix A, I note the following experience that is uniquely relevant to the subject matter at issue in this proceeding.

5. I currently am the manager and founder of Applied Biopharmaceutics, LLC. I founded Applied Biopharmaceutics in 2007. Applied Biopharmaceutics provides scientific and technical consulting services for the pharmaceutical industry. For instance, Applied Biopharmaceutics assists clients in developing new dosage forms for Abbreviated New Drug Application (ANDA) and New Drug Application (NDA) submissions with the Food and Drug Administration (FDA).

6. I have been an affiliate professor at the Virginia Commonwealth University School of Pharmacy in Richmond, Virginia since 2006. I have been an adjunct associate professor at the University of Maryland School of Pharmacy in Baltimore, Maryland since 1995.

7. From 2001-2006, I was the Vice President, Biopharmaceutics, at Sandoz, Inc. (formerly Eon Labs) in Wilson, North Carolina. From 1997-2001, I was the Vice President and Technical Director at the National Association of Pharmaceutical Manufacturers in Ronkonkoma, New York. From 1996-1997, I was a Senior Research Pharmacist at Johns Hopkins Bayview Medical Center in Baltimore, Maryland.

8. From 1995-1996, I was an Adjunct Visiting Associate Professor of Pharmacy at Howard University School of Pharmacy and Pharmacal Sciences in Washington, DC. In 1995, I served as the Vice President, Scientific Affairs, at Pharmakinetics Laboratories, Inc. in Baltimore, Maryland. From 1993-1994, I was the Director of Biochemistry and Pharmacokinetics at Forest Laboratories, Inc. in New York, New York. From 1991-1993, I was the Director of Pharmacokinetics at Chelsea Laboratories, Inc. in West Hempstead, New York.

9. From 1982-1991, I was an Associate Professor of Pharmacy and Pharmacology and the Director of Pfeiffer Pharmaceutical Sciences Laboratory, Inc. at Massachusetts College of Pharmacy and Allied Health Sciences in Boston, Massachusetts. From 1975-1982, I was the Section Leader, Pharmaceutics, and an Associate Professor of Pharmacy and Pharmacology at Northeastern University College of Pharmacy and Allied Health Professions in Boston, Massachusetts. From 1969-1975, I was an Associate Research Biologist and Group Leader of Drug Metabolism and Disposition at Sterling-Winthrop Research Institute in Rensselaer, New York.

10. I hold a Bachelor of Science in Pharmacy from the University of Maryland and a Doctor of Philosophy (Ph.D.) in Pharmacology (with minors in Physiology, Biochemistry, and Drug Metabolism) from the George Washington

University Medical Center in Washington, D.C. I am a Registered Pharmacist in the state of Maryland, the state of Massachusetts, and the District of Columbia.

11. I am an active member of several professional societies and have served on various national and international committees. I have organized and participated in many workshops and symposia, and have lectured widely on biopharmaceutics, generic drug development, bioequivalence, and pharmacokinetics.

12. I have authored over 150 publications and several leading textbooks in pharmacy and the pharmaceutical industry, including *Applied Biopharmaceutics and Pharmacokinetics*, which will be published in its 7<sup>th</sup> edition by McGraw-Hill later this year.

13. I am being compensated at a rate of \$425 per hour for my non-testifying work and \$500 per hour of my testifying work in this matter. My compensation is not conditioned on the outcome of this matter.

**B. Materials Reviewed**

14. In preparing this declaration, I reviewed the following materials:

<b>Exhibit No.</b>	<b>Description</b>
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”)

Exhibit No.	Description
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”)
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)
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)

<b>Exhibit No.</b>	<b>Description</b>
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)
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, <a href="http://www.horizonpharma.com/vimovo/">http://www.horizonpharma.com/vimovo/</a> (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

<b>Exhibit No.</b>	<b>Description</b>
1035	Inhibit, <a href="http://www.merriam-webster.com/dictionary/inhibit">http://www.merriam-webster.com/dictionary/inhibit</a> (last visited June 4, 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. Pat. No. 6,262,085
1041	U.S. Pat. Pub. No. 2001/0000468
1042	U.S. Pat. No. 5,051,262
1043	U.S. Pat. No. 5,314, 697
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, <a href="http://www.merriam-webster.com/dictionary/prevent">http://www.merriam-webster.com/dictionary/prevent</a> (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”)



Exhibit No.	Description
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)
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., Alim. Pharmacol. Ther., 32:414-424 (2010) (“Miner”)
1054	FDA Response to Horizon’s Citizen Petition (July 3, 2014)

### C. Legal Principles Used In Analysis

15. I have been asked to provide my opinions as to whether claims 1-19 of the '996 Patent would have been anticipated or obvious to a person of ordinary skill in the art (POSA) at the time of the invention of the '996 Patent. I understand that a POSA is a hypothetical person who is presumed to have known the relevant art at the time of the invention. I also understand that this hypothetical person is a

person of ordinary creativity, and that this person in many cases will be able to fit the teachings of multiple patents together like pieces of a puzzle. I also understand that the inferences and creative steps that a POSA would employ may be considered in an obviousness analysis.

16. I provide my opinions in this declaration based on the following legal principles that were provided to me by counsel for Petitioner.

17. I understand that my analysis requires an understanding of the scope of claims 1-19 of the '996 Patent. I understand that patent claims subject to *inter partes* review are given the “broadest reasonable construction in light of the specification of the patent in which it appears.” 42 C.F.R. § 42.100(b).

18. I understand that, pursuant to 35 U.S.C. § 311(b), a petitioner in an *inter partes* review may request to cancel, as unpatentable, one or more claims of a patent only on a ground that could be raised under 35 U.S.C. § 102 (anticipation) or 35 U.S.C. § 103 (obviousness), and only on the basis of prior art consisting of patents or printed publications.

19. I understand that a claim is unpatentable under 35 U.S.C. § 102 if it is anticipated. I understand that the anticipation analysis involves comparing a claim to a prior art reference to determine whether each and every element of the claimed invention is disclosed in a single prior art reference, either expressly or inherently.

I also understand that material not expressly recited in a single prior art document may still be considered for purposes of anticipation if that material is incorporated by reference into the document. I further understand that an anticipation analysis may include one or more extra references when the extra references are cited to: (A) prove the primary reference contains an “enabled disclosure,” (B) explain the meaning of a term used in the primary reference, or (C) show that a characteristic not disclosed in the reference is inherent.

20. I understand that a claim is unpatentable under 35 U.S.C. § 103 if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the alleged invention was made. I understand that the obviousness analysis involves a consideration of the scope and content of the prior art, the level of ordinary skill in the pertinent art, and the differences between the claimed invention and the prior art. I understand that, where there is a range disclosed in the prior art and the claimed invention overlaps even slightly within the prior art’s range, there is a presumption of obviousness. I also understand that, when a POSA would have reached the claimed invention through routine experimentation, the invention may be deemed obvious.

21. I also understand that obviousness can be established by combining or modifying the teachings of the prior art. Specific teachings, suggestions, or motivations to combine any prior art reference with additional prior art references can be explicit or implicit. I understand that the references themselves may be one source of specific teachings, suggestions, or motivations to combine features of the prior art, but that such teachings, suggestions, or motivations to combine art may come from other sources as well. Specifically, the sources may include logic, judgment, and common sense available to a person of ordinary skill rather than explicit statements in the prior art. For example, I understand that, in claims directed to a combination of two known pharmaceutical compositions, increasing patient compliance provides a motivation to combine the two compositions.

22. I further understand that whether there is a reasonable expectation of success from combining references in a particular way is also relevant to the analysis. I understand there may be a number of rationales that may support a reasonable expectation of success, including:

- combining prior art elements according to known methods to yield predictable results;
- substitution of one known element for another to obtain predictable results;

- use of a known technique to improve similar devices (methods or products) in the same way;
- applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
- “obvious to try,” in other words, choosing from a finite number of identified, predictable solutions with a reasonable expectation of success;
- when a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one; and
- a teaching, suggestion, or motivation to modify or combine references.

23. I understand that an invention may be unpatentable when it is “obvious to try.” For example, when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under § 103.

I understand that for a claimed invention to be “obvious to try,” the number of options to try should be small or easily tested, with a reasonable expectation of success.

24. I understand that when a patent claim arranges prior art elements in a new combination, with each element performing the same function it had been known to perform and yielding no more than one would expect from such an arrangement, the combination is obvious.

25. I understand that it is not proper to use hindsight to combine references or elements of references to reconstruct the invention using the claims as a guide. My analysis of the prior art is based on what a POSA would have understood prior to June 1, 2001, i.e., the time before the earliest claimed priority date for the '996 Patent.

26. I understand that secondary considerations may be relevant to the determination of whether a claim is obvious should Pozen Inc. (“Patent Owner”) raise such allegations or evidence. Such secondary considerations can include evidence of commercial success caused by an invention, evidence of a long-felt need that was solved by an invention, evidence that others copied an invention, evidence that the prior art teaches away, or evidence that an invention achieved an unexpected result. I understand that such evidence must have a nexus, or causal

relationship, to the elements of a claim in order to be relevant to the obviousness or nonobviousness of the claim. I am unaware of any such secondary considerations of nonobviousness having a nexus to the claims at issue in this proceeding.

27. I understand that it may not be proper to combine references when the prior art teaches away from such a combination. However, a reference's mere disclosure of more than one alternative does not constitute teaching away from any of these alternatives.

28. I understand that it may not be proper to combine references when the claimed invention possessed some superior property or advantage that the POSA would have found surprising or unexpected ("unexpected results"). I understand that the results must be shown to be unexpected compared with the closest prior art and be a difference in kind, not of degree.

29. I understand that for a reference to be used to show a claim is obvious, the reference must be analogous art to the claimed invention. I understand that a reference is analogous to the claimed invention if the reference is from the same field of endeavor as the claimed invention, even if the reference addresses a different problem, or if the reference is reasonably pertinent to the problem faced by the inventor, even if the reference is not in the same field of endeavor as the claimed invention. I understand that a reference is reasonably pertinent based on

the problem faced by the inventor as reflected in the specification, either explicitly or implicitly.

## **II. Background**

### **A. State of the Art**

30. Non-steroidal anti-inflammatory drugs (NSAIDs) refer to a group of drugs that reduce pain, inflammation, and fever. *See, e.g.*, U.S. Patent No. 4,757,060 (Ex. 1012), col. 1 ll. 24-26. Aspirin is one type of NSAID. *Id.* Bayer first chemically synthesized aspirin in the 1890s and began selling aspirin in 1899. Since that time, aspirin has become the most widely used medicine ever. “The Mechanism of Action of Aspirin,” J.R. Vane, et al., Pergamon, 2003 (Ex. 1013). Syntex Corporation disclosed its synthesis of naproxen, another NSAID, in 1968. G.B. Patent No. 1211134 (Ex. 1014), at 15 ll. 55-56. However, since at least 1971, NSAIDs like aspirin, diclofenac, ibuprofen, and naproxen have been known to increase gastric acid production and, thus, increase the incidence of gastric ulcers. *See, e.g.*, “Drug-Induced Peptic Ulcer Disease,” Valerie Vella, Journal of the Malta College of Pharmacy Practice, 2005 (Ex. 1015). Accordingly, a POSA would understand that prolonged use of NSAIDs carries a risk of gastrointestinal injury.

31. Acid inhibitors refer to a group of agents that reduce gastric acid secretion and gastric acidity. *See* “Goodman & Gilman’s The Pharmacological



Basis of Therapeutics,” Joel G. Hardman, et al., McGraw-Hill Publ’g Co., Ninth Edition, 1996, at 902-03 (Ex. 1016). *See also* Ex. 1001, col. 3 ll. 38-40 (“The term ‘acid inhibitor’ refers to agents that inhibit gastric acid secretion and increase gastric pH.”). Accordingly, a POSA would understand that known acid inhibitors may be administered to increase the gastric pH above its normal, fasted state range of from about 1 to about 3.5. *See, e.g.*, “Upper Gastrointestinal (GI) pH in Young, Healthy Men and Women, Jennifer B. Dressman, et al., *Pharmaceutical Research*, Vol. 7, No. 7, 756-761 (1990) (Ex. 1017).

32. Prostaglandins, H<sub>2</sub> blockers, and proton pump inhibitors (PPIs) are all types of acid inhibitors. *See* Ex. 1016, at 902-03. Since at least 1973, prostaglandins have been known to inhibit gastric acid production. *See, e.g.*, “Effect of Orally Administered Prostaglandin E<sub>2</sub> and its 15-Methyl Analogues on Gastric Secretion,” *British Med. Journal*, Jan. 20, 1973 (Ex. 1018). 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. *See* Ex. 1016, at 914. In 1970, it was discovered that cimetidine, an H<sub>2</sub> blocker, inhibited gastric acid production. “Tagamet: The Discovery of Histamine H<sub>2</sub>-Receptor Antagonists,” SmithKlein Beecham Pharmas., *Am. Chem. Soc.*, Nov. 24, 1997 (Ex. 1019). Similarly, in the early 1980s, it was discovered that picoprazole, a PPI,

inhibited gastric acid production. “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 (Ex. 1020). Omeprazole, another PPI, and its inhibition of gastric action production, also were discovered in the early 1980s. *See* U.S. Patent No. 4,255,431 (Ex. 1021). *See also* Notice of Final Determination, In re: Patent Term Extension for U.S. Patent No. 6,143,771 (Ex. 1022). Omeprazole (sold commercially as Prilosec®) is a racemic mixture that contains both the (R) and (S) enantiomers. In 1987, a group led by Gunnel Sundén separated esomeprazole (sold commercially as Nexium®), which is the enantiopure (S)-isomer of omeprazole. “Drug Discovery: Practices, Processes, and Perspectives,” Jie Jack Li, et al., John Wiley & Sons, Apr. 3, 2013 (Ex. 1023), at 33.

33. The efficacy of various acid inhibitors on prevention of NSAID-related injury has been studied, for example in “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 (Ex. 1024) having the following abstract:

The associations between nonsteroidal anti-inflammatory drugs (NSAIDs) and the presence and complications of gastroduodenal

erosions and ulcers are well established. Evidence that acid aggravates NSAID-induced Injury provides a rationale for minimising such damage by acid suppression. Other strategies discussed include avoidance of NSAIDs or minimising their dosage, selecting NSAIDs known to cause less damage, and co-prescription of various agents.

Cytoprotection with misoprostol, a prostaglandin analogue, has been shown to be effective in reducing NSAID-related peptic ulcers and their complications. Unfortunately, adverse effects may limit compliance in some patients. Histamine H<sub>2</sub> antagonists have only limited efficacy in the prevention of NSAID-induced ulcers in humans, particularly in the stomach, except at higher than standard dosages. This may relate to their relatively modest effect in elevating gastric pH, especially in comparison with proton pump inhibitors.

Several studies now confirm the efficacy of proton pump inhibitors in the short and longer term prevention of NSAID-induced upper gastrointestinal injury. Placebo-controlled studies suggest reductions of over 70% in gastric and duodenal ulcer rates over 3 to 6 months. The [1998] ASTRONAUT (Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer

Treatment) study documented the greater prophylactic efficacy of omeprazole over ranitidine at standard dosages for 6 months. The OMNIUM (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management) study (1998) showed omeprazole to be slightly more effective overall than misoprostol in preventing the upper gastrointestinal adverse effects of NSAIDs. With both substantially more effective than placebo, although misoprostol was somewhat less well tolerated.

Although substantial reductions in NSAID ulceration are now achievable when co-therapy with a proton pump inhibitor is given, a few patients will still develop ulcers and their complications. Hence the judicious use of NSAIDs in the first instance cannot be overemphasised.

34. Although NSAIDs provide certain therapeutic benefits, their tendency to increase the incidence of gastric ulcers may limit their use. U.S. Patent App. Pub. 2002/0045184 (“Chen,” Ex. 1025), at ¶ 2. In order to avoid such limitations, NSAIDs have been used with acid inhibitors at least as early as 1986. *See, e.g.*, Ex. 1012, col. 3 ll. 13-18. For decades before that time, doctors had recommended that patients take over-the-counter gastric acid neutralizers like Maalox® along

with NSAIDs. However, administration of separate drugs causes various patient compliance issues. Ex. 1025, at ¶ 4; U.S. Patent No. 5,698,225 (“Gimet,” Ex. 1006), col. 12 ll. 20-30. For instance, patients may not remember when to take each drug or how much of each drug to take. Ex. 1025, at ¶ 4. Thus, Chen teaches “a single packaging system that would provide [both an NSAID and an acid inhibitor] for easy distribution and administration.” *Id.* at ¶ 5. In a preferred embodiment, Chen teaches a combination of 500 milligrams (mg) of naproxen and 20 mg of omeprazole. *Id.* at ¶ 111. The literature is replete with therapies that include NSAIDs for their therapeutic effects of reducing pain and inflammation and that include acid inhibitors to address the side effects of the NSAIDs. *See, e.g.* “Management of NSAID-related gastrointestinal mucosal injury,” AF Barrison, et al., *Inflammopharmacology* 7(3) (1999) (Ex. 1026), at 277-86; “Prevention of NSAID-Induced Gastroduodenal Ulcers,” A. Rostom, et al., *Cochrane Database of Systematic Reviews* (2000) (Ex. 1027); “Abolition by Omeprazole of Aspirin Induced Gastric Mucosal Injury in Man,” T K Daneshmend et al., *Gut*, 31 at 514-517 (1990) (Ex. 1028); and U.S. Pat. No. 6,319,519 at col. 1, l. 21-30 (Ex.1029) (“*It has been found experimentally that it is necessary for the prostaglandin to be released before the NSAID so as to protect the stomach from the effects of the NSAID.*” It is therefore preferable that the NSAID is coated to delay release. The

coating may be a standard hydroxypropyl methyl cellulose coat of a thickness sufficient to delay release in the stomach for a short period, an enteric coat to delay NSAID release until it reaches the intestine, or a delay release coating to allow drug release over a period of time to permit less frequent dosing.”) (emphasis added)). Accordingly, a POSA would understand that known acid inhibitors can be co-administered with known NSAIDs in order to mitigate the risk of gastrointestinal injury associated with prolonged NSAID use. Further, a POSA would understand that there may be benefits in releasing the acid inhibitor first, followed by the NSAID, and that the NSAID may be coated to delay its release.

35. Enteric coatings were known in the prior art. Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. “Remington’s Pharmaceutical Sciences”, Alfonso R. Gennaro, et al., Mack Publ’g Co., Seventeenth Edition, 1985 (“Remington,” Ex. 1005), at 1637. The purpose of the enteric coatings is to prevent the release of the drug in the stomach and allow the release of the drug in the small intestine (duodenum). Thus, the drug’s release from the tablet is delayed until the enteric-coated drug moves from the stomach into the duodenum. In the duodenum, the enteric coating dissolves at the higher pH and releases the drug. For some patients, the release of certain drugs (e.g.,

aspirin and other NSAIDS) in the stomach may cause nausea or bleeding by irritating the gastric mucosa. Thus, enteric coatings are designed to remain intact in the low pH environment of the stomach, which typically has a pH of about 1-3.5, but readily dissolve when the pH rises to about 4 or 5 in the areas of the gastrointestinal tract beyond the stomach (e.g., in the small intestine).

