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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

HORIZON PHARMA, INC. and POZEN INC.,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, INC. and
DR. REDDY'S LABORATORIES, LTD.,

Defendants.

Civil Action No. 3:13-cv-00091-JAP-
DEA

(consolidated for discovery purposes
with Civ. A. Nos. 3:11-cv-02317-JAP-
DEA, 3:11-cv-04275-JAP-DEA, and
3:11-cv-06348-JAP-DEA)

**HORIZON PHARMA, INC.'S AND POZEN INC.'S PRELIMINARY RESPONSES TO
DR. REDDY'S LABORATORIES, INC. AND DR. REDDY'S LABORATORIES, LTD.'S
INVALIDITY CONTENTIONS PURSUANT TO L. PAT. R. 3.6(i)**

On March 7, 2014, Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "DRL") served Invalidity Contentions for United States Patent No. 8,557,285 ("the '285 patent"). Plaintiffs Pozen, Inc. and Horizon Pharma, Inc. (collectively, "Plaintiffs") hereby provide, pursuant to N.J. Loc. Pat. R. 3.6(i), their Responses to DRL's Invalidity Contentions for the '285 patent as set forth below and in Exhibit A. Plaintiffs reserve the right to amend or supplement these contentions as discovery proceeds in this case, as the Court construes the claims, and as permitted by the Court and the Local Patent Rules.

I. Responses to DRL's Contentions that the '285 Patent is Invalid (L. Pat. R. 3.4A)

DRL contends that claims 1-4 of the '285 patent (the "Asserted Claims") are invalid as obvious. As discussed below, all of the Asserted Claims of the '285 patent are valid.

A. The Claims of the '285 Patent

The claims of the '285 patent relate to pharmaceutical compositions comprising esomeprazole and naproxen, a non-steroidal anti-inflammatory drug (NSAID), wherein the naproxen is surrounded by a coating that inhibits its release unless the pH of the surrounding medium is 3.5 or higher, and at least a portion of the esomeprazole is released upon introduction into the medium regardless of the pH. Claim 1 of the '285 patent states:

1. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:

(a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and

(b) naproxen surrounded by 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;

wherein said unit dosage form provides for release of said esomeprazole such that 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.

The remaining claims of the '285 patent add limitations relating to the amounts of esomeprazole or naproxen in the pharmaceutical composition.

B. The Claims of the '285 Are Valid and Not Anticipated

DRL contends that claims 1-4 of the '285 Patent are anticipated by:

- U.S. Pat. No. 5,601,843 (“’843 Patent” or “Gimet”)
- PCT Pat. App. Pub. WO 00/01368 (“WO ’368” or “Woolfe”)
- European Pat. App. Pub. EP 1 068 867 (“EP ’867” or “Sherman”)

None of the asserted references anticipate any claims of the '285 Patent.

1. The Law of Anticipation

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in “possession” of that invention.¹ In other words, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as is contained in the claim.² The claim limitations must also be “arranged” in the prior art reference, just as they are in the claim,³ rather than as “multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.”⁴ In addition, public “possession” requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.⁵ Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the

¹ *Akzo N.V. v. U.S. Intern. Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

² *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

³ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

⁴ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

⁵ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.⁶ This inquiry is objective, and thus evidence of undue experimentation need not be prior art.⁷

2. The '843 Patent (Gimet) Does Not Describe the Claimed Inventions

The '843 Patent does not anticipate claims 1-4 of the '285 Patent, as DRL asserts. The '843 Patent describes a dosage form having an enteric coated NSAID core (diclofenac or piroxicam) surrounded by mantle coating comprising a prostaglandin, such as misoprostol.⁸ The '843 Patent does not disclose a dosage form comprising esomeprazole in an amount effective to raise the gastric pH of a patient to at least 3.5. Further, the '843 Patent does not disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH.

3. WO '368 (Woolfe) Does Not Describe the Claimed Inventions

WO '368 does not anticipate claims 1-4 of the '285 Patent as DRL asserts. WO '368 describes a dosage form having enteric coated NSAID pellets combined with misoprostol.⁹ WO '368 does not disclose a dosage form comprising esomeprazole in an amount effective to raise the gastric pH of a patient to at least 3.5. Further, WO '368 does not disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH.

⁶ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

⁷ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir. 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

⁸ The '843 Patent, Abstract.

⁹ WO '368, Abstract.

4. EP '867 (Sherman) Does Not Describe the Claimed Inventions

EP '867 does not anticipate claims 1-4 of the '285 Patent as asserted by DRL. EP '867