36. As discussed further herein, acid inhibitors have been combined with NSAIDs in a single tablet at least as early as 1986. *See* Ex. 1012, at col. 3 ll. 13-18; Ex. 1006, at col. 3 ll. 8-14 (describing “a pharmaceutical composition including a core of an NSAID . . . surrounded by a mantle coating of a prostaglandin”). U.S. Patent No. 6,365,184 to Depui, et al., provides another example of a single tablet comprising both an NSAID and an acid inhibitor, the latter of which may be a prostaglandin, an H<sub>2</sub> blocker, or a PPI. U.S. Patent No. 6,365,184 (“Depui,” Ex. 1030), at col. 1 ll. 11-20 and 45-54. Such a single tablet, Depui recognizes, is “[t]he most promising solution to the problem of healing and preventing NSAID-associated upper gastrointestinal problems like ulcers and dyspeptic symptoms.” *Id.* at col. 1 ll. 45-54. Furthermore, the single tablet addresses the issue of patient compliance when those patients take the active ingredients separately. *Id.* at col. 2 ll. 32-41. Accordingly, a POSA would understand that patient compliance concerns related to separately dosing a

combination therapy (e.g., the extra burden of taking multiple pills having different active ingredients) can be addressed by combining the active ingredients of the combination therapy into a single unit dosage form (e.g., a single tablet or pill).

37. A combination of an NSAID and an acid inhibitor is just one example of what is called a combination therapy. A combination therapy usually consists of two or more active ingredients combined into a single entity. Combination therapies have been used for many indications including cough and cold preparations, antibiotic therapy, asthma products, and others. Many of the active ingredients for these combination therapies were originally approved by the FDA as single entities and were prescribed concurrently. Many of the patents related to these active ingredients have expired.

38. Pharmaceutical companies have sought new ways to obtain patents related to these active ingredients by combining these active ingredients into a single dosage form. These patented combination therapy products are more expensive for the patient compared to taking each active ingredient separately. Through the marketing of a patented combination therapy product, the pharmaceutical companies can increase their revenue greatly by decreasing or hindering the consumer's access to known, tested, safe, and affordable drugs.



39. Vimovo® is a combination therapy of naproxen and esomeprazole magnesium. Vimovo's® ingredients, naproxen and esomeprazole magnesium, are available separately as generic drug products. *See* <http://www.horizonpharma.com/vimovo/> (last visited May 9, 2015) (Ex. 1031). As also discussed above, naproxen (commercially available as generic enteric-coated tablets) has been known since at least 1968 and esomeprazole (commercially available over the counter as Nexium®) has been known since at least 1987. Ex. 1014, at 15 ll. 55-56; Ex. 1023, at 33. 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," Horizon Pharma Public Limited Company, Apr. 9, 2015 (Ex. 1032), at 35. It is my experience that drug companies will promote their branded drugs to physicians for prescribing for their patients and will minimize the fact that the same APIs may be purchased separately at a greatly reduced cost.

40. This is a common strategy when APIs are not themselves patent worthy. For that reason, the applicant for the '996 Patent applicant did not obtain the '996 Patent based on claiming either the long-known API naproxen or the long-

known API esomeprazole. The applicant did not obtain the '996 Patent based on combining those two APIs into a single tablet either. It is my understanding that the applicant obtained the '996 Patent based on esomeprazole either releasing regardless of the pH of the medium or based on esomeprazole having a non-enteric film coating that, upon ingestion, released the esomeprazole. *See* Notice of Final Determination, In re: Patent Term Extension for U.S. Patent No. 6,143,771 (Ex. 1002) at 66. As shown herein, those elements were also long-known.

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.

41. Vimovo® cannot be purchased without a prescription from a licensed physician; however, the two APIs of Vimovo® can be purchased without a prescription. To estimate the cost of Vimovo® versus the cost of purchasing the two APIs separately, I obtained a prescription and purchased a sample of twelve Vimovo® tablets. I also purchased over-the-counter (OTC) esomeprazole magnesium capsules, 22.3 mg and OTC naproxen sodium tablets, 220 mg. I recently purchased all three drug products from a Walmart near my home in Raleigh, North Carolina. *See* Shargel Walmart Receipts (Ex. 1033). The small difference in dose of the naproxen component (500 mg in Vimovo® versus 440 mg

in naproxen) will not have a significant difference in anti-arthritic inflammation activity. My findings are shown in the table below:

**COST OF VIMOVO VERSUS ACTIVE DRUGS BOUGHT SEPARATELY**

<u>Item</u>	<u>Strength</u>	<u>Quantity</u>	<u>Total Cost</u>	<u>Unit Cost per tablet or capsule</u>	<u>Dosage</u>	<u>Cost per day</u>	<u>Comments</u>
<b>Vimovo tablets</b>	Naproxen, 500 mg; Esomeprazole magnesium, 20 mg	12	\$317.48	\$26.46	One tablet twice a day	<b>\$52.91</b>	Requires physician prescription
<b>Esomeprazole magnesium capsule (Nexium)</b>	22.3 mg	28	\$18.44	\$0.66	one capsule once a day	\$0.66	OTC - No prescription
<b>Naproxen sodium tablets</b>	220 mg	100	\$5.48	\$0.05	two tablets twice a day	\$0.22	OTC - No prescription
Total patient cost per day bought separately:						<b>\$0.88</b>	

42. The Vimovo® combination product does not allow flexibility of dosage of each component. Purchasing the APIs separately allows individualization of the dosage so that a patient can titrate up or down the PPI or NSAID dosage.

## **B. Overview of the '996 Patent**

43. The '996 Patent is titled "Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs" and claims priority to June 1, 2001 based on

U.S. Prov. Patent App. No. 60/294,588. Ex. 1001, at (54) and (60). Independent claims 1 and 12 are directed to pharmaceutical compositions in unit dosage form comprising a combination of naproxen and esomeprazole. *Id.* at col. 21 ll. 25-35 and col. 22 ll. 18-27. Independent claim 10 is directed to a method of treating a patient for pain or inflammation by administering the pharmaceutical composition of claim 1. *Id.* at col. 22 ll. 13-15. Independent claim 16 is directed to a method of treating a patient for pain or inflammation by administering the pharmaceutical composition of claim 12. *Id.* at col. 22 ll. 38-40. Independent claim 18 is directed to a method of treating a patient for pain or inflammation by administering the pharmaceutical composition of claim 15, which provides specific dosages. *Id.* at col. 22 ll. 34-37 and 43-45. Claims 2-9, 11, 13-15, 17, and 19 are dependent claims specifying further limitations, for example, the structure and secondary ingredients of the pharmaceutical compositions.

44. During prosecution, the examiner issued a notice of allowance, which provides the following:

The following is an examiner's statement of reasons for allowance: the general state of the art is that solid oral dosage forms comprising proton pump inhibitors (PPIs) such as esomeprazole are enterically coated to prevent the acid sensitive PPI from being degraded by the acidic

environment of the stomach before it can be absorbed. While some art teaches that enteric coatings need not be applied to dosage forms containing PPIs for oral administration like those of the instant claims, those prior art documents do not disclose a combination dosage form as in the present claims of esomeprazole with naproxen. Prior art that discloses a combination of an NSAID such as naproxen enterically coat the naproxen and PPI portions of the dosage form. Compositions in which at least a portion of the esomeprazole is released regardless of the pH of the medium in combination with naproxen have been previously allowed (US 8,557,285). The instant claims are narrower, specifying dosages in milligrams or having a non-enteric film coat layer with esomeprazole that releases the esomeprazole to the stomach upon ingestion.

Ex. 1002, at 66.

**A. Applicant's Admitted Prior Art**

45. The Background of the Invention in the '996 Patent specification acknowledges that it was known in the art that the administration of NSAIDs can lead to the development of gastroduodenal ulcers and erosions. Ex. 1001, at col. 1 ll. 35-38.

46. The Background of the Invention also explains that “a major factor contributing to the development of lesions is the presence of acid in the stomach and upper small intestine of patients.” *Id.* at col. 1 ll. 38-41. The patent cites clinical studies that demonstrate an improvement in the tolerability of NSAIDs when patients also take doses of acid inhibitors. *Id.* at col. 1 ll. 41-47.

47. The Background of the Invention acknowledges that a POSA would have known, prior to the invention, that combination therapies of NSAIDs and proton pump inhibitors (PPIs) were effective at reducing NSAID-induced GI damage:

Recognizing the potential benefits of PPIs for the prevention of NSAID-induced gastroduodenal damage, others have disclosed strategies for combining the two active ingredients for therapeutic purposes. However, these suggestions do not provide for coordinated release or for reducing intragastric acid levels to a non-toxic level prior to the release of NSAID (U.S. Pat. Nos. 5,204,118; 5,417,980; 5,466,436; 5,037,815).

*Id.* at col. 2 ll. 31-41.

48. The Background of the Invention also acknowledges that in 1998 Searle began marketing the combination dosage form Arthrotec™ “for the

treatment of arthritis in patients at risk for development GI ulcers,” and that Arthrotec™ contains the “cytoprotective agent” misoprostol and the NSAID diclofenac. *Id.* at col. 2 ll. 59-63.

49. The Background of the Invention further recognizes that enteric-coated NSAIDs already had been developed. *Id.* at col. 3 ll. 1-2.

50. The Background of the Invention also states that PPIs were considered to be “more potent and longer lasting” and “more protective” than H2 antagonists, citing the prior art. *Id.* at col. 1 ll. 53-54.

51. The Detailed Description of the Invention also explains that the methods for making the “[claimed] formulations are well known in the art” and cites the treatise Remington’s Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton, Pa. (1980). *Id.* at col. 6 ll. 51-53.

**B. Person of Ordinary Skill in the Art (POSA)**

52. I understand that a POSA is one who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity.

53. The field of the ’996 Patent is pharmacology. In my opinion, a POSA in that field at the time of the alleged invention of the ’907 Patent 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. 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.

### **III. Claim Construction**

54. I reviewed Petitioner's proposed claim constructions for this proceeding, and, as discussed below, I agree that those constructions reflect the broadest reasonable construction in light of the specification of the '996 Patent.

55. I understand that the Board has not yet construed the claims in this proceeding. I reserve the right to supplement this declaration based on alternative constructions proposed by Patent Owner, based on alternative constructions proposed or adopted by the Board, and based on a different invention date if Patent Owner establishes such a date.

#### **A. "Inhibited"**

56. Claim 1 includes the term "inhibited" to refer to the release of naproxen. *Id.* at col. 21 ll. 33-35. 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, at 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.

57. 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 the following dictionary definition to support its construction: “to prevent or slow down the activity or occurrence of (something).” April 4, 2014 Patent Owner responses to invalidity contentions (Ex. 1034), at 51; Inhibit, <http://www.merriam-webster.com/dictionary/inhibit> (last visited June 4, 2015) (Ex. 1035). Other dictionaries are consistent in defining “inhibit,” “inhibitor,” and “inhibition” to include “slow down,” “hinder,” and “prevent.” *See Organic Chemistry*, Robert Thornton Morrison, Sixth Edition, 1992 (Ex. 1036), at 49-50; *The Random House Dictionary of the English Language*, Random House, First Printing, 1966 (Ex. 1037), at 732; *The Oxford Encyclopedic*

English Dictionary, Joyce M. Hawkins, et al., 1991 (Ex. 1038), at 730. 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.”

58. The meaning of “inhibit” is broader than the meaning of “prevent.” “Prevent” means “to stop.” *See* Ex. 1046. Accordingly, the meaning of “inhibited” is broader than the meaning of “prevented.” “Prevented” means “stopped.” *See id.*

**B. “Inhibits”**

59. Claims 2 and 12 use the term “inhibits.” Ex. 1001, at col. 21 l. 38 and col. 22 l. 21. “Inhibits” and “inhibited” share the same root word, namely “inhibit.” Thus, the broadest reasonable interpretation of “inhibits” in light of the specification of the ’996 Patent is “slows down, hinders, or prevents.”

**C. All Remaining Terms**

60. I understand and agree that all remaining terms in claims 1-19 should be given their broadest reasonable construction in light of the specification of the ’996 Patent.

**D. The Invalidity Grounds**

**1. Ground 1: Claims 1-19 Are Obvious Under 35 U.S.C. § 103(a)**

61. Claims 1-19 of the '996 Patent are unpatentable under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,204,118 ("Goldman") (Ex. 1004) in view of "Remington's Pharmaceutical Sciences," Alfonso R. Gennaro, et al., Mack Publ'g Co., Seventeenth Edition, 1985 ("Remington") (Ex. 1005) and in further view of U.S. Patent No. 5,204,118 ("Lindberg") (Ex. 1007). Goldman has a publication (issue) date of April 20, 1993. Remington published in 1985. Lindberg has a publication (issue) date of February 3, 1998. Each of Goldman, Remington and Lindberg were publically available more than one year before the '996 Patent's "purported" earliest effective filing date of June 1, 2001. Goldman, Remington, and Lindberg are available as prior art under 35 U.S.C. § 102(b).

**2. Ground 2: Claims 1-19 Are Obvious Under 35 U.S.C. § 103(a)**

62. Claims 1-19 of the '996 Patent are unpatentable under 35 U.S.C. § 103(a) as obvious over Gimet in view of Goldman and Remington. Gimet has a publication (issue) date of December 16, 1997; Goldman has a publication (issue) date of April 20, 1993; and Remington published in 1985. Thus, Gimet, Goldman, and Remington were publically available more than one year before the '996

Patent's "purported" earliest effective filing date of June 1, 2001. Gimet, Goldman, and Remington are available as prior art under 35 U.S.C. § 102(b).

**IV. Ground 1: Goldman in View of Remington in Further View of Lindberg Renders Claims 1-19 Obvious Under U.S.C. § 103(a)**

63. I agree with and incorporate the claim chart for this ground, which is attached hereto as Appendix B and discussed as follows.

**1. A POSA Would Have been Motivated to Combine Goldman, Remington, and Lindberg**

64. Goldman teaches a unit dosage form suitable for oral administration that comprises an NSAID and an acid inhibitor (e.g., a proton pump inhibitor such as omeprazole). Ex. 1005, col. 5 ll. 9-31.

65. Furthermore, Goldman provides the POSA with 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, thereby providing a design incentive to prepare or improve tablets via known techniques including enteric and non-enteric coatings to yield predictable results. *Id.*

66. Additionally, a POSA would have recognized that acid inhibitors are a well-known class of drugs that provide gastric acid inhibiting efficacy; therefore, a 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.

67. Further, 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 employing more recently obtained and therapeutically more effective compounds in therapies over previously known, less therapeutically effective compounds.

68. Accordingly, it would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for Goldman's disclosed omeprazole because Lindberg specifically teaches that "[i]t 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 at col. 1, ll. 50-63.

69. Moreover, a POSA would have also understood that “the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.” *Id.* at col. 3, ll. 48-55.

**B. Claim 1:**

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

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

71. Goldman discloses this limitation.

72. Specifically, Goldman discloses “the oral administration of one tablet of [a] pharmaceutical composition.” Ex. 1005, col. 8 ll. 4-7.

73. Goldman provides a POSA with a rationale (e.g., a specific teaching, suggestion, and motivation) for a combination therapy, coordinated release, oral unit dosage form comprising an acid inhibitor and an NSAID. *Id.* at col. 5 ll. 9-31.

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

74. Goldman discloses this limitation.

75. Specifically, Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

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

76. Goldman in view of Remington in further view Lindberg discloses this limitation.

77. Specifically, Goldman discloses compositions containing “proton pump inhibitor drugs including omeprazole.” Ex. 1004, col. 5 ll. 9-31.

78. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

79. A POSA would have understood that this active compound is esomeprazole. *See* WO 98/54171 (Ex. 1039) p. 1, ll 4-5; *see also* U.S. Pat. No. 6,262,085 (Ex. 1040) at col. 2 ll. 17-19.

80. 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.

81. As discussed above, 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 Goldman’s disclosed omeprazole with Lindberg’s disclosed esomeprazole because doing so

would be a simple substitution of one known element for another to obtain predictable results. *See supra*.

**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**

82. Goldman in view of Remington in further view of Lindberg discloses this limitation.

83. First of all, Lindberg discloses “a pure solid state alkaline salt of the (–)- enantiomer of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

84. A POSA would have understood that this active compound is esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

85. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets, Ex. 1007, col. 5 ll. 25-36, and esomeprazole pellets “coated with a solution of hydroxypropyl methylcellulose.” Ex. 1007, col. 13 ll. 3-5.

86. Secondly, 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.

87. Goldman provides the following:

Various 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. Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms," pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.

Ex. 1004, col. 6 ll. 26-33.

88. A POSA faced with a common task such as manufacturing a combination therapy oral dosage form comprising known ingredients would have a rationale (e.g. motivation) and a reasonable expectation of success in consulting one or more reputable reference publications such as Remington providing conventional techniques to perform the task.

89. Furthermore, 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.

90. Lastly, Remington, in turn, expressly discloses a multilayered unit dosage form "where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract." Ex. 1005, at 1637.

91. In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ an uncoated drug and/or a drug coated with non-enteric coatings, and that, following administration, such formulations may release their drug quickly upon contact with the surrounding medium (e.g., immediate release upon entering the stomach). *See* U.S. Pat. No. 5,314, 697 (Ex. 1043) at col. 3 ll. 18-19.

92. Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having an immediate release component, for example an uncoated drug (e.g., acid inhibitor) and/or a drug coated with a non-enteric coating that releases regardless of the pH of the surrounding medium.

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

93. Goldman in view of Remington discloses this limitation.

94. Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

95. Goldman discloses that the tablets comprising known ingredients can be prepared as described in Remington (Ex. 1005).

96. Goldman incorporates Remington by reference. Ex. 1004, col. 6 ll. 26-33.

97. Remington, in turn, discloses using enteric coatings to inhibit the release of drugs such as naproxen:

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.

98. Thus, Remington teaches that the release of naproxen is inhibited (e.g., slowed down, hindered, or prevented) until after the enteric coating has ionized at a pH of about 4 or 5. Ex. 1007, at 1637.

99. Based on the foregoing, a POSA would have rationale and a reasonable expectation of success in preparing a unit dosage form tablet having an immediate release component, for example an uncoated drug (e.g., esomeprazole) and/or drug coated with a non-enteric coating which releases regardless of the pH of the surrounding medium, and a delayed release component, for example an enterically coated drug (e.g., naproxen), the release thereof which is inhibited until the medium's pH is 3.5 or higher.

**C. Claim 2:**

100. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.

101. Goldman in view of Remington further discloses each limitation of claim 2 as follows.

**1. The pharmaceutical composition of claim 1, wherein said naproxen is present in a core layer,**

102. Goldman in view of Remington discloses this limitation.

103. 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.

104. Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

105. Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

106. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

107. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen. Ex. 1005, at 1637.

- 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.**

108. Goldman in view of Remington discloses this limitation.

109. 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.

110. Remington further discloses using enteric coatings to delay the release of drugs such as naproxen:

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.

111. Thus, Remington teaches that the release of naproxen is inhibited (e.g., slowed down, hindered, or prevented) until after the enteric coating has ionized at a pH of about 4 or 5. Ex. 1005, at 1637.

**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.**

112. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.

113. Goldman in view of Remington further discloses this limitation of claim 3.

114. 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.

115. Specifically, Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

116. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

117. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen with the enteric coating forming a layer outside the naproxen core. Ex. 1005, at 1637.

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

118. As discussed above, Goldman in view of Remington in further view of Lindberg renders claims obvious.

119. Goldman in view of Remington further discloses this limitation of claim 4.

120. 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.

121. Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

122. Remington further discloses using enteric coatings to delay the release of drugs such as naproxen. Ex. 1005, at 1637.

123. Specifically, Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

124. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

125. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen. Ex. 1005, at 1637.

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

126. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.

127. Goldman in view of Remington in further view of Lindberg further discloses this limitation of claim 5.

128. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

129. A POSA would have understood that this active compound is esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

130. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets. Ex. 1007, col. 5 ll. 25-36.



131. 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.

132. Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

133. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

134. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen. Ex. 1005, at 1637.

135. A POSA would have understood that Lindberg’s disclosed uncoated esomeprazole could have been coated over the enterically-coated core layer of naproxen pursuant to the teachings of Remington. Ex. 1005, at 1637.

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

136. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 3 obvious.

137. Goldman in view of Remington in further view of Lindberg further discloses this limitation of claim 6.

138. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

139. A POSA would have understood that this active compound is esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

140. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets. Ex. 1007, col. 5 ll. 25-36.

141. 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.

142. Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the

remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

143. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

144. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen. Ex. 1005, at 1637.

145. A POSA would have understood that Lindberg’s disclosed uncoated esomeprazole could have been coated over the enterically-coated core layer of naproxen pursuant to the teachings of Remington. Ex. 1005, at 1637.

146. A POSA would have understood that an enterically-coated core layer of naproxen coated with an uncoated layer of esomeprazole would have resulted in no layers outside the core layer containing naproxen.

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

147. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.

148. Lindberg further discloses this limitation of claim 7.

149. Specifically, Lindberg discloses that “[t]he pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier.” Ex. 1007, col. 5 ll. 12-19.

**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.**

150. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.

151. Lindberg further discloses this limitation of claim 8.

152. Specifically, Lindberg discloses that the pharmaceutical formulations “may be mixed with . . . lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.” Ex. 1007, col. 5 ll. 25-35.

153. It is my understanding that, because claim 8 uses the phrase “chosen from the group consisting of,” only one of the subsequent elements need be shown for invalidity.

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

154. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.

155. Lindberg further discloses this limitation of claim 9.

156. Specifically, Lindberg discloses that the pharmaceutical formulations “may be mixed with . . . 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.

157. A POSA would have understood that Lindberg’s alkaline compounds would have adjusted pH. *See, e.g.*, U.S. Pat. Pub. No. 2001/0000468 (Ex. 1041) at ¶ [0075] (“The pH can be adjusted to the desired level using an acid and/or alkaline material.”); and U.S. Pat. No. 5,051,262 (Ex. 1042) at col. 5 ll. 61-64 (“Similarly, any non-toxic basic substance may be used as the alkaline pH adjustor, including alkaline salts of organic acids, alkaline carbonates, alkaline bicarbonates, etc.”).

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

158. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.

159. As such, Goldman in view of Remington in further view of Lindberg disclose the pharmaceutical composition of claim 1.

160. Goldman in view of Remington in further view of Lindberg discloses each limitation of claim 10.

161. 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.

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

162. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 10 obvious.

163. Lindberg further discloses this limitation of claim 11.

164. 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. 17-37.

**M. Claim 12:**

165. 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:**

166. Goldman discloses this limitation.

167. Specifically, Goldman discloses “one tablet of [a] pharmaceutical composition.” Ex. 1004, col. 8, ll. 4-7.

**2. a core layer comprising naproxen, wherein**

168. Goldman in view of Remington discloses this limitation.

169. 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

170. 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

171. As discussed above, 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 reference publications such as Remington providing conventional techniques to perform the task.

172. Furthermore, 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.

173. Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

174. Remington further discloses using enteric coatings to delay the release of drugs such as naproxen. Ex. 1005, at 1637.

175. Specifically, Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

176. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

177. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen. Ex. 1005, at 1637.



- 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**

178. Goldman in view of Remington discloses this limitation.

179. 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.

180. Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

181. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

182. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen. Ex. 1005, at 1637.

183. Remington further discloses using enteric coatings to delay the release of drugs such as naproxen:

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.

184. Thus, Remington teaches that the release of naproxen is inhibited until after the enteric coating has ionized at a pH of about 4 or 5. Ex. 1005, at 1637.

**4. a layer comprising esomeprazole, wherein**

185. Goldman in view Remington in further view of Lindberg discloses this limitation.

186. Specifically, Goldman discloses compositions containing “proton pump inhibitor drugs including omeprazole.” Ex. 1004, col. 5 ll. 9-31.

187. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

188. A POSA would have understood that this active compound is esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

189. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets. Ex. 1007, col. 5 ll. 25-36.

190. 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.

191. Remington discloses a multilayered unit dosage form “where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.” Ex. 1005, at 1637.

192. A POSA would have understood Remington to disclose using an enteric coating to form a protected core of a drug to delay the release of said drug. Ex. 1005, at 1637.

193. A POSA would have understood that using an enteric coating to form a protected core of a drug could have formed a core layer of naproxen. Ex. 1005, at 1637.

194. A POSA would have understood that Lindberg’s disclosed uncoated esomeprazole could have been coated over the enterically-coated core layer of naproxen pursuant to the teachings of Remington to form a layer of esomeprazole. Ex. 1005, at 1637.

195. As discussed above, 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 Goldman's disclosed omeprazole with Lindberg's disclosed esomeprazole because doing so would be a simple substitution of one known element for another to obtain predictable results.

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

196. Goldman in view of Remington in further view of Lindberg discloses this limitation.

197. 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.

198. 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.

199. In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ a film coating which, following administration, may release its drug quickly upon contact with the surrounding medium regardless

of the pH of said medium (e.g., immediate release upon entering the stomach). *See* U.S. Pat. No. 5,314, 697 (Ex. 1043) at col. 3 ll. 18-19.

200. Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having an immediate release component, for example a film-coated drug (e.g., esomeprazole) that releases regardless of the pH of the surrounding medium.

201. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

202. A POSA would have understood that this active compound is esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

203. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets, Ex. 1007, col. 5 ll. 25-36, and esomeprazole pellets “coated with a solution of hydroxypropyl methylcellulose.” Ex. 1007, col. 13 ll. 3-5.

**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.**

204. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious.

205. Goldman further discloses this limitation of claim 13.

206. Specifically, Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

**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.**

207. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious.

208. Lindberg further discloses this limitation of claim 14.

209. Specifically, Lindberg discloses “a pure solid state alkaline salt of the (–)- enantiomer of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

210. A POSA would have understood that this active compound is esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

211. 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.

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

212. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious.

213. Goldman in view of Remington in further 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**

214. Goldman discloses this limitation of claim 15.

215. Specifically, Goldman discloses a composition containing “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

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

216. Lindberg discloses this limitation of claim 15.

217. Specifically, Lindberg discloses “a pure solid state alkaline salt of the (–)- enantiomer of 5-methoxy-2[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

218. A POSA would have understood that this active compound is esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

219. 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.

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

220. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious.

221. As such, Goldman in view of Remington in further view of Lindberg disclose the pharmaceutical composition of claim 12.

222. Goldman in view of Remington in further view of Lindberg discloses each limitation of claim 16.

223. 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.

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

224. As discussed above, Goldman in view of Remington in further view of Lindberg renders 16 obvious.

225. Lindberg claim further discloses this limitation of claim 17.

226. 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. 17-37.

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

227. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 15 obvious.

228. As such, Goldman in view of Remington in further view of Lindberg disclose the pharmaceutical composition of claim 15.



229. Goldman in view of Remington in further view of Lindberg discloses each limitation of claim 18.

230. 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.

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

231. As discussed above, Goldman in view of Remington in further view of Lindberg renders claim 18 obvious.

232. Lindberg further discloses this limitation of claim 19.

233. 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. 17-37.

**U. Conclusion**

234. Goldman in view of Remington in further view of Lindberg discloses each element of claims 1-19. Based on my understanding of 35 U.S.C. § 103(a), the combination of Goldman, Remington, and Lindberg renders those claims unpatentable.

**V. Ground 2: Gimet in View of Goldman and Lindberg Renders Claims 1-19 Obvious Under 35 U.S.C. § 103(a)**

235. I agree with and incorporate the claim chart for this ground, which is attached hereto as Appendix C and discussed as follows.

**A. A POSA Would Have Been Motivated to Combine Gimet, Goldman, and Lindberg**

236. A POSA would have known that Gimet's disclosed prostaglandin, misoprostol, is an acid inhibitor. *See* "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 (Ex. 1044), at 1265. 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.

237. Similarly, a POSA would have understood that Goldman discloses a combination therapy oral unit dosage form comprising an acid inhibitor (e.g., H2 blockers and proton pump inhibitors) in combination with an NSAID (e.g., naproxen).

238. 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.

239. 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 (i.e., diclofenac or 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.

240. 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 diclofenac or piroxicam used in the NSAID/acid inhibitor combination therapies of Gimet.

241. Furthermore, a POSA 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.

242. Further, the 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 employing more recently obtained and therapeutically more effective compounds in therapies over previously known, less therapeutically effective compounds.

243. Accordingly, it would have been obvious to a POSA to select Lindberg's disclosed PPI, esomeprazole, and substitute it for Gimet's disclosed prostaglandin because PPIs were known to have greater therapeutic efficacy in preventing the gastrointestinal adverse effects of NSAIDs." Ex. 1024 at 503-512.

244. Alternatively, it would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for Goldman's disclosed omeprazole because Lindberg specifically teaches that "[i]t 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 at col. 1, ll. 50-63.

245. Moreover, a POSA would have also understood that “the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.” *Id.* at col. 3, ll. 48-55.

246. 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 prostaglandin or Goldman’s disclosed omeprazole with Lindberg’s disclosed esomeprazole because doing so would be a simple substitution of one known element for another to obtain predictable results.

**B. Claim 1:**

247. 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:**

248. Gimet discloses this limitation.

249. Specifically, Gimet discloses, in unit dosage form, “a pharmaceutical composition which is a core/mantle tablet.” Ex. 1006, col. 3 ll. 8-14.

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

250. Gimet in view of Goldman discloses this limitation.

251. Specifically, Gimet discloses that “[t]he tablet 10 includes an inner core 12 which is comprised of an NSAID.” Ex. 1006, col. 3 l. 63 – col. 4, l. 11.

252. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

253. 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 (i.e., diclofenac or 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.

254. 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 diclofenac or 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,**

255. Gimet in view of Lindberg discloses this limitation.

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

257. A POSA would have known that Gimet’s disclosed prostaglandin, misoprostol, is an acid inhibitor. *See* Ex. 1044 at 1265.

258. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

259. A POSA would have understood that this active compound, an acid inhibitor, is the PPI esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

260. 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.

261. As discussed above, it would have been obvious to a POSA to select Lindberg’s disclosed acid inhibitor, the PPI esomeprazole, and substitute it for Gimet’s disclosed acid inhibitor (prostaglandin) or for Goldman’s disclosed PPI omeprazole because PPIs are more effective as acid inhibitors than prostaglandins and esomeprazole is more stable than omeprazole.

262. 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) or Goldman's disclosed PPI omeprazole with Lindberg's disclosed acid inhibitor, the PPI esomeprazole, because doing so would be a simple substitution of one known element for another to obtain predictable results.

**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**

263. Gimet in view of Lindberg discloses this limitation.

264. Specifically, Gimet discloses "a core/mantle tablet" and that "[s]urrounding the core is a mantle coating." Ex. 1006, col. 3 ll. 8-14.

265. Lindberg discloses "a pure solid state alkaline salt of the (-)-enantiomer of 5-methoxy-2[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole." Ex. 1007, col. 14 ll. 6-10.

266. A POSA would have understood that this active compound, an acid inhibitor, is the PPI esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

267. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets. Ex. 1007, col. 5 ll. 25-36.



268. In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ an uncoated drug and/or a drug coated with non-enteric coatings, and that, following administration, such formulations would release their drug upon contact with the surrounding medium (e.g., about immediate release upon entering the stomach) regardless of pH. *See* U.S. Pat. No. 5,314, 697 (Ex. 1043) at col. 3 ll. 18-19.

269. Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having an immediate release component, for example an uncoated drug (e.g., acid inhibitor) and/or a drug coated with a non-enteric coating that releases regardless of the pH of the surrounding medium.

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

270. Gimet in view of Goldman discloses this limitation.

271. 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.

272. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

273. 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.

274. A POSA would have known that a typical patient would have a pH in the small intestine after exiting the stomach of greater than about 3.5.

275. Also, a POSA would have known that Gimet’s disclosure means that the acid inhibitor is released first due to its direct contact with stomach fluids and the release of the NSAID does not occur until after the enteric coating breaks down in a more alkaline pH, e.g., a pH of 4.0-7.0 as is found in the lower G.I tract. *See, e.g.,* Ex. 1005, at 1637 (“[M]any 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.”); and “Measurement of gastrointestinal pH profiles in normal ambulant human subjects,” D. F. Evans, et al., *Gut*, 1988, Vol. 29, 1035-1041 (“Evans”) (Ex. 1045), at 1038, Fig. 3 (As shown in Figure 3, a patient’s stomach has a pH below 3.5 and its lower G.I. tract has a pH greater than 3.5, thus Gimet’s disclosed enteric coating “directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach would “prevent[] the release of

essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher.”).

276. A 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.

277. Based on the foregoing, a POSA would have rationale and a reasonable expectation of success in preparing a unit dosage form tablet having an immediate release component, for example an uncoated drug (e.g., esomeprazole) and/or drug coated with a non-enteric coating which releases regardless of the pH of the surrounding medium, and a delayed release component, for example an enterically coated drug (e.g., naproxen), the release thereof which is inhibited until the medium’s pH is 3.5 or higher.

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

278. As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.

279. Gimet in view of Goldman further discloses each limitation of claim 2.

**1. said naproxen is present in a core layer,**

280. Gimet in view of Goldman discloses this limitation.

281. Specifically, Gimet discloses that “[t]he tablet 10 includes an inner core 12 which is comprised of an NSAID.” Ex. 1006, col. 3 l. 63 – col. 4, l. 11, Fig. 2.

282. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

**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.**

283. Gimet in view of Goldman discloses this limitation.

284. 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.

285. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

286. 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.

287. A POSA would have known that a typical patient would have a pH in the small intestine after exiting the stomach of greater than about 3.5.

288. Also, a POSA would have known that Gimet's disclosure means that the release of the NSAID does not occur until after the enteric coating breaks down in a more alkaline pH, e.g., a pH of 4.0-7.0 as is found in the lower G.I tract. *See, e.g.,* Ex. 1005, at 1637 (“[M]any 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.”); and Ex. 1045 at 1038, Fig. 3 (As shown in Figure 3, a patient's stomach has a pH below 3.5 and its lower G.I. tract has a pH greater than 3.5, thus Gimet's disclosed enteric coating “directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach would “prevent[] the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher.”).

289. 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

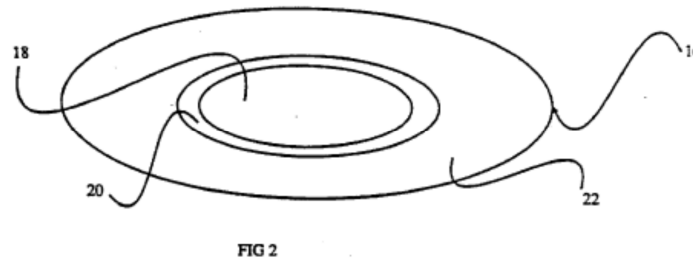
release of the drug from the dosage form unless the pH of the surrounding medium (e.g., portions of the G.I. tract after exiting the stomach) is 3.5 or higher.

**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.**

290. As discussed above, Gimet in view of Goldman and Lindberg renders claim 3 obvious.

291. Gimet further discloses this limitation of claim 3

292. Specifically, Gimet discloses a multilayered “core/mantle tablet”:



Ex. 1006, col. 3 ll. 8-14, Fig. 2.

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

293. As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.

294. Gimet further discloses this limitation of claim 4.

295. Specifically, Gimet discloses that “[t]he tablet 10 includes an inner core 12 which is comprised of an NSAID.” Ex. 1006, col. 3 l. 63 – col. 4, l. 11.

296. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

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

297. As discussed above, Gimet in view of Goldman and Lindberg renders claim 3 obvious.

298. Gimet in view of Goldman and Lindberg further discloses this limitation of claim 5.

299. 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.

300. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” (Ex. 1007, col. 14 ll. 6-10.)

301. A POSA would have understood that this active compound, an acid inhibitor, is the PPI esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

302. 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 (prostaglandin).

303. As such, a POSA would have understood that the substitution of Gimet's prostaglandin in the mantle with Lindberg's esomeprazole would have resulted in esomeprazole being present in a layer outside the core layer.

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

304. As discussed above, Gimet in view of Goldman and Lindberg renders claim 3 obvious.

305. Gimet further discloses this limitation of claim 6.

306. Specifically, Gimet discloses a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) and that surrounding the core is a mantle coating which consists of an acid inhibitor. Ex. 1006, col. 6 ll. 24-44.

307. Gimet further discloses that the composition of the mantle consists only of misoprostol, HPMC, crospovidone, colloidal silicon dioxide, hydrogenated castor oil, and microcrystalline cellulose. Ex. 1006, col. 7 ll. 25-44.

308. Thus, a POSA would have understood that no layer of the tablet (e.g., the mantle or enteric coating), except for the core layer, contains naproxen.



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

309. As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.

310. Gimet in view of Lindberg further discloses this limitation of claim 7.

311. Specifically, Gimet discloses that the composition of the tablet includes “cornstarch.” Ex. 1006, col. 7 ll. 25-44.

312. A POSA would have understood that cornstarch is a carrier. Ex. 1005 at 1318.

313. Lindberg further discloses that “[t]he pharmaceutical formulations contain . . . a pharmaceutically acceptable carrier.” Ex. 1007, col. 5 ll. 12-19.

**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.**

314. As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.

315. Gimet in view of Goldman and Lindberg further discloses this limitation of claim 8.

316. Specifically, Gimet discloses that various auxiliary agents “such as binders, bulking agents, lubricants, fillers and the like” can be combined with the composition. Ex. 1006, col. 4 ll. 28-33.

317. Lindberg further discloses that the pharmaceutical formulations may be mixed with auxiliary agents, for example, “lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.” Ex. 1007, col. 5 ll. 25-35.

318. It is my understanding that, because claim 8 uses the phrase “chosen from the group consisting of,” only one of the subsequent elements need be shown for invalidity.

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

319. As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.

320. Gimet in view of Goldman and Lindberg further discloses this limitation of claim 9.

321. Specifically, Gimet discloses that the composition includes “sodium hydroxide.” Ex. 1006, 8 ll. 18-45.

322. 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.

323. A POSA would have understood that Gimet’s sodium hydroxide and Lindberg’s alkaline compounds would have adjusted pH. *See, e.g.*, Ex. 1041 at ¶ [0075] (“The pH can be adjusted to the desired level using an acid and/or alkaline material.”); and Ex. 1042 at col. 5 ll. 61-64 (“Similarly, any non-toxic basic substance may be used as the alkaline pH adjustor, including alkaline salts of organic acids, alkaline carbonates, alkaline bicarbonates, etc.”).

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

324. As discussed above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.

325. As such, Gimet in view of Goldman and Lindberg disclose the pharmaceutical composition of claim 1.

326. Gimet in view of Goldman and Lindberg discloses each limitation of claim 10.

327. Specifically, Gimet discloses “[a] method of treating inflammation.” Ex. 1006, col. 12 ll. 41-44.

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

328. As discussed above, Gimet in view of Goldman and Lindberg renders claim 10 obvious.

329. Gimet further discloses this limitation of claim 11.

330. 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.

**M. Claim 12:**

331. 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:**

332. Gimet discloses this limitation.

333. Specifically, Gimet discloses, in unit dosage form, “a pharmaceutical composition which is a core/mantle tablet.” Ex. 1006, col. 3 ll. 8-14.

**2. a core layer comprising naproxen, wherein**

334. Gimet in view of Goldman discloses this limitation.

335. Specifically, Gimet discloses that “[t]he tablet 10 includes an inner core 12 which is comprised of an NSAID.” Ex. 1006, col. 3 l. 63 – col. 4, l. 11.

336. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

337. 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 (i.e., diclofenac or 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.

338. 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 diclofenac or 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**

339. Gimet in view of Goldman discloses this limitation.

340. 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.

341. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

342. 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.

343. A POSA would have known that a typical patient would have a pH in the small intestine after exiting the stomach of greater than about 3.5.

344. Also, a POSA would have known that Gimet’s disclosure means that the release of the NSAID does not occur until after the enteric coating breaks down in a more alkaline pH, e.g., a pH of 4.0-7.0 as is found in the lower G.I tract. *See, e.g.*, Ex. 1005, at 1637 (“[M]any 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.”); and Ex. 1045 at 1038, Fig. 3 (As shown in Figure 3, a patient’s stomach has a pH below 3.5 and its lower G.I. tract has a pH greater than 3.5, thus Gimet’s disclosed enteric coating “directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach would “prevent[] the

release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher.”).

345. 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.

**4. a layer comprising esomeprazole, wherein**

346. Gimet in view Lindberg discloses this limitation.

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

348. A POSA would have known that Gimet’s disclosed prostaglandin, misoprostol, is an acid inhibitor. *See* Ex. 1044 at 1265.

349. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

350. A POSA would have understood that this active compound, an acid inhibitor, is the PPI esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

351. As discussed above, it would have been obvious to a POSA to select Lindberg's disclosed acid inhibitor, the PPI esomeprazole, and substitute it for Gimet's disclosed acid inhibitor (prostaglandin) or for Goldman's disclosed PPI omeprazole because PPIs are more effective as acid inhibitors and esomeprazole is more stable than omeprazole. *See, e.g.*, Ex. 1004 at col. 1, ll. 25-27 and Ex. 1007 at col. 1, ll. 50-63.

352. 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) or Goldman's disclosed PPI omeprazole with Lindberg's disclosed acid inhibitor, the PPI esomeprazole, because doing so would be a simple substitution of one known element for another to obtain predictable results.

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

353. Gimet in view of Lindberg discloses this limitation.

354. Specifically, Gimet discloses "a core/mantle tablet" and that "[s]urrounding the core is a mantle coating." Ex. 1006, col. 3 ll. 8-14, Fig. 1.



355. Gimet further discloses that the composition of the mantle includes “hydroxypropyl methylcellulose (HPMC).” Ex. 1006, col. 7 ll. 25-44. A POSA would have understood HPMC to be a film coating.

356. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

357. A POSA would have understood that this active compound, an acid inhibitor, is the PPI esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

358. Lindberg further discloses uncoated dosage units of esomeprazole in the form of tablets, Ex. 1007, col. 5 ll. 25-36, and esomeprazole pellets “coated with a solution of hydroxypropyl methylcellulose.” Ex. 1007, col. 13 ll. 3-5.

359. In contrast to enteric coatings, a POSA would have understood that a given dosage form may employ an uncoated drug and/or a drug coated with non-enteric coatings, and that, following administration, such formulations would release their drug upon contact with the surrounding medium (e.g., about immediate release upon entering the stomach) regardless of pH. *See* Ex. 1043 at col. 3 ll. 18-19.

360. Based on the foregoing, a POSA would have rationale and a reasonable expectation of success in preparing a unit dosage form tablet having an immediate release component, for example an uncoated drug (e.g., esomeprazole) and/or drug coated with a non-enteric coating which releases regardless of the pH of the surrounding medium, and a delayed release component, for example an enterically coated drug (e.g., naproxen), the release thereof which is inhibited until the medium's pH is 3.5 or higher.

**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.**

361. As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious.

362. Gimet in view of Goldman further discloses this limitation of claim 13.

363. Specifically, Gimet discloses that “[t]he tablet 10 includes an inner core 12 which is comprised of an NSAID.” Ex. 1006, col. 3 l. 63 – col. 4, l. 11.

364. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

**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.**

365. As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious.

366. Gimet in view Lindberg further discloses this limitation of claim 14.

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

368. A POSA would have known that Gimet’s disclosed prostaglandin, misoprostol, is an acid inhibitor. See Ex. 1044 at 1265.

369. Lindberg discloses “a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.” Ex. 1007, col. 14 ll. 6-10.

370. A POSA would have understood that this active compound, an acid inhibitor, is the PPI esomeprazole. See Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

371. 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.

372. As discussed above, it would have been obvious to a POSA to select Lindberg’s disclosed acid inhibitor, the PPI esomeprazole, and substitute it for

Gimet's disclosed acid inhibitor (prostaglandin) or for Goldman's disclosed PPI omeprazole because PPIs are more effective as acid inhibitors and esomeprazole is more stable than omeprazole. *See, e.g.*, Ex. 1004 at col. 1, ll. 25-27 and Ex. 1007 at col. 1, ll. 50-63.

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

373. As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious.

374. 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**

375. Gimet in view of Goldman discloses this limitation.

376. Specifically, Gimet discloses that “[t]he tablet 10 includes an inner core 12 which is comprised of an NSAID.” Ex. 1006, col. 3 l. 63 – col. 4, l. 11.

377. Goldman discloses a composition containing the NSAID “naproxen from 200 to 500 mg per dose.” Ex. 1004, col. 5 ll. 9-19.

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

378. Gimet in view of Lindberg further discloses this limitation.

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

380. A POSA would have known that Gimet's disclosed prostaglandin, misoprostol, is an acid inhibitor. *See* Ex. 1044 at 1265.

381. Lindberg discloses "a pure solid state alkaline salt of the (–)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole." (Ex. 1007, col. 14 ll. 6-10.)

382. A POSA would have understood that this active compound, an acid inhibitor, is the PPI esomeprazole. *See* Ex. 1039 p. 1, ll 4-5; *see also* Ex. 1040 at col. 2 ll. 17-19.

383. 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.

384. As discussed above, it would have been obvious to a POSA to select Lindberg's disclosed acid inhibitor, the PPI esomeprazole, and substitute it for Gimet's disclosed acid inhibitor (prostaglandin) or for Goldman's disclosed PPI omeprazole because PPIs are more effective as acid inhibitors and esomeprazole is more stable than omeprazole. *See, e.g.*, Ex. 1004 at col. 1, ll. 25-27 and Ex. 1007 at col. 1, ll. 50-63.

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

385. As discussed above, Gimet in view of Goldman and Lindberg renders claim 12 obvious.

386. As such, Gimet in view of Goldman and Lindberg disclose the pharmaceutical composition of claim 12.

387. Gimet in view of Goldman and Lindberg discloses each limitation of claim 16.

388. Specifically, Gimet discloses “[a] method of treating inflammation.” Ex. 1006, col. 12 ll. 41-44.

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

389. As discussed above, Gimet in view of Goldman and Lindberg renders claim 16 obvious.

390. Gimet further discloses this limitation of claim 17.

391. 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.

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

392. As discussed above, Gimet in view of Goldman and Lindberg renders claim 15 obvious.

393. As such, Gimet in view of Goldman and Lindberg disclose the pharmaceutical composition of claim 15.

394. Gimet in view of Goldman and Lindberg discloses each limitation of claim 18.

395. Specifically, Gimet discloses “[a] method of treating inflammation.” Ex. 1006, col. 12 ll. 41-44.

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

396. As discussed above, Gimet in view of Goldman and Lindberg renders claim 18 obvious.

397. Gimet further discloses this limitation of claim 19.

398. 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.

**U. Conclusion**

399. Gimet in view of Goldman and Lindberg discloses each element of claims 1-19. Based on my understanding of 35 U.S.C. § 103(a), the combination of Gimet, Goldman, and Lindberg renders those claims unpatentable.

**VI. Additional Considerations Support a Finding of Obviousness**

**A. The Prior Art Does Not Teach Away from the Use of Non-Enterically Coated PPIs**

400. Omeprazole need not be enterically coated to provide a therapeutic effect. Omeprazole is disclosed in a number of references as a non-enterically coated tablet. For example, the original omeprazole patent, U.S. Pat. No. 4,255,431, does not make any reference to enteric coatings or the need therefor. Ex. 1021, col. 5 l. 59 – col. 7 l. 12. Another reference discloses uncoated granules of omeprazole when it summarizes the results of prior art experiments that investigated the properties of omeprazole. “Omeprazole,” Stephen P. Clissold, et al., *Drugs*, vol. 32, 1986 (“Clissold”) (Ex. 1047), at 32 Table V. Still another reference discloses the results of a study on formulating solid oral dosage forms of omeprazole, specifically a conventional (uncoated) dosage form and an enteric coated dosage form. “Development of an Oral Formulation of Omeprazole,” Pilbrant and Cederberg, *Scand. J. Gastroenterol.*, 20(Suppl. 108):113-120 (1985) (“Pilbrant”) (Ex.1048). While Pilbrant concludes that the enteric coated tablet



“offers the best possibilities,” Pilbrant nonetheless teaches that 44% of uncoated, unbuffered omeprazole is bioavailable as evidenced by area under the curve (AUC) values in Figure 4. *Id.* at 115-16. In other words, non-enterically coated, unbuffered omeprazole is indisputably bioavailable upon administration to a human. Based on the results shown in Pilbrant, a POSA would recognize that a fraction of the omeprazole administered in a non-enterically coated tablet would be absorbed into the bloodstream and thereby provide a therapeutic effect. Pilbrant further discloses that the therapeutic effect of omeprazole on gastric acid secretion:

is not a direct function of blood concentration of omeprazole at any time, but is rather a function of the total amount of omeprazole reaching the general circulation, i.e., directly proportional to the AUC (2, 10). This means that the same pharmacological effect is achieved with dosage forms of omeprazole producing equal AUCs. The shapes of the plasma concentration-time curves are of no importance.

*Id.* at 118.

401. Furthermore, a comparison of the plasma concentration of the omeprazole suspension without buffer of Figure 4 to the plasma concentration of enteric-coated granules of Figure 5 shows that the non-enterically coated omeprazole absorbs in the range of several minutes as compared to several hours

for an enterically coated formulation. *Id.* at 116-17. Accordingly, recognizing the bioavailability of non-enterically coated omeprazole and the relationship between therapeutic effect and the total amount of omeprazole reaching the general circulation (i.e., directly proportional to AUC), a POSA would be readily motivated, and have a reasonable expectation of success, to formulate omeprazole as a non-enterically coated tablet to obtain rapid absorption, and as needed, alter the dosage amount of omeprazole by routine experimentation to account for acidic degradation thereof when formulating in a non-enterically coated tablet suitable for oral administration.

402. Furthermore, the POSA would have known that PPIs are safe and have minimal side effects and thus adjustments to dosing carried little risk. *See, e.g.,* “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”) (Ex.1049), at 708 (“No side effects were encountered with omeprazole.”) and 709 (“It is of considerable interest that the drug had no observed haematological, biochemical, or subjective side effects, despite its extremely powerful action on gastric acid secretion.”).

403. Also, a POSA would understand that there is a synergistic effect associated with repeated administration of acid-labile PPIs in that their

bioavailability increases through repeated administration. Bioavailability is the fraction of a drug's dose that absorbs into a person's bloodstream. The self-amplification of bioavailability of omeprazole was disclosed in at least Howden, Ex.1049, at 709; "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") (Ex.1050), at 64; Clissold, Ex.1047, at 32; and "The Effects of Oral Doses of Lansoprazole and Omeprazole on Gastric pH," Tolman et al., *J. Clin. Gastroenterol*, 24(2):65-70 (1997) ("Tolman") (Ex.1051), at 69. With each subsequent administration of omeprazole the pH of the stomach increases and thus less omeprazole is susceptible to degradation and accordingly more is absorbed. Ex.1050, at 67. Both Howden and Prichard report increases in Cmax and area under the plasma concentration-time curve (AUC) after repeated once daily administration for 5 to 7 days. Ex.1049, at 708-09; Ex.1050, at 67. Howden discloses that on the seventh day of treatment with omeprazole there was no difference in the effect of 60 and 30 mg doses. Ex.1049, at 709. Clissold is another reference that also discloses this self-enhancing bioavailability of omeprazole:

Two interesting trends in the studies summarized in table V are the disproportionately large elevations of the maximal plasma

concentration (C<sub>max</sub>) of omeprazole with increasing dosage (Londong et al. 1983; Regårdh et al. 1985) and the significant increases in C<sub>max</sub> and area under the plasma concentration-time curve (AUC) after repeated once daily administration for 5 to 7 days (Howden et al. 1984b; Prichard et al. 1985b). Both of these findings could possibly be explained by the gastric acid inhibitory properties of omeprazole. *Thus, omeprazole, a highly acid-labile compound, may increase its own relative bioavailability by virtue of its antisecretory activity which reduces the acid degradation of the parent molecule, consequently enhancing the extent of its absorption.*

Ex.1047, at 31-32 (emphasis added). A subsequent study by Tolman confirms this point:

With omeprazole, C<sub>max</sub> and AUC levels were significantly higher on day 5 than on day 1, an effect also described by Clissold and Campoli-Richards (24), suggesting that omeprazole's bioavailability increases with repeated administration.

Ex.1051, at 69. Accordingly, a POSA would understand that while approximately half of the non-enterically coated omeprazole might be expected to degrade under certain conditions, the remaining half would survive and be active, thereby

gradually increasing its own bioavailability over the next few days.

**B. There is Nothing Surprising and Unexpected Achieved by the Claimed Acid Inhibitor/NSAID Combination**

404. I disagree that there is anything surprising in the claimed formulations related to the use of a non-enterically coated PPI. A POSA would have understood from Pilbrant and Clissold that immediate release formulations of a PPI could be used (i.e., would provide bioavailability and have a resultant therapeutic effect) and would have a reasonable expectation of success that the dosage of a non-enterically coated PPI could be adjusted, as needed, to compensate for some acid degradation.

405. To the extent that various prior art may teach the use of non-enteric coated omeprazole in combination with a buffering agent (e.g., sodium bicarbonate), I do not read the asserted claims to exclude the use of, or otherwise prohibit the presence of, a buffering agent. In fact, two examples in the specification of the '996 Patent, Example 7 and Example 8, contain "sodium bicarbonate" as a buffering agent. Ex. 1001, at col. 17 ll. 53-54; col. 18, ll. 25 and 36-37; and col. 19, ll. 40 and 50. Furthermore, Pilbrant unequivocally teaches that non-enterically coated, unbuffered omeprazole is bioavailable upon administration to a human. Ex.1048, at 115-16.

406. Furthermore, there is nothing surprising and unexpected about the “coordinated release” recited in the claims. On February 3, 2104, Horizon filed a Citizen Petition (Ex.1052). In the petition, Horizon stated that Vimovo’s sequential release mechanism is “essential” to reduction of gastrointestinal adverse effects, relying on the Miner study. *Id.* at 5. *See also* “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., *Alim. Pharmacol. Ther.*, 32:414-424 (2010) (“Miner”) (Ex.1053), at 414-24. The FDA, however, soundly rejected Horizon’s argument. The FDA noted that Horizon does not have any data to support its unsubstantiated claims as follows:

**The Petition provides no data (and FDA is not aware of any data) showing that the gastroprotective effect of the esomeprazole is related to or materially enhanced by the fact that in the Vimovo formulation, esomeprazole is released before naproxen. The two clinical trials described in section I.A. of this response do not support the petitioner’s claim that the relative timing of release of esomeprazole and naproxen is clinically meaningful. Rather, they demonstrate that the combination of esomeprazole and naproxen in Vimovo results in a reduced risk of gastric ulcers, compared to naproxen alone. Moreover, FDA’s approval of Vimovo does not reflect a finding as to the clinical significance, if any, of the sequence of release of the active ingredients.**<sup>23</sup>

FDA Response to Horizon’s Citizen Petition (July 3, 2014) (Ex. 1054), at 7.

407. As my expert background shows, I have interacted with the FDA in setting regulatory policy and with the United States Pharmacopoeia in setting drug

standards. As such, I served as Chair, Biopharmaceutics Technical Committee, Product Quality Research Institute (PQRI), 2002 – 2003; Member, USP Panel of Experts, Biopharmaceutics Expert Committee, United States Pharmacopeia Convention, 2000 – 2010; and Industry Guest Participant, Advisory Committee for Pharmaceutical Science, Center for Drug Evaluation and Research, U.S. FDA, 2001 – 2003. Additionally, I was Vice President, Biopharmaceutics, Sandoz, Inc. (division of Novartis) 2001 – 2006. As part of my responsibilities, I interacted with the FDA on numerous occasions including writing and replying to Citizen Petitions, attending NDA and ANDA meetings and actively participated in FDA/Industry workshops. Accordingly, I am familiar with citizen petitions and related FDA proceedings, and in this instance the FDA found that “coordinated release” is not “clinically meaningful.” *Id.* at 7. The FDA’s finding supports my opinion that the “coordinated release” feature cannot be considered an unexpected or surprising result by a POSA. There is nothing challenging or surprising about designing this type of formulation for this drug combination.

**C. No Skepticism in the Art**

408. The patentee may argue that a POSA would have been skeptical that PPIs could be formulated into a unit dosage form without the protection of an enteric coating or buffering agent. I disagree, as explained above, that a POSA

would read Pilbrant as teaching away from use of non-enterically coated, non-buffered PPIs. Not only does Pilbrant teach that uncoated, unbuffered omeprazole is absorbed into the patient's system, but it also teaches that uncoated, unbuffered omeprazole is absorbed dramatically faster than the enteric-coated version.

Ex.1048, at 116-17. Thus, a POSA would not have been skeptical that PPIs could be formulated without an enteric coating or buffering agent and moreover would have been able to select the amount of non-enterically coated PPI (e.g., omeprazole or esomeprazole) as a matter of routine experimentation.

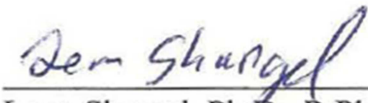
409. In summary, the claimed subject matter represents nothing more than the predictable use of known active pharmaceutical ingredients having known therapeutic effects, and represents a strong case for obviousness that overcomes any evidence of secondary considerations.



**VII. Conclusion**

410. I hereby declare that all statements made herein of my own knowledge are true and that all statements on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on June 5, 2015.

  
\_\_\_\_\_  
Leon Shargel, Ph.D., R.Ph.

# Appendix A

## LEON SHARGEL, Ph.D., R.Ph.

### ***APPLIED BIOPHARMACEUTICS, LLC***

1535 Caraleigh Mills Court, Suite 228

Raleigh, NC 27603

[www.appliedbiopharmaceutics.com](http://www.appliedbiopharmaceutics.com)

Email: [lshargel@appliedbiopharmaceutics.com](mailto:lshargel@appliedbiopharmaceutics.com)

Email: [leonshargel@aol.com](mailto:leonshargel@aol.com)

Tel: 919-846-5509

Mobile: 516-263-6765

Affiliate Professor, School of Pharmacy

VIRGINIA COMMONWEALTH UNIVERSITY, Richmond, VA

2006 - present

Adjunct Associate Professor, School of Pharmacy

UNIVERSITY OF MARYLAND, Baltimore, MD

1995- present

### **EXPERIENCE**

Manager and Founder

*APPLIED BIOPHARMACEUTICS, LLC*

Raleigh, NC

2007 - present

Vice President, Biopharmaceutics

SANDOZ, INC. (formerly Eon Labs), Wilson, NC

2001- 2006

Vice President and Technical Director

NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS

Ronkonkoma, NY

1997 - 2001

Senior Research Pharmacist

JOHNS HOPKINS BAYVIEW MEDICAL CENTER, Baltimore, MD

1996 -1997

Adjunct Visiting Associate Professor of Pharmacy

School of Pharmacy and Pharmacal Sciences

HOWARD UNIVERSITY, Washington, DC

1995 - 1996

Vice President, Scientific Affairs

PHARMAKINETICS LABORATORIES, INC., Baltimore, MD

1995

Director of Biochemistry and Pharmacokinetics

FOREST LABORATORIES, INC., New York, NY

1993 - 1994

Director of Pharmacokinetics

CHELSEA LABORATORIES, INC., West Hempstead, NY

1991- 1993

Associate Professor, Pharmacy and Pharmacology

Director, Pfeiffer Pharmaceutical Sciences Laboratory, Inc.,

MASSACHUSETTS COLLEGE OF PHARMACY AND ALLIED HEALTH SCIENCES,

Boston, MA

1982-1991

Section Leader, Pharmaceutics 1975-1982  
 Associate Professor of Pharmacy and Pharmacology  
 NORTHEASTERN UNIVERSITY, College of Pharmacy and Allied Health Professions,  
 Boston, MA

Associate Research Biologist and Group Leader,  
 Drug Metabolism and Disposition, 1969-1975  
 STERLING-WINTHROP RESEARCH INSTITUTE, Rensselaer, NY

## EDUCATION

Ph.D. Major: Pharmacology, Minors: Physiology, Biochemistry, Drug Metabolism  
 The George Washington University, Medical Center, Washington, DC

B.S. (Cum laude) Pharmacy, University of Maryland, Baltimore, Maryland

## REGISTERED PHARMACIST

Maryland, District of Columbia, Massachusetts

## TEXTBOOKS

Shargel L and Yu ABC	First Edition 1980
<i>Applied Biopharmaceutics and Pharmacokinetics</i>	Italian Translation, 1 <sup>st</sup> edition 1984
McGraw-Hill	Second Edition 1985
New York, NY	Third Edition 1993
	Fourth Edition 1999
	Chinese Translation, 4 <sup>th</sup> edition, 2002

Shargel L, Wu-Pong S and Yu ABC	Fifth Edition 2005
<i>Applied Biopharmaceutics and Pharmacokinetics</i>	Chinese Translation, 5 <sup>th</sup> edition, 2006
McGraw-Hill, New York, NY	Indonesian Translation, 5 <sup>th</sup> edition, 2012
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Shargel L, Yu ABC (editors)  
*Shargel & Yu's Applied Biopharmaceutics & Pharmacokinetics*, 7<sup>th</sup> edition (in press, 2015)  
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Shargel L	First Edition 1989
Editor, <i>Comprehensive Pharmacy Review</i>	First Canadian Edition 1992
Lippincott William & Wilkins	Second Edition 1994, Third Edition 1997
Baltimore, MD	Fourth Edition, 2001, Fifth Edition 2004
	Sixth Edition, 2007, Seventh Edition, 2009
	Eighth Edition, 2012

Shargel L, Associate Editor

*Study Guide and Board Review. Pharmacy Practice Exam*

Lippincott Williams & Wilkins  
Baltimore, MD

First Edition 1989

Second Edition 1994, Third Edition 1998

Fourth Edition, 2001, Fifth Edition, 2004

Sixth Edition 2007, Seventh Edition, 2009

Eighth Edition 2012

Shargel L, Editor

*Comprehensive Pharmacy Review*, CD-ROM

Lippincott William & Wilkins, Baltimore, MD

First Edition 2003

Second Edition 2004, Third Edition 2007,

Fourth Edition, 2001, Fifth Edition, 2004

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Eighth Edition, 2012

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*Development of Generic Drug Products: Solid Oral Dosage Forms*

Taylor & Francis, Inc., New York, NY

CRC Press, FL

First Edition, 2005

Second edition, 2014

Kanfer I and Shargel L (eds)

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Shargel L and Kanfer I (eds)

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## ORAL PRESENTATIONS AND INVITED LECTURES

Shargel L: *Analysis of Drugs in Biological Tissue*, Presented before the Boston Bacteriological Club, Boston, MA, February 25, 1976.

Shargel L: *Are All Drugs Created Equal?* A discussion of bioavailability and bioequivalence of drug products, Presented to the U.S. Naval Research Company 1-1, MIT, Boston, MA, March 29, 1976.

Shargel L: *Career Opportunities Discussion*, Presented to SAPHa and Rho Chi Meeting, Boston, MA May 3, 1976.

Shargel L: Research Seminar presented to the Department of Medicinal Chemistry and Pharmacology Colloquia, Northeastern University, Boston, MA, May 10, 1976.

Shargel L: *Problems of Human Drug Research*, Presented before the Boston Association of Retail Druggists, July 17, 1976.

Shargel L: *Inhibition of Hepatic Microsomal Enzymes by Chloramphenicol*, J.P.E.T., 203:338 (1977). Presented before the Pharmacology Journal Club, Northeastern University, Boston, MA, April, 1977.

Shargel L: *Toxicity of Fluorinated Hydrocarbons (Freons)*, Presented to the Naval Reserve, NR VTU Research 0103, MIT, Boston, MA, June, 1977.

Shargel L: *Brand Name vs. Generic Name Drug/Does Price Make the Difference?* Presented to the Boston Association of Retail Druggists, July, 1978.

Shargel L: *Where this College should be in 1984*, Retreat, College of Pharmacy and Allied Health Professions, Northeastern University, September, 1978.

Shargel L: *Interdisciplinary Research*, Retreat, College of Pharmacy and Allied Health Professions, Northeastern University, December, 1978.

Shargel L: *Problems of Human Studies*, Seminar, Pharmacology Section Northeastern University, June, 1979.

Shargel L: *Product Selection on Bioavailability*, Maine Pharmaceutical Association Meeting, September, 1979 (sponsored by the Upjohn Company).

Shargel L: *Considerations in Human Drug Research*, Presented to the Northeastern University Health Care Faculty, Northeastern University, Boston, MA April, 1980.

Shargel L: *Bioavailability and Biopharmaceutics*, Continuing Education Program on Drug Product selection, Northeastern University, June, 1980.

Shargel L: *Bridging the Gap Between Basic Sciences and Clinical Practice: Teaching, Research and Service" Opportunities in Pharmaceutics*,. NABP/AACP District I Annual Meeting, Providence, Rhode Island, October, 1980.

Shargel L: *Drug Interaction for the Health Practitioner*, Continuing Education Program Northeastern University, Boston, MA, November, 1980.

Shargel L: *Therapeutic Drug Monitoring*, Guest Lectures for Advanced Clinical Chemistry Course, Northeastern University, Boston, MA, December, 1981-1983.

Shargel L: *Pharmacokinetic Principles in Clinical Medicine*, Veteran's Administration Hospital, Boston, MA, February, 1982.

Shargel L: *Effect of Antacid on Theophylline Pharmacokinetics*, Presented to the Department of Pharmacology and Experimental Therapeutics, Boston, University Medical Center, March, 1983.

Shargel L: *Biopharmaceutic/Pharmacokinetic Study Procedures and Laboratory Practices*, Associates of Clinical Pharmacology, Annual Meeting, Boston, October 1984.

Breen PJ, Jambhekar S, Shargel L: *Relationship of Drug Protein Binding Constants Derived from the Scatchard Equation to the Fraction of Drug Bound*, Society of Toxicology, New England Chapter, Cambridge, MA, June, 1985.

DeFelice M, Shargel L: *Pharmacy Prescription Survey*, American Association of Colleges of Pharmacy (AACP/NAPB), District I, September, 1985, Burlington, VT.

Shargel L: *Effect of Cimetidine or Ranitidine on Hepatic Mixed Function Oxidase Activity in the Rat* Presented to the School of Pharmacy, University of Connecticut, Storrs, CT, March, 1986

Shargel L: *Toxicokinetics - Practical Pharmacokinetics: Applications to Toxicology*, Chemical Carcinogenesis Branch, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC, April, 1991

Shargel L: *The FDA's Orange Book Coding System*, Continuing Education Seminar, North Carolina Mutual Wholesale Company, Durham, NC, October, 1991

Shargel L: *Strategies and Problems in the Development of Generic Drug Products*, Fourth Phoenix International Symposium, Montreal, Canada. May, 1993

Shargel L: *Pharmacokinetics of Hydromorphone (Dilaudid)*, National Institutes of Drug Abuse, Division of Intramural Research, Baltimore, MD, September, 1996.

Shargel L: *Economic Impact of Current Legislative and Regulatory Issues on the Generic Drug Industry: Overview of Issues*, presented at the NAPM Workshop on Current Regulatory and Legislative Issues for API Manufacturers, New York, NY, March, 1998

Shargel L: *Generic Drug Substitution and Narrow Therapeutic Index Drugs*, NAPM Mid-Year Meeting and Educational Conference, Washington, D.C., June, 1998

Shargel L: *Scientific, Regulatory and Legislative Aspects of Generic Pharmaceutical Development and Sale*, The National Congress on the Future of Pharmaceuticals in Medicare. Innovation and Cost Management, Arlington, VA, December 9, 1999.

Shargel L: *Current Issues and Challenges in Generic Drug Development*, Academy of Pharmaceutical Sciences, 21st Annual Congress, Rhodes University, Grahamstown, South Africa, September 12, 2000

Shargel L: *The Generic Drug Industry: Current Issues and Challenges*, Andrew J. Bartilucci 42nd Pharmacy Congress, St. John's University College of Pharmacy and Allied Health Professions, Jamaica, NY, November 1, 2000

Shargel L: *Dissolution – A Generic Perspective*, AAPS Workshop, Dissolution: Current and Emerging Practices – Methodology, Technology and Regulatory Issues, Arlington, VA, May7, 2001.

Shargel L: *In Vitro and In Vivo Correlation in Drug Product Development*, FDA/OGD Regulatory Training Workshop, Gaithersburg, MD, September 24, 2002.

Shargel L: *Update from PQRI Biopharmaceutics Technical Committee*, Fall Technical Workshop, Generic Pharmaceutical Association, Bethesda, MD, October 16, 2002.

Shargel, L: *Generic Drug Industry in the United States, Legislative, Regulatory and Scientific Issues*, The Pharmacological and Therapeutic Society of Thailand and the Faculty of Science, Mahidol University, Bangkok, Thailand, September 22, 2003.

Shargel L: *Generic Drug Industry Product Development – Regulatory and Scientific Issues*, School of Pharmacy, MCV-Virginia Commonwealth University, Richmond, VA, February, 2004

Shargel L: *Bioavailability and Bioequivalence*, Guest Lecturer, Undergraduate Pharmacy Program, School of Pharmacy, MCV-Virginia Commonwealth University, Richmond, VA, 2004, 2005

Shargel L: *Generic Drug Product Development: Regulatory and Scientific Issues*, School of Pharmacy, Campbell University, Buis Creek, NC, April 15, 2004

Shargel L: *Design and conduct of bioavailability and bioequivalence studies*, Febrafarma-USP Discussion Forum, Sao Paulo, Brazil, August 23, 2004



Shargel L: *Generic Drug Industry In The United States: Legislative, Regulatory and Scientific Issues* 25th Congress of the Academy of Pharmaceutical Sciences, Rhodes University, Grahamstown, South Africa, September, 2004

Shargel L: *Introduction to Generic Drug Development*, SFBC Anapharm Symposium, Newark, NJ, March, 2005.

Shargel L: *Generic Drug Development – Legislative, Regulatory and Scientific Issues*, North Carolina Regulatory affairs Forum, Research Triangle Park, NC February, 2006.

Shargel L: *Challenges in the Development of Generic Drug Products*, Eino Nelson Conference, Coral Gables, FL, March 2006

Shargel L: *Generic Drug Development – Scientific issues and Regulatory Policy*, Seminar lecture series on Drug Discovery and Product Development, US Food and Drug Administration, Center for Devices and Radiological Health, Rockville, MS, March 2006

Shargel L: *Planning A Successful Career in The Pharmaceutical Industry*, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, October 2006

Shargel L: *Generic Drug Development in Non-Traditional Drug Delivery Systems (With Zero or Near Zero Bioavailability)*, Roundtable discussion, AAPS Annual Meeting, San Antonio, TX, October 2006.

Shargel L: *Challenges in New Drug Development: PhRMA and the FDA*, Keynote Address, 7th Annual Graduate Student Awards Luncheon, Virginia Commonwealth University, School of Pharmacy, Richmond, VA, May 2008 (sponsor, Wyeth)

Shargel L: *Assessment of Drug Product Performance—Bioavailability, Bioequivalence, and Dissolution, Quality of Manufactured Medicines – Drug Products*, USP Annual Scientific Meeting, Kansas City, MO, September 2008

Shargel L: *Use of an International Reference Listed Drug Product, RLD as a Standard, Identify the Problem*, Bio-International 2008, London, UK, October, 2008

Shargel L: *Technical Writing*, Cameron Village Library, Raleigh, NC, December 2008.

Shargel L: *Development of Generic Drug Products - Legislative, Regulatory and Scientific Issues*, AAPS North Carolina Pharmaceutical Discussion Group, Research Triangle Park, NC, December 2008

Shargel L: *Drug Product Performance, In Vivo - Bioavailability & Bioequivalence*, Workshop on In Vitro and In Vivo Evaluation of Dosage Forms, Sindusfarma, Sao Paulo, Brazil, August, 2004

Shargel L: *Drug Product Performance In Vivo- Assessment of Bioavailability & Challenges in the Demonstration of Bioequivalence*, University of Concepcion, Concepcion, Chile, October 2009

Shargel L: *Drug Product Performance In Vivo - Special Issues in Bioequivalence Studies*, la Sociedad de Farmacología de Chile, el XXXI Congreso Annual, University of Concepcion, Concepcion, Chile, October 2009

Shargel L: *International Reference Listed Drug Product*, presented in roundtable discussion *Bioequivalence Requirements: Challenges in Global Drug Development and Harmonization*, American Association of Pharmaceutical Scientists, Annual Meeting, Los Angeles, CA, November 2009

Shargel L: *Therapeutic Equivalence and Drug Product Performance*, AAPS/VCU Workshop on *Therapeutic Equivalence: Regulatory and Scientific Issues in Drug Product Development*, Virginia Commonwealth University, Richmond, VA April 2012.

## WORKSHOPS

Shargel L: *Advanced Dissolution and Drug Release Testing*, USP Pharmacopeial Education, United States Pharmacopeia, Rockville, MD December, 2007

Shargel L: *Drug Product Performance, In Vitro Dissolution and Drug Release*, VCU School of Pharmacy, Richmond, VA May 20-21, 2008

Shargel L: *Bioavailability and Bioequivalence – General Considerations and Special Issues in Bioequivalence, Studies* – Workshop on In Vitro and In Vivo Evaluation of Dosage Forms, Sindusfarma, Sao Paulo, Brazil, August 2009

## PROFESSIONAL ACTIVITIES

PMA Coordinated Industry Program for Pharmacy Faculty, Visitation to Endo Laboratories, Inc., Subsidiary of I.E. duPont de Nemours and Co., Inc., 1980.

Visiting Scientist for Minority Institutions (Sponsored by NIGMS, National Institutes of Health, 1982-1991.

National Institutes of Health Special Study Section for Grant Reviews, 1982.

National Institute of Environmental Health Sciences Special Study Section for Grant Reviews, Bioanalytical Chemistry Support, 1991

Member, Controlled Substances Advisory Board, Commonwealth of Massachusetts, Department of Public Health, 1982-1984.

Member, Drug Formulary Commission, Commonwealth of Massachusetts, 1987 - 1991 (Member, Subcommittee for Public Comment)

Reviewer, Chapter 19, "*Weight Control Products*" in Handbook of Nonprescription Drugs, 9th edition, American Pharmaceutical Association, Washington, DC, 1990, 1993

Organizer and Founder, "Graduate Research Day" Annual event at MCP/AHS, Boston, MA, 1983-1990.

Advisor, Chinese Student Organization, MCP/AHS, 1985-1991.

PMA Pharmaceutical Industry Visiting Scientist

University of Minnesota, College of Pharmacy, January, 1992

University of Kentucky, College of Pharmacy, April, 1993

External Examiner, Rhodes University, Grahamstown, South Africa, February, 1992, 2001

American Association of Pharmaceutical Sciences (AAPS), Charter Member, Pharmacokinetics, Pharmacodynamics and Drug Metabolism (PPDM) Section, Member, 1994, Co-Chair, 1997, Chair, 1998 - 1999 - Eastern Regional Meeting; Program Chair, Eastern Regional Meeting, June, 2000, Chair, Bioequivalence Focus Group, 2006-2008

Member, Institutional Review Board (IRB), National Institutes of Health, National Institute on Drug Abuse, Division of Intramural Research, Baltimore, MD, 1996 - 1997

Moderator: *Pharmaceutical Equivalents of Biological Drugs: Regulatory/Scientific Hurdles and Policy Issues*, NAPM Annual Meeting and Educational Conference, Westin Rio Grande, PR, February, 1998

Moderator, Drug Abuse, AAPS Eastern Regional Meeting, Parsippany, NJ, June, 1998

Moderator: *Generic Drug Substitution and Narrow Therapeutic Index Drugs*, NAPM Mid-Mid-Year Meeting and Educational Conference, Washington, D.C., June, 1998

Moderator, Bioequivalence Issues, Generic Trade Associations/FDA Fall Technical Workshop, The Generic Pharmaceutical Industry: Regulatory and Scientific Challenges," Bethesda, MD, November, 1998

Moderator: *Generic Drug Substitution Issues*, NAPM Mid-Mid-Year Meeting and Educational Conference, Newark, NJ, May, 1999

Moderator: PPDM Symposium: *Bioavailability/Bioequivalence Issues*, Eastern Regional Meeting, American Association of Pharmaceutical Scientists, Parsippany, NJ, June 1999

Product Quality Research Institute (PQRI), Member, Steering Committee, 1998 - 2001, Chair, Biopharmaceutics Technical Committee, 2002 - 2003

Delegate, United States Pharmacopeia Convention, 2000 – 2005

Member, USP Panel of Experts, Biopharmaceutics Expert Committee, United States Pharmacopeia Convention, 2000 – 2010

Industry Guest Participant, Advisory Committee for Pharmaceutical Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 2001 - 2003

Generic Pharmaceutical Association, Vice-Chair, CRO Committee, Member of Technical Advisory Committee, 2002 - 2003

Moderator, Biopharmaceutics Session, Fall Technical Workshop, Generic Pharmaceutical Association, Bethesda, MD, October 16, 2002.

Moderator, Biopharmaceutics Technical Committee and Roundtable Discussion, PQRI Conference, Good Regulation Through Good Science, April 3-4, 2003.

Moderator, *Biopharmaceutics and Drug Product Quality: Using performance tests as specifications for drug products*, USP Annual Scientific Meeting, Iselin, NJ, September 27, 2004.

Chair, USP Ad Hoc Advisory Panel on Dosage Form Performance – Injectables, 2004 – 2010

Topic Manager, *Dissolution and QbD, Dissolution – Short and Long-term Opportunities, Comparator Pharmaceutical Product Reference Material*, USP Annual Scientific Meeting, Kansas City, MO September 2008

Moderator, *International BE requirements and Comparator Drug Product*, Bio-International 2008, London, UK, October, 2008

Moderator, *Bioequivalence Requirements: Challenges in Global Drug Development and Harmonization*, American Association of Pharmaceutical Scientists, Annual Meeting, Los Angeles, CA, November 2009

Moderator and Member, Planning Committee: *Harmonization of Regulatory Approaches for Evaluating Therapeutic Equivalence and Interchangeability of Multisource and Complex Drug Products*, AAPS/EUFEPS/FIP Workshop, New Orleans, LA, November 2010.

Chair, Bioequivalence Focus Group, American Association of Pharmaceutical Sciences, 2010

Member, Review Panel: *Risk of Therapeutic Failure Due to Ineffectiveness of Medication*, NASA Human Research Program, Lyndon N Johnson Space Center, Houston, TX, 2010 - present

Section Chair-elect, Basic Sciences Section of the APhA Academy of Pharmaceutical Research and Science, 2013-2014. Chair, 2014-2015

Delegate, American Pharmacists Association (APhA) House of Delegates, 2014 -2015

## COMMUNITY SERVICE

Member, Board of Directors, Literacy Council of Wake County, Raleigh, NC, 2010 – present.

ESL Teacher, Literacy Council of Wake County. Accredited to teach Adult Basic Education (ABE) and English as a Second Language (ESL), 2008 – present.

Precinct Judge, Wake County Board of Elections, 2012

## AWARDS

Fulbright Specialists Award , Fulbright Specialists Project in Kingston, Jamaica at the Department of Basic Medical Sciences, University of the West Indies, Mona, 2012

# APPENDIX B

<p><b>U.S. Pat. No. 8,858,996</b></p> <p><b>Filed: April 3, 2014</b></p> <p><b>Earliest Priority:</b> <b>May 16, 2005</b></p>	<p><b>U.S. Patent No. 5,204,118 (“Goldman”)</b> <b>Issued: April 20, 1993</b></p> <p><b>in view of</b></p> <p><b>Remington’s Pharmaceutical Sciences (“Remington”)</b> <b>Published: 1985</b></p> <p><b>in further view of</b></p> <p><b>U.S. Patent No. 5,714,504 (“Lindberg”)</b> <b>Issued: February 3, 1998</b></p> <p><b>Ground 1 (§ 103(a))</b> <b>Claims 1-19</b></p>
<p><b>Claim 1</b></p>	<p><b>Goldman in view of Remington in further view of Lindberg</b></p>
<p>A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:</p>	<p>Goldman at col. 1 ll. 10-16:</p> <p>This invention relates to <b>pharmaceutical compositions</b> for treating the symptoms of overindulgence. More particularly, the invention comprises treating the symptoms of overindulgence with a combination of non-steroidal anti-inflammatory drug or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition.</p> <p>Goldman at col. 6 ll. 18-33:</p> <p>The invention will now be illustrated by examples. The examples are not intended to be</p>

	<p>limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention. <b><u>Example 1-10 disclose various formulations for preparing tablets</u></b> or caplets <b><u>in accordance with the invention.</u></b> Various 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. Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>Goldman at col. 8 ll. 4-7:</p> <p>A patient exhibiting the symptoms or suffering from the symptoms of overindulgence is treated by <b><u>the oral administration of one tablet of the pharmaceutical composition in accordance with any of Examples 1-10.</u></b></p>
naproxen in an amount of 200-600 mg per unit dosage form; and	<p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen from 200 to 500 mg</u></b> per dose . . . .</p>
esomeprazole in an amount of from 5 to 100 mg per unit dosage form,	<p>Goldman at col. 5 ll. 9-31:</p> <p><b><u>The composition of the present invention shall preferably contain</u></b> a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in</p>

combination with the [] **proton pump inhibitor drugs including omeprazole** . . . .

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (–)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

A POSA 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.

Further, the 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 employing more recently obtained and therapeutically more effective compounds in therapies over previously known, less therapeutically effective compounds. Accordingly, it would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for Goldman's disclosed omeprazole because Lindberg specifically teaches that "[i]t 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



	<p>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.” Lindberg, at col. 1 ll. 50-63. Moreover, a POSA would have also understood that “the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy.” <i>Id.</i> at col. 3 ll. 48-55.</p> <p>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 Goldman’s disclosed omeprazole with Lindberg’s disclosed esomeprazole because doing so would be a simple substitution of one known element for another to obtain predictable results.</p> <p>Lindberg at col. 6 ll. 21-25:</p> <p>The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, <b><u>oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.</u></b></p>
<p>wherein upon introduction of said unit dosage form into a medium, at least a portion of said</p>	<p>Goldman at col. 6 ll. 26-33:</p> <p><b><u>Various 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</u></b></p>

<p>esomeprazole is released regardless of the pH of the medium, and</p>	<p><b><u>example by Remington's Pharmaceutical Sciences.</u></b> Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>The 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 reference publications such as Remington providing conventional techniques to perform the task. Furthermore, 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.</p> <p>Remington at 1637:</p> <p>Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). In addition, they can be used to give a simple repeat-action effect where <b><u>unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.</u></b></p> <p>In contrast to enteric coatings, a person of ordinary skill in the art (POSA) would have understood that a given dosage form may employ an uncoated drug and/or a drug coated with non-enteric coatings, and that, following administration, such formulations may release their drug quickly upon contact with the surrounding medium (e.g., immediate release upon entering the stomach). Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form</p>
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having an immediate release component, for example an uncoated drug (e.g., acid inhibitor) and/or a drug coated with a non-enteric coating that releases regardless of the pH of the surrounding medium.

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (-)-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

Lindberg at col. 5 ll. 25-36:

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets.

Lindberg at col. 13 ll. 3-5:

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose. 30 g. in water, 750 g. using a fluidized bed coater. After drying. the pellets were coated with a second coating as given below:

	<table border="1"> <tr> <td colspan="2">Coating solution:</td></tr> <tr> <td>Hydroxypropyl methylcellulose phthalate</td><td>70 g</td></tr> <tr> <td>Cetyl alcohol</td><td>4 g</td></tr> <tr> <td>Acetone</td><td>200 g</td></tr> <tr> <td>Ethanol</td><td>600 g</td></tr> </table>	Coating solution:		Hydroxypropyl methylcellulose phthalate	70 g	Cetyl alcohol	4 g	Acetone	200 g	Ethanol	600 g
Coating solution:											
Hydroxypropyl methylcellulose phthalate	70 g										
Cetyl alcohol	4 g										
Acetone	200 g										
Ethanol	600 g										
<p>release of at least a portion of said naproxen is inhibited unless the pH of said medium is 3.5 or higher.</p>	<p>Goldman at col. 6 ll. 26-33:</p> <p><b><u>Various 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.</u></b> Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen</u></b> from 200 to 500 mg per dose . . . .</p> <p>Remington at 1637:</p> <p><b><u>Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach,</u></b> but will dissolve and release the contents of the dosage form once they arrive at the small intestine. <b><u>Their purpose is to delay the release of drugs which</u></b> are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or <b><u>may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids).</u></b> <b><u>In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder,</u></b></p>										

	<p><b><u>being protected by the coating, is released further down the gastrointestinal tract.</u></b></p> <p>The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties. Although there have been repeated attempts to produce coatings which are subject to intestinal enzyme breakdown, this approach is not popular since enzymatic decomposition of the film is rather slow. <b><u>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.</u></b></p>
<b>Claim 2</b>	<b>Goldman in view of Remington in further view of Lindberg</b>
The pharmaceutical composition of claim 1, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.
said naproxen is present in a core layer,	<p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen</u></b> from 200 to 500 mg per dose . . . .</p> <p>Goldman at col. 6 ll. 26-33:</p> <p><b><u>Various 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.</u></b> Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is</p>

	<p>hereby incorporated herein by reference.</p> <p>Remington at 1637:</p> <p>Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). <b><u>In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.</u></b></p>
<p>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.</p>	<p>Goldman at col. 6 ll. 26-33:</p> <p><b><u>Various conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed or example by Remington's Pharmaceutical Sciences.</u></b> Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>Remington at 1637:</p> <p><b><u>Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach,</u></b> but will dissolve and release the contents of the dosage form once they arrive at the small intestine. <b><u>Their purpose is to delay the release of drugs which</u></b> are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or <b><u>may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin,</u></b> steroids). <b><u>In addition, they can be used to give a simple repeat-action effect where unprotected</u></b></p>

	<p><b><u>drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.</u></b></p> <p>The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties. Although there have been repeated attempts to produce coatings which are subject to intestinal enzyme breakdown, this approach is not popular since enzymatic decomposition of the film is rather slow. <b><u>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.</u></b></p>
<b>Claim 3</b>	<b>Goldman in view of Remington in further view of Lindberg</b>
The pharmaceutical composition of claim 1, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.
said unit dosage form is a multilayer tablet comprising a core layer and one or more layers outside of said core layer.	<p>Goldman at col. 6 ll. 26-33:</p> <p><b><u>Various conventional techniques for preparing medicament tablets</u></b> 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. Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>Remington at 1637:</p> <p>Enteric Coatings-By definition, enteric coatings are those which remain intact in the</p>

	<p>stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). <b><u>In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.</u></b></p>
<b>Claim 4</b>	<b>Goldman in view of Remington in further view of Lindberg</b>
The pharmaceutical composition of claim 3, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 3 obvious.
said core layer comprises naproxen.	<p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen</u></b> from 200 to 500 mg per dose . . . .</p> <p>Goldman at col. 6 ll. 26-33:</p> <p><b><u>Various 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.</u></b> Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p>



	<p>Remington at 1637:</p> <p>Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). <b><u>In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.</u></b></p>
<b>Claim 5</b>	<b>Goldman in view of Remington in further view of Lindberg</b>
The pharmaceutical composition of claim 3, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 3 obvious.
at least one of said one more layers outside said core layer comprises esomeprazole.	<p>Goldman at col. 5, ll. 9-31:</p> <p><b><u>The composition of the present invention shall preferably contain</u></b> a combination of the following compositions or their pharmaceutically acceptable salts...in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] <b><u>proton pump inhibitor drugs including omeprazole</u></b> . . . .</p> <p>Remington at 1637:</p> <p>Enteric Coatings-By definition, enteric coatings are those which remain intact in the</p>

stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). **In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.**

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

Lindberg at col. 5 ll. 25-36:

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets.

Claim 6	Goldman in view of Remington in further view of Lindberg
The pharmaceutical composition of claim 3, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 3 obvious.
said one or more layers outside of said core layer do not contain naproxen.	<p>Goldman at col. 6 ll. 26-33:</p> <p>Various 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. Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>Remington at 1637:</p> <p>Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). <b><u>In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.</u></b></p>

Claim 7	Goldman in view of Remington in further view of Lindberg
The pharmaceutical composition of claim 1, further comprising	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.
at least one carrier.	<p>Lindberg at col. 5 ll. 12-19:</p> <p>For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with <b><u>a pharmaceutically acceptable carrier</u></b>. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule . . . .</p>
Claim 8	Goldman in view of Remington in further view of Lindberg
The pharmaceutical composition of claim 1, further comprising	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.
at least one auxiliary agent chosen from the group consisting of lubricants, preservatives, disintegrants,	<p>Lindberg at col. 5 ll. 25-35:</p> <p>In the preparation of pharmaceutical formulations in form of dosage units for oral administration <b><u>the optically pure compound may be mixed with</u></b> a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose</p>

stabilizers, wetting agents, emulsifiers, salts, buffers, coloring agents, flavoring agents, and aromatic substances.	derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with <b><u>lubricating agents</u></b> such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.
<b>Claim 9</b>	<b>Goldman in view of Remington in further view of Lindberg</b>
The pharmaceutical composition of claim 1, further comprising	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 1 obvious.
at least one ingredient to adjust pH.	<p>Lindberg at col. 5 ll. 25-35:</p> <p>In the preparation of pharmaceutical formulations in form of dosage units for oral administration <b><u>the optically pure compound may be mixed with</u></b> a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, <b><u>stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like</u></b> as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.</p> <p>A POSA would have understood that Lindberg's alkaline compounds would have adjusted pH.</p>

Claim 10	Goldman in view of Remington in further view of Lindberg
A method of treating a patient for pain or inflammation, comprising	<p>Lindberg at col. 2 ll. 17-37:</p> <p><b><u>The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man.</u></b> In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. <b><u>The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions</u></b> in mammals, including man, especially those involving lysozmal enzymes. Conditions that may be specifically mentioned for treatment are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.</p>
administering to said patient the pharmaceutical composition of claim 1.	See claim 1.
Claim 11	Goldman in view of Remington in further view of Lindberg
The method of claim 10,	As shown above, Goldman in view of Remington in further view of Lindberg renders

wherein	claim 10 obvious.
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	<p>Lindberg at col. 2 ll. 17-37:</p> <p><b><u>The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man.</u></b> In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. <b><u>The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man,</u></b> especially those involving lysozmal enzymes. <b><u>Conditions that may be specifically mentioned for treatment are rheumatoid arthritis</u></b> and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.</p>
<b>Claim 12</b>	<b>Goldman in view of Remington in further view of Lindberg</b>
A pharmaceutical composition in unit dosage form in the form of a tablet, said composition	<p>Goldman at col. 1 ll. 10-16:</p> <p>This invention relates to <b><u>pharmaceutical compositions</u></b> for treating the symptoms of overindulgence. More particularly, the invention comprises treating the symptoms of overindulgence with a combination of non-steroidal anti-inflammatory drug or</p>

<p>comprising:</p>	<p>acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition.</p> <p>Goldman at col. 6 ll. 18-33:</p> <p>The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention. <b><u>Example 1-10 disclose various formulations for preparing tablets or caplets in accordance with the invention.</u></b> Various 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. Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>Goldman at col. 8 ll. 4-7:</p> <p>A patient exhibiting the symptoms or suffering from the symptoms of overindulgence is treated by <b><u>the oral administration of one tablet of the pharmaceutical composition in accordance with any of Examples 1-10.</u></b></p>
<p>a core layer comprising naproxen, wherein</p>	<p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen</u></b> from 200 to 500 mg per dose . . . .</p> <p>Goldman at col. 6 ll. 26-33:</p>



	<p><b><u>Various 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.</u></b> Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>The 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 reference publications such as Remington providing conventional techniques to perform the task. Furthermore, 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.</p> <p>Remington at 1637:</p> <p>Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). <b><u>In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.</u></b></p>
<p>said core layer has a coating that inhibits release of said naproxen from said core</p>	<p>Goldman at col. 6 ll. 26-33:</p> <p><b><u>Various conventional techniques for preparing medicament tablets or caplets can</u></b></p>

layer unless said dosage form is in a medium with a pH of 3.5 or higher; and

**be employed as would be known to those skilled in the art as is disclosed for example by Remington's Pharmaceutical Sciences.** Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.

Goldman at col. 5 ll. 9-19:

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several **NSAIDs from the group of . . . naproxen** from 200 to 500 mg per dose . . .

Remington at 1637:

**Enteric Coatings-By definition, enteric coatings are those which remain intact in the stomach,** but will dissolve and release the contents of the dosage form once they arrive at the small intestine. **Their purpose is to delay the release of drugs which** are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or **may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids).** **In addition, they can be used to give a simple repeat-action effect where unprotected drug coated over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.**

The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties. Although there have been repeated attempts to produce coatings which are subject to intestinal enzyme breakdown, this approach is not popular since enzymatic decomposition of the film is rather slow. **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.**

a layer comprising  
esomeprazole, wherein

Goldman at col. 5 ll. 9-31:

**The composition of the present invention shall preferably contain** a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H<sub>2</sub> receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole** . . . .

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (-)-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

A POSA 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.

Further, the 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 employing more recently obtained and therapeutically more effective compounds in therapies over previously known, less therapeutically effective

	<p>compounds. Accordingly, it would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for Goldman's disclosed omeprazole because Lindberg specifically teaches that "[i]t 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." Lindberg at col. 1, ll. 50-63. Moreover, a POSA would have also understood that "the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy." <i>Id.</i> at col. 3, ll. 48-55.</p> <p>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 Goldman's disclosed omeprazole with Lindberg's disclosed esomeprazole because doing so would be a simple substitution of one known element for another to obtain predictable results.</p>
<p>said layer has a non-enteric film coating that, upon ingestion by a patient, releases said esomeprazole</p>	<p>Goldman at col. 6 ll. 26-33</p> <p><b><u>Various 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.</u></b> Mack Publishing Co., Chapter 90,</p>

<p>into the stomach of said patient.</p>	<p>"Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.</p> <p>Remington at 1604, 1633, and 1634:</p> <p><b><u>Film-Coated Tablets</u></b> (FCT)- These are compressed tablets which are covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. <b><u>Film coating imparts the same general characteristics as sugar coating</u></b> with the added advantage of a greatly reduced time period required for the coating operation.</p> <p>Any introduction to tablet coating must be prefaced by an important question-"Why coat tablets?"-since in many instances, the coating is being applied to a dosage form that is already functionally complete. In attempting to answer this question, if one examines the market, it will be immediately obvious that a significant proportion of pharmaceutical solid dosage forms are coated. The reasons for this range from the aesthetic to a desire to control the bioavailability of the drug, and include the following:</p> <ol style="list-style-type: none"> <li>1. Protection of the drug from its surrounding environment (particularly air, moisture, and light) with a view to improving stability.</li> <li>2. Masking of unpleasant taste and odor.</li> <li>3. Increasing the ease by means of which the product can be ingested by the patient.</li> <li>. . . .</li> <li>9. Modification of drug release, as in enteric-coated, repeat-action, and sustained-release products.</li> </ol> <p>Basically, there are four major techniques for applying coatings to pharmaceutical solid</p>
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dosage forms: (1) Sugar Coating, (2) **Film Coating**, (3) Microencapsulation and (4) Compression Coating.

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 may release their drug quickly upon contact with the surrounding medium (e.g., immediate release upon entering the stomach). Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having an immediate release component, for example a film-coated drug (e.g., esomeprazole) that releases regardless of the pH of the surrounding medium.

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (-)-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

Lindberg at col. 5 ll. 25-36:

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is

	<p>then processed into granules or pressed into tablets.</p> <p>Lindberg at col. 13 ll. 3-5:</p> <p>500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose. 30 g. in water, 750 g. using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:</p> <table> <tr> <td colspan="2">Coating solution:</td></tr> <tr> <td>Hydroxypropyl methylcellulose phthalate</td><td>70 g</td></tr> <tr> <td>Cetyl alcohol</td><td>4 g</td></tr> <tr> <td>Acetone</td><td>200 g</td></tr> <tr> <td>Ethanol</td><td>600 g</td></tr> </table>	Coating solution:		Hydroxypropyl methylcellulose phthalate	70 g	Cetyl alcohol	4 g	Acetone	200 g	Ethanol	600 g
Coating solution:											
Hydroxypropyl methylcellulose phthalate	70 g										
Cetyl alcohol	4 g										
Acetone	200 g										
Ethanol	600 g										
<b>Claim 13</b>	<b>Goldman in view of Remington in further view of Lindberg</b>										
The pharmaceutical composition of claim 12, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious.										
naproxen is present in said unit dosage form in an amount of 200-600 mg.	<p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen from 200 to 500 mg</u></b> per dose . . . .</p>										

Claim 14	Goldman in view of Remington in further view of Lindberg
The pharmaceutical composition of claim 12, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious.
esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.	<p>Lindberg at col. 14 ll. 6-10:</p> <p>1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of <u>the (–)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole</u> and a pharmaceutically acceptable carrier.</p> <p>A POSA would have understood that this active compound is esomeprazole.</p> <p>Lindberg at col. 6 ll. 21-25:</p> <p>The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, <u>oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.</u></p>
Claim 15	Goldman in view of Remington in further view of Lindberg
The pharmaceutical composition of claim 12,	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 12 obvious.



wherein	
naproxen is present in said unit dosage form in an amount of between 200-600 mg and	<p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen from 200 to 500 mg</u></b> per dose . . . .</p>
esomeprazole in an amount of from 5 to 100 mg per unit dosage form.	<p>Goldman at col. 5 ll. 9-31:</p> <p><b><u>The composition of the present invention shall preferably contain</u></b> a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] <b><u>proton pump inhibitor drugs including omeprazole</u></b> . . . .</p> <p>Lindberg at col. 14 ll. 6-10:</p> <p>1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of <b><u>the (-)-enantiomer of 5-methoxy-2[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole</u></b> and a pharmaceutically acceptable carrier.</p> <p>A POSA would have understood that this active compound is esomeprazole.</p> <p>Lindberg at col. 6 ll. 21-25:</p> <p>The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the</p>

	disease. In general, <b><u>oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.</u></b>
<b>Claim 16</b>	<b>Goldman in view of Remington in further view of Lindberg</b>
A method of treating a patient for pain or inflammation, comprising	<p>Lindberg at col. 2 ll. 17-37:</p> <p><b><u>The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man.</u></b> In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. <b><u>The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions</u></b> in mammals, including man, especially those involving lysozmal enzymes. Conditions that may be specifically mentioned for treatment are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.</p>
administering to said patient the pharmaceutical composition of claim 12.	See claim 12.

Claim 17	Goldman in view of Remington in further view of Lindberg
The method of claim 16, wherein	As shown above, Goldman in view of Remington in further view of Lindberg renders claim 16 obvious.
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	<p>Lindberg at col. 2 ll. 17-37:</p> <p><b><u>The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man.</u></b> In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. <b><u>The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man,</u></b> especially those involving lysozmal enzymes. <b><u>Conditions that may be specifically mentioned for treatment are rheumatoid arthritis</u></b> and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.</p>

Claim 18	Goldman in view of Remington in further view of Lindberg
A method of treating a patient for pain or inflammation, comprising	<p>Lindberg at col. 2 ll. 17-37:</p> <p><b><u>The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man.</u></b> In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. <b><u>The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions</u></b> in mammals, including man, especially those involving lysozmal enzymes. Conditions that may be specifically mentioned for treatment are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.</p>
administering to said patient the pharmaceutical composition of claim 15.	See claim 15.
Claim 19	Goldman in view of Remington in further view of Lindberg
The method of claim 18,	As shown above, Goldman in view of Remington in further view of Lindberg renders

wherein	claim 18 obvious.
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	<p>Lindberg at col. 2 ll. 17-37:</p> <p><b><u>The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man.</u></b> In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. <b><u>The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man,</u></b> especially those involving lysozmal enzymes. <b><u>Conditions that may be specifically mentioned for treatment are rheumatoid arthritis</u></b> and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.</p>

# APPENDIX C

<p><b>U.S. Pat. No. 8,858,996</b></p> <p><b>Filed: April 3, 2014</b></p> <p><b>Earliest Priority:</b> <b>May 16, 2005</b></p>	<p><b>U.S. Patent No. 5,698,225 (“Gimet”)</b> <b>Issued: December 16, 1997</b></p> <p><b>in view of</b></p> <p><b>U.S. Patent No. 5,204,118 (“Goldman”)</b> <b>Issued: April 20, 1993</b></p> <p><b>and</b></p> <p><b>U.S. Patent No. 5,714,504 (“Lindberg”)</b> <b>Issued: February 3, 1998</b></p> <p><b>Ground 2 (§ 103(a))</b> <b>Claims 1-19</b></p>
<p><b>Claim 1</b></p>	<p><b>Gimet in view of Goldman and Lindberg</b></p>
<p>A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:</p>	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to <b><u>a pharmaceutical composition which is a core/mantle tablet</u></b> consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam.</p> <p>Gimet at col. 7 ll. 23-25:</p> <p>A <b><u>pharmaceutical tablet composition</u></b> was prepared consisting of a diclofenac sodium central core and a misoprostol mantle.</p>

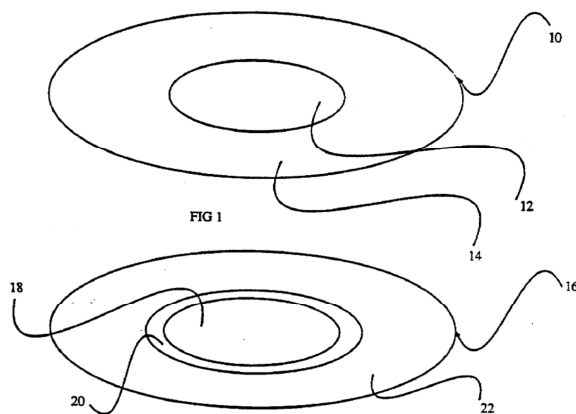
naproxen in an amount of 200-600 mg per unit dosage form; and

Gimet at col 2, l. 65 – col. 3, l. 2:

FIG. 1 is a schematic representation of a tableted pharmaceutical composition herein illustrating the core/mantle structure;

FIG. 2 is a schematic representation of another embodiment of a tableted pharmaceutical composition herein . . . .

Gimet at FIGS. 1 and 2:



Gimet at col. 3 l. 63 – col. 4, l. 11:

For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. **A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID** that is compatible with the prostaglandin as will



be described in further detail hereinafter. The inner core 12 can consist of the NSAID, diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

Gimet at col. 6 ll. 24-33:

A second embodiment of the composition is shown in FIG. 2. In FIG. 2 a tablet 16 is schematically illustrated in cross section. The tablet 16 includes an inner core 18 of an NSAID diclofenac, piroxicam or their salts such as disclosed with regard to the core 12 of FIG. 1. Surrounding the core 18 is an enteric coating 20. The enteric coating 20 can be formulated from any suitable enteric coating material, many of which are known to those skilled in the art and many of which are employed for coating commercially available NSAID's.

Goldman at col. 5 ll. 9-19:

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several **NSAIDs from the group of . . . naproxen from 200 to 500 mg** per dose . . . .

A POSA would have known that Gimet's disclosed prostaglandin, misoprostol, is an acid inhibitor. *See* "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 (Ex. 1044), at 126S.

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.

	<p>Similarly, a POSA would have understood that Goldman discloses a combination therapy oral unit dosage form comprising an acid inhibitor (e.g., H2 blockers and proton pump inhibitors) in combination with an NSAID (e.g., naproxen).</p> <p>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.</p> <p>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 (i.e., diclofenac or 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 diclofenac or piroxicam used in the NSAID/acid inhibitor combination therapies of Gimet.</p>
esomeprazole in an amount of from 5 to 100 mg per unit dosage form,	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. <b><u>Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</u></b></p> <p>Gimet at col. 12, ll. 14-19:</p>

That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby **the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.**

Gimet at col. 6, l. 20:

When the prostaglandin is **misoprostol, . . . the misoprostol is present in an amount from about 50 to about 500 mcg . . . .**

Goldman at col. 5 ll. 9-31:

**The composition of the present invention shall preferably contain** a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H<sub>2</sub> receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole . . . .**

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (–)-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

A POSA 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.

Further, the 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 employing more recently obtained and therapeutically more effective compounds in therapies over previously known, less therapeutically effective compounds. Accordingly, it would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for Gimet's disclosed prostaglandin because Goldman specifically teaches that "[p]roton pump inhibitors have been recently introduced as effective gastric acid inhibitors." Goldman at col. 1 ll. 25-27. It also would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for Goldman's disclosed omeprazole because Lindberg specifically teaches that "[i]t 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." Lindberg at col. 1 ll. 50-63. Moreover, a POSA would have also understood that "the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy." *Id.* at col. 3 ll. 48-55.

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 prostaglandin or Goldman's

	<p>disclosed omeprazole with Lindberg's disclosed esomeprazole because doing so would be a simple substitution of one known element for another to obtain predictable results.</p> <p>Lindberg at col. 6 ll. 21-25:</p> <p>The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, <b><u>oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.</u></b></p>
<p>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</p>	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. <b><u>Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</u></b></p> <p>Gimet at col. 12, ll. 14-19:</p> <p>That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby <b><u>the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.</u></b></p> <p>Gimet at col. 6, l. 20:</p> <p>When the prostaglandin is <b><u>misoprostol, . . . the misoprostol is present in an amount from about 50 to about 500 mcg . . . .</u></b></p>

Goldman at col. 5 ll. 9-31:

**The composition of the present invention shall preferably contain** a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H<sub>2</sub> receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole** . . . .

Lindberg at col. 14 ll. 6-10:

In contrast to enteric coatings, a person of ordinary skill in the art (POSA) would have understood that a given dosage form may employ an uncoated drug and/or a drug coated with non-enteric coatings, and that, following administration, such formulations may release their drug quickly upon contact with the surrounding medium (e.g., about immediate release upon entering the stomach). Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having an immediate release component, for example an uncoated drug (e.g., acid inhibitor) and/or a drug coated with a non-enteric coating that releases regardless of the pH of the surrounding medium.

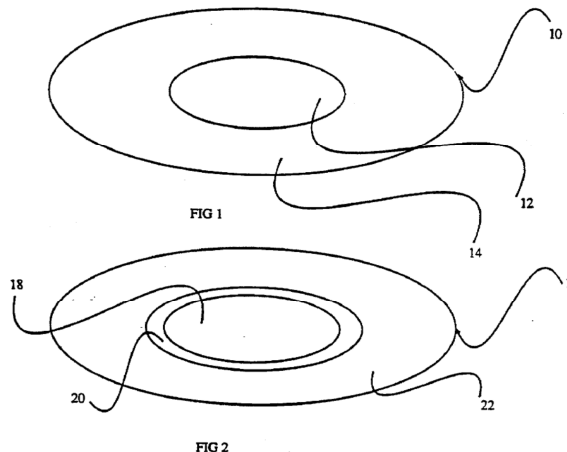
1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

Lindberg at col. 5 ll. 25-36:

In the preparation of pharmaceutical formulations in form of dosage units for oral

	<p>administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets.</p> <p>Lindberg at col. 13 ll. 3-5:</p> <p>500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose. 30 g. in water, 750 g. using a fluidized bed coater. After drying. the pellets were coated with a second coating as given below:</p> <table border="1" data-bbox="615 764 1283 938"> <thead> <tr> <th colspan="2">Coating solution:</th></tr> </thead> <tbody> <tr> <td>Hydroxypropyl methylcellulose phthalate</td><td>70 g</td></tr> <tr> <td>Cetyl alcohol</td><td>4 g</td></tr> <tr> <td>Acetone</td><td>200 g</td></tr> <tr> <td>Ethanol</td><td>600 g</td></tr> </tbody> </table>	Coating solution:		Hydroxypropyl methylcellulose phthalate	70 g	Cetyl alcohol	4 g	Acetone	200 g	Ethanol	600 g
Coating solution:											
Hydroxypropyl methylcellulose phthalate	70 g										
Cetyl alcohol	4 g										
Acetone	200 g										
Ethanol	600 g										
<p>release of at least a portion of said naproxen is inhibited unless the pH of said medium is 3.5 or higher.</p>	<p>Gimet at FIGS. 1 and 2:</p>										



Gimet at col. 3 l. 63 – col. 4, l. 11:

For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID, diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

Gimet at col. 6 ll. 24-36:

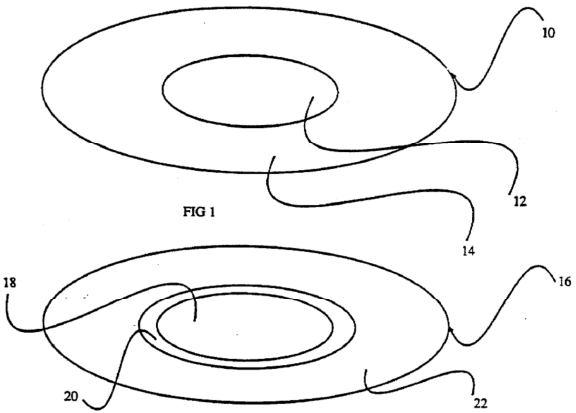


A second embodiment of the composition is shown in FIG. 2. In FIG. 2 a tablet 16 is schematically illustrated in cross section. **The tablet 16 includes an inner core 18 of an NSAID** diclofenac, piroxicam or their salts such as disclosed with regard to the core 12 of FIG. 1. **Surrounding the core 18 is an enteric coating 20.** The enteric coating 20 can be formulated from any suitable enteric coating material, many of which are known to those skilled in the art and many of which are employed for coating commercially available NSAID's. **The coating 20 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.**

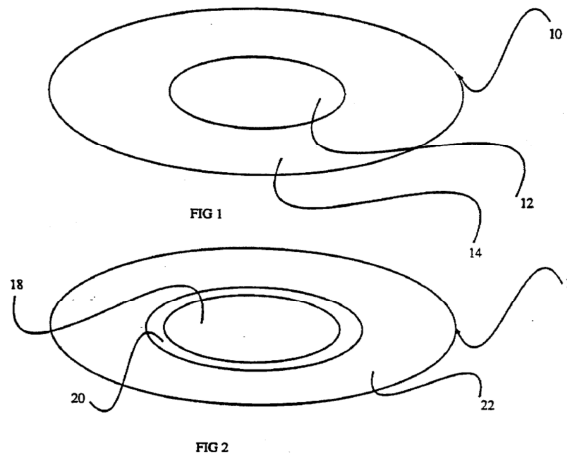
A POSA would have understood that a typical purpose associated with enteric coatings is to delay release of a drug until after the drug has exited the stomach. Also, the POSA would know that a typical patient would have a pH in the small intestine after exiting the stomach of greater than about 3.5. 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.

Goldman at col. 5 ll. 9-19:

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several **NSAIDs from the group of . . . naproxen** from 200 to 500 mg per dose . . . .

Claim 2	Gimet in view of Goldman and Lindberg
The pharmaceutical composition of claim 1, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.
said naproxen is present in a core layer,	<p>Gimet at FIGS. 1 and 2:</p>  <p>Gimet at col. 3 l. 63 – col. 4, l. 11:</p> <p>For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID,</p>

	<p>diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.</p> <p>Gimet at col. 4 ll. 34-39:</p> <p><b><u>If the inner core is piroxicam</u></b>, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam.</p> <p>Gimet at col. 6 ll. 26-27:</p> <p>The tablet 16 includes an inner core 18 of <b><u>an NSAID diclofenac, piroxicam or their salts such</u></b> as disclosed with regard to the core 12 of FIG. 1.</p> <p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen</u></b> from 200 to 500 mg per dose . . . .</p>
<p>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.</p>	<p>Gimet at FIGS. 1 and 2:</p>



Gimet at col. 3 l. 63 – col. 4, l. 11:

For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID, diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

Gimet at col. 2 ll. 38-49:

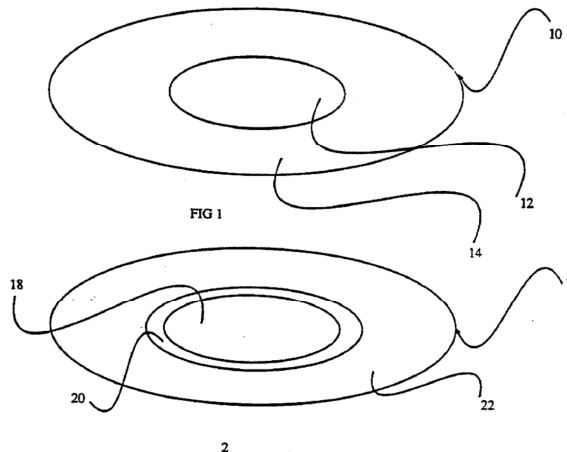
Another embodiment of the invention herein is a pharmaceutical composition wherein a coating is provided which is an intermediate coating that surrounds the core but lies underneath the mantle coating. Such an intermediate coating can be an additional coating for preventing contact between the NSAID and the prostaglandin to thereby inhibit any deleterious or otherwise non-beneficial interaction of the NSAID and prostaglandin such as degradation of the prostaglandin. Such an intermediate coating can be an enteric coating which aids in reducing the likelihood of the NSAID dissolving in the stomach and thereby directly exposing the stomach to the NSAID.

Gimet at col. 6 ll. 24-36:

A second embodiment of the composition is shown in FIG. 2. In FIG. 2 a tablet 16 is schematically illustrated in cross section. **The tablet 16 includes an inner core 18 of an NSAID** diclofenac, piroxicam or their salts such as disclosed with regard to the core 12 of FIG. 1. **Surrounding the core 18 is an enteric coating 20.** The enteric coating 20 can be formulated from any suitable enteric coating material, many of which are known to those skilled in the art and many of which are employed for coating commercially available NSAID's. **The coating 20 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.**

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. Also, the 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. 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.

Claim 3	Gimet in view of Goldman and Lindberg
The pharmaceutical composition of claim 1, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.
said unit dosage form is a multilayer tablet comprising a core layer and one or more layers outside of said core layer.	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to <b><u>a pharmaceutical composition which is a core/mantle tablet</u></b> consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</p>
Claim 4	Gimet in view of Goldman and Lindberg
The pharmaceutical composition of claim 3, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 3 obvious.
said core layer comprises naproxen.	Gimet at FIGS. 1 and 2:



Gimet at col. 3 l. 63 – col. 4, l. 11:

For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID, diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

Gimet at col. 4 ll. 34-39:

**If the inner core is piroxicam**, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam.

	<p>Gimet at col. 6, ll. 26-27:</p> <p>The tablet 16 includes an inner core 18 of <b><u>an NSAID diclofenac, piroxicam or their salts such</u></b> as disclosed with regard to the core 12 of FIG. 1.</p> <p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen</u></b> from 200 to 500 mg per dose . . . .</p>
<b>Claim 5</b>	<b>Gimet in view of Goldman and Lindberg</b>
The pharmaceutical composition of claim 3, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 3 obvious.
at least one of said one more layers outside said core layer comprises esomeprazole.	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. <b><u>Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</u></b></p> <p>Gimet at col. 12, ll. 14-19:</p> <p>That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby <b><u>the prostaglandin can be administered</u></b></p>



**for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.**

Gimet at col. 6, l. 20:

When the prostaglandin is **misoprostol, . . . the misoprostol is present in an amount from about 50 to about 500 mcg . . . .**

Goldman at col. 5 ll. 9-31:

**The composition of the present invention shall preferably contain** a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole . . . .**

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (–)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

Lindberg at col. 5 ll. 25-36:

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, stabilizing substances such as alkaline

	compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets.
<b>Claim 6</b>	<b>Gimet in view of Goldman and Lindberg</b>
The pharmaceutical composition of claim 3, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 3 obvious.
said one or more layers outside of said core layer do not contain naproxen.	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. <b><u>Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</u></b></p> <p>Gimet at col. 7 ll. 25-44:</p> <p>The tablet had the following composition.</p>

	<table> <tr> <th colspan="2">Unit Formula (mg)</th></tr> <tr> <td colspan="2"><u>Core</u></td></tr> <tr> <td>diclofenac sodium</td><td>50.0</td></tr> <tr> <td>lactose (monohydrate)</td><td>13.0</td></tr> <tr> <td>microcrystalline cellulose</td><td>12.9</td></tr> <tr> <td>cornstarch</td><td>8.4</td></tr> <tr> <td>povidone K-30</td><td>4.8</td></tr> <tr> <td>magnesium stearate</td><td>0.9</td></tr> <tr> <td>purified water</td><td></td></tr> <tr> <td colspan="2"><u>Mantle</u></td></tr> <tr> <td colspan="2"><u>misoprostol:HPMC dispersion (1:100)</u></td></tr> <tr> <td>misoprostol</td><td>0.2</td></tr> <tr> <td>hydroxypropyl methylcellulose (HPMC)</td><td>20.0</td></tr> <tr> <td>crospovidone</td><td>10.0</td></tr> <tr> <td>colloidal silicon dioxide</td><td>0.5</td></tr> <tr> <td>hydrogenated castor oil</td><td>1.0</td></tr> <tr> <td>microcrystalline cellulose</td><td>233.3</td></tr> </table> <p>A POSA would have understood that, because the mantle only consisted of misoprostol, HPMC, crospovidone, colloidal silicon dioxide, hydrogenated castor oil, and microcrystalline cellulose, the mantle did not contain naproxen.</p>	Unit Formula (mg)		<u>Core</u>		diclofenac sodium	50.0	lactose (monohydrate)	13.0	microcrystalline cellulose	12.9	cornstarch	8.4	povidone K-30	4.8	magnesium stearate	0.9	purified water		<u>Mantle</u>		<u>misoprostol:HPMC dispersion (1:100)</u>		misoprostol	0.2	hydroxypropyl methylcellulose (HPMC)	20.0	crospovidone	10.0	colloidal silicon dioxide	0.5	hydrogenated castor oil	1.0	microcrystalline cellulose	233.3
Unit Formula (mg)																																			
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<b>Claim 7</b>	<b>Gimet in view of Goldman and Lindberg</b>																																		
The pharmaceutical composition of claim 1, further comprising	As shown above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.																																		
at least one carrier.	<p>Gimet at col. 7 ll. 25-44:</p> <p>The tablet had the following composition.</p>																																		

Unit Formula (mg)	
<u>Core</u>	
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
purified water	
<u>Mantle</u>	
<u>misoprostol:HPMC dispersion (1:100)</u>	
misoprostol	0.2
hydroxypropyl methylcellulose (HPMC)	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

A POSA would have understood that cornstarch is a carrier.

Lindberg at col. 5 ll. 25-36:

In the preparation of pharmaceutical formulations in form of dosage units for oral administration **the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier**, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets.

Claim 8	Gimet in view of Goldman and Lindberg
The pharmaceutical composition of claim 1, further comprising	As shown above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.
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.	<p>Gimet at col. 4 ll. 28-33:</p> <p><b><u>Various excipients such as</u></b> binders, bulking agents, <b><u>lubricants</u></b>, fillers and the like, can be combined with the diclofenac in the core as is well known in the pharmaceutical art. Excipients used are selected from those which do not exhibit a destabilizing effect on either the diclofenac or prostaglandin.</p> <p>Lindberg at col. 5 ll. 25-36:</p> <p>In the preparation of pharmaceutical formulations in form of dosage units for oral administration <b><u>the optically pure compound may be mixed with</u></b> a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, <b><u>stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like</u></b> as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets.</p>

Claim 9	Gimet in view of Goldman and Lindberg
The pharmaceutical composition of claim 1, further comprising	As shown above, Gimet in view of Goldman and Lindberg renders claim 1 obvious.
at least one ingredient to adjust pH.	<p>Gimet at col. 8 ll. 18-45:</p> <p>The tablet had the following composition.</p>

	Unit Formula (mg)
<u>Core</u>	
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Enteric coating (aqueous)	
<u>methacrylic acid</u>	
copolymer type C	3.68
sodium hydroxide	0.049
talcum	1.84
triethyl citrate	0.37
<u>Overcoating</u>	
HPMC	2.72
polyethylene glycol (PEG 400)	0.054
<u>Mantle</u>	
<u>misoprostol:HPMC dispersion (1:100)</u>	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

A POSA would have understood that Gimet's sodium hydroxide would have adjusted pH.

Lindberg at col. 5 ll. 25-35:

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, **stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides** and oxides of sodium, potassium, calcium,

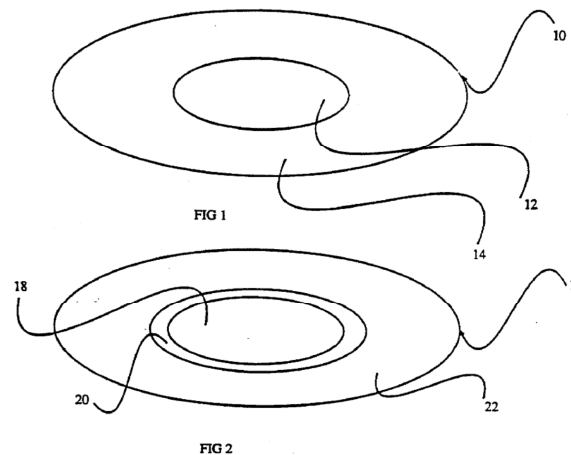
	<p>magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.</p> <p>A POSA would have understood that Lindberg's alkaline compounds would have adjusted pH.</p>
<b>Claim 10</b>	<b>Gimet in view of Goldman and Lindberg</b>
A method of treating a patient for pain or inflammation, comprising	<p>Gimet at col. 12 ll. 41-44:</p> <p>2. <b><u>A method of treating inflammation comprising</u></b> orally administering to a patient in need of such treatment, a therapeutically effective amount to treat inflammation of a composition comprising . . . .</p>
administering to said patient the pharmaceutical composition of claim 1.	<i>See claim 1.</i>
<b>Claim 11</b>	<b>Gimet in view of Goldman and Lindberg</b>
The method of claim 10, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 10 obvious.
said pain or inflammation is due to either osteoarthritis	<p>Gimet at col. 1 ll. 18-23:</p> <p>Nonsteroidal anti-inflammatory drugs <b><u>(NSAIDs) . . . have long been recognized as</u></b></p>



or rheumatoid arthritis.	<p><b><u>having high therapeutic value especially for the treatment of inflammatory conditions such as . . . osteoarthritis (OA) and rheumatoid arthritis (RA).</u></b></p> <p>Gimet at col. 4, ll. 34-39:</p> <p>If the inner core is piroxicam, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam . . . <b><u>[P]iroxicam be administered in a single daily dose of 20 mg for rheumatoid arthritis and osteoarthritis.</u></b></p>
<b>Claim 12</b>	<b>Gimet in view of Goldman and Lindberg</b>
A pharmaceutical composition in unit dosage form in the form of a tablet, said composition comprising:	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to <b><u>a pharmaceutical composition which is a core/mantle tablet</u></b> consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</p> <p>Gimet at col. 7 ll. 23-25:</p> <p>A <b><u>pharmaceutical tablet composition</u></b> was prepared consisting of a diclofenac sodium central core and a misoprostol mantle.</p>
a core layer comprising naproxen, wherein	<p>Gimet at col 2, l. 65 – col. 3, l. 2:</p> <p>FIG. 1 is a schematic representation of a tableted pharmaceutical composition herein illustrating the core/mantle structure;</p>

FIG. 2 is a schematic representation of another embodiment of a tableted pharmaceutical composition herein . . . .

Gimet at FIGS. 1 and 2:



Gimet at col. 3 l. 63 – col. 4, l. 11:

For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. **A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID** that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID,

diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

Gimet at col. 6 ll. 24-33:

A second embodiment of the composition is shown in FIG. 2. In FIG. 2 a tablet 16 is schematically illustrated in cross section. The tablet 16 includes an inner core 18 of an NSAID diclofenac, piroxicam or their salts such as disclosed with regard to the core 12 of FIG. 1. Surrounding the core 18 is an enteric coating 20. The enteric coating 20 can be formulated from any suitable enteric coating material, many of which are known to those skilled in the art and many of which are employed for coating commercially available NSAID's.

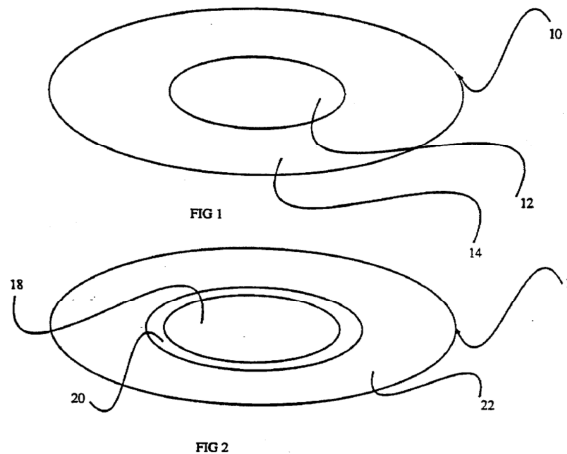
Goldman at col. 5 ll. 9-19:

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several **NSAIDs from the group of . . . naproxen from 200 to 500 mg** per dose . . . .

A POSA would have known that Gimet's disclosed prostaglandin, misoprostol, is an acid inhibitor. *See* "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 (Ex. 1044), at 126S.

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.

	<p>Similarly, a POSA would have understood that Goldman discloses a combination therapy oral unit dosage form comprising an acid inhibitor (e.g., H2 blockers and proton pump inhibitors) in combination with an NSAID (e.g., naproxen).</p> <p>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.</p> <p>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 (i.e., diclofenac or 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 diclofenac or piroxicam used in the NSAID/acid inhibitor combination therapies of Gimet.</p>
<p>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</p>	<p>Gimet at FIGS. 1 and 2:</p>



Gimet at col. 3 l. 63 – col. 4, l. 11:

For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID, diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

Gimet at col. 2 ll. 38-49:

Another embodiment of the invention herein is a pharmaceutical composition wherein a coating is provided which is an intermediate coating that surrounds the core but lies underneath the mantle coating. Such an intermediate coating can be an additional coating for preventing contact between the NSAID and the prostaglandin to thereby inhibit any deleterious or otherwise non-beneficial interaction of the NSAID and prostaglandin such as degradation of the prostaglandin. Such an intermediate coating can be an enteric coating which aids in reducing the likelihood of the NSAID dissolving in the stomach and thereby directly exposing the stomach to the NSAID.

Gimet at col. 6 ll. 24-36:

A second embodiment of the composition is shown in FIG. 2. In FIG. 2 a tablet 16 is schematically illustrated in cross section. **The tablet 16 includes an inner core 18 of an NSAID** diclofenac, piroxicam or their salts such as disclosed with regard to the core 12 of FIG. 1. **Surrounding the core 18 is an enteric coating 20.** The enteric coating 20 can be formulated from any suitable enteric coating material, many of which are known to those skilled in the art and many of which are employed for coating commercially available NSAID's. **The coating 20 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.**

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. Also, the 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. 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.

	<p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen</u></b> from 200 to 500 mg per dose . . . .</p>
<p>a layer comprising esomeprazole, wherein</p>	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. <b><u>Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</u></b></p> <p>Gimet at col. 12, ll. 14-19:</p> <p>That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby <b><u>the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.</u></b></p> <p>Gimet at col. 6, l. 20:</p> <p>When the prostaglandin is <b><u>misoprostol, . . . the misoprostol is present in an amount from about 50 to about 500 mcg . . . .</u></b></p> <p>Goldman at col. 5 ll. 9-31:</p> <p><b><u>The composition of the present invention shall preferably contain</u></b> a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose;</p>

ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole** . . . .

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (-)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

A POSA 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.

Further, the 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 employing more recently obtained and therapeutically more effective compounds in therapies over previously known, less therapeutically effective compounds.

Accordingly, it would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for Gimet's disclosed prostaglandin because Goldman specifically teaches that "[p]roton pump inhibitors have been recently introduced as effective gastric acid inhibitors." Goldman at col. 1 ll. 25-27. It also would have been obvious to a POSA to select Lindberg's disclosed esomeprazole and substitute it for



	<p>Goldman's disclosed omeprazole because Lindberg specifically teaches that "[i]t 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." Lindberg at col. 1 ll. 50-63. Moreover, a POSA would have also understood that "the optically pure salts are stable resisting racemization both in neutral pH and basic pH, which is surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulfur atom was expected to cause racemization under alkaline conditions. This high stability against racemization makes it possible to use a single enantiomeric salt of the invention in therapy." <i>Id.</i> at col. 3 ll. 48-55.</p> <p>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 prostaglandin or Goldman's disclosed omeprazole with Lindberg's disclosed esomeprazole because doing so would be a simple substitution of one known element for another to obtain predictable results.</p>
<p>said layer has a non-enteric film coating that, upon ingestion by a patient, releases said esomeprazole into the stomach of said patient.</p>	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. <b><u>Surrounding the core is a mantle coating</u></b> which consists of a prostaglandin . . . .</p> <p>Gimet at col. 7 ll. 25-44:</p>

The tablet had the following composition.

	Unit Formula (mg)
<u>Core</u>	
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
purified water	
<u>Mantle</u>	
<u>misoprostol:HPMC dispersion (1:100)</u>	
misoprostol	0.2
hydroxypropyl methylcellulose (HPMC)	20.0
croscopvidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of **the (–)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole** and a pharmaceutically acceptable carrier.

A POSA would have understood that this active compound is esomeprazole.

Lindberg at col. 5 ll. 25-36:

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin or another suitable carrier, stabilizing substances such as alkaline

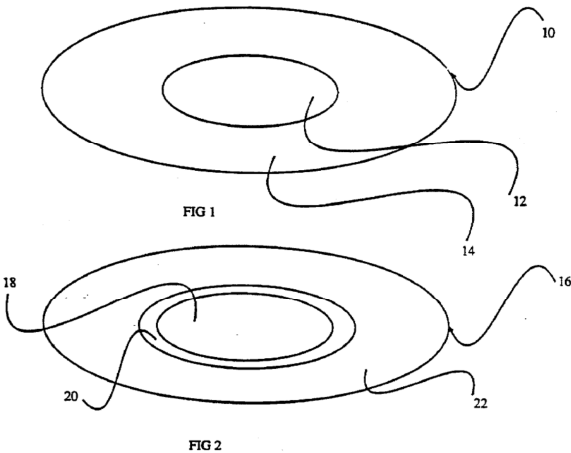
compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets.

Lindberg at col. 13 ll. 3-5:

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose. 30 g. in water, 750 g. using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:	
Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

In contrast to enteric coatings, a person of ordinary skill in the art (POSA) would have understood that a given dosage form may employ an uncoated drug and/or a drug coated with non-enteric coatings, and that, following administration, such formulations may release their drug quickly upon contact with the surrounding medium (e.g., about immediate release upon entering the stomach). Thus, the POSA would have had a rationale and a reasonable expectation of success in preparing a combination therapy unit dosage form having an immediate release component, for example an uncoated drug (e.g., acid inhibitor) and/or a drug coated with a non-enteric coating that releases regardless of the pH of the surrounding medium.

Claim 13	Gimet in view of Goldman and Lindberg
The pharmaceutical composition of claim 12, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 12 obvious.
naproxen is present in said unit dosage form in an amount of 200-600 mg.	<p>Gimet at FIGS. 1 and 2:</p>  <p>Gimet at col. 3 l. 63 – col. 4, l. 11:</p> <p>For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID,</p>

	<p>diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.</p> <p>Gimet at col. 4 ll. 34-39:</p> <p><b><u>If the inner core is piroxicam</u></b>, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam.</p> <p>Gimet at col. 6 ll. 26-27:</p> <p>The tablet 16 includes an inner core 18 of <b><u>an NSAID diclofenac, piroxicam or their salts such</u></b> as disclosed with regard to the core 12 of FIG. 1.</p> <p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen from 200 to 500 mg</u></b> per dose . . . .</p>
<b>Claim 14</b>	<b>Gimet in view of Goldman and Lindberg</b>
The pharmaceutical composition of claim 12, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 12 obvious.

esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.

Gimet at col. 3 ll. 8-14:

The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. **Surrounding the core is a mantle coating which consists of a prostaglandin . . . .**

Gimet at col. 12, ll. 14-19:

That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby **the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.**

Gimet at col. 6, l. 20:

When the prostaglandin is **misoprostol, . . . the misoprostol is present in an amount from about 50 to about 500 mcg . . . .**

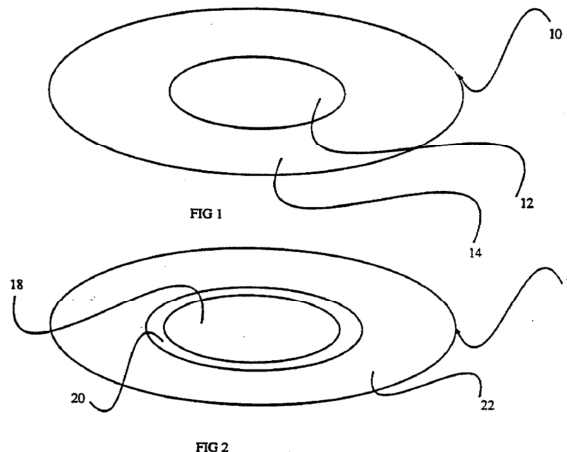
Goldman at col. 5 ll. 9-31:

**The composition of the present invention shall preferably contain** a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole . . . .**

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state

	<p>alkaline salt of <u>the (–)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole</u> and a pharmaceutically acceptable carrier.</p> <p>A POSA would have understood that this active compound is esomeprazole.</p> <p>Lindberg at col. 6 ll. 21-25:</p> <p>The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, <b><u>oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.</u></b></p>
<b>Claim 15</b>	<b>Gimet in view of Goldman and Lindberg</b>
The pharmaceutical composition of claim 12, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 12 obvious.
naproxen is present in said unit dosage form in an amount of between 200-600 mg and	Gimet at Figs. 1 and 2:



Gimet at col. 3 l. 63 – col. 4, l. 11:

For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in FIG. 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID, diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

Gimet at col. 4 ll. 34-39:

**If the inner core is piroxicam**, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam.



	<p>Gimet at col. 6 ll. 26-27:</p> <p>The tablet 16 includes an inner core 18 of <b><u>an NSAID diclofenac, piroxicam or their salts such</u></b> as disclosed with regard to the core 12 of FIG. 1.</p> <p>Goldman at col. 5 ll. 9-19:</p> <p>The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts . . . one of several <b><u>NSAIDs from the group of . . . naproxen from 200 to 500 mg</u></b> per dose . . . .</p>
<p>esomeprazole in an amount of from 5 to 100 mg per unit dosage form.</p>	<p>Gimet at col. 3 ll. 8-14:</p> <p>The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. <b><u>Surrounding the core is a mantle coating which consists of a prostaglandin . . . .</u></b></p> <p>Gimet at col. 12, ll. 14-19:</p> <p>That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby <b><u>the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.</u></b></p> <p>Gimet at col. 6, l. 20:</p> <p>When the prostaglandin is <b><u>misoprostol, . . . the misoprostol is present in an amount from about 50 to about 500 mcg . . . .</u></b></p>

Goldman at col. 5 ll. 9-31:

**The composition of the present invention shall preferably contain** a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole** . . . .

Gimet at col. 12, ll. 14-19:

That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby **the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.**

Gimet at col. 6, l. 20:

When the prostaglandin is **misoprostol, . . . the misoprostol is present in an amount from about 50 to about 500 mcg** . . . .

Goldman at col. 5 ll. 9-31:

**The composition of the present invention shall preferably contain** a combination of the following compositions or their pharmaceutically acceptable salts . . . in combination with the H2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the [] **proton pump inhibitor drugs including omeprazole** . . . .

Lindberg at col. 14 ll. 6-10:

1. A pharmaceutical formulation for oral administration comprising a pure solid state

	<p>alkaline salt of <u>the (–)-enantiomer of 5-methoxy-2[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole</u> and a pharmaceutically acceptable carrier.</p> <p>A POSA would have understood that this active compound is esomeprazole.</p> <p>Lindberg at col. 6 ll. 21-25:</p> <p>The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, <b><u>oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.</u></b></p>
<b>Claim 16</b>	<b>Gimet in view of Goldman and Lindberg</b>
A method of treating a patient for pain or inflammation, comprising	<p>Gimet at col. 12 ll. 41-44:</p> <p>2. <b><u>A method of treating inflammation comprising</u></b> orally administering to a patient in need of such treatment, a therapeutically effective amount to treat inflammation of a composition comprising . . . .</p>
administering to said patient the pharmaceutical composition of claim 12.	See claim 12.

Claim 17	Gimet in view of Goldman and Lindberg
The method of claim 16, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 16 obvious.
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	<p>Gimet at col. 1 ll. 18-23:</p> <p>Nonsteroidal anti-inflammatory drugs <u>(NSAIDs) . . . have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as . . . osteoarthritis (OA) and rheumatoid arthritis (RA).</u></p> <p>Gimet at col. 4, ll. 34-39:</p> <p>If the inner core is piroxicam, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam . . . <u>[P]iroxicam be administered in a single daily dose of 20 mg for rheumatoid arthritis and osteoarthritis.</u></p>
Claim 18	Gimet in view of Goldman and Lindberg
A method of treating a patient for pain or inflammation, comprising	<p>Gimet at col. 12 ll. 41-44:</p> <p>2. <u>A method of treating inflammation comprising</u> orally administering to a patient in need of such treatment, a therapeutically effective amount to treat inflammation of a composition comprising . . . .</p>

administering to said patient the pharmaceutical composition of claim 15.	See claim 15.
<b>Claim 19</b>	<b>Gimet in view of Goldman and Lindberg</b>
The method of claim 18, wherein	As shown above, Gimet in view of Goldman and Lindberg renders claim 18 obvious.
said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.	<p>Gimet at col. 1 ll. 18-23:</p> <p>Nonsteroidal anti-inflammatory drugs <u>(NSAIDs) . . . have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as . . . osteoarthritis (OA) and rheumatoid arthritis (RA).</u></p> <p>Gimet at col. 4, ll. 34-39:</p> <p>If the inner core is piroxicam, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam . . . <u>[P]iroxicam be administered in a single daily dose of 20 mg for rheumatoid arthritis and osteoarthritis.</u></p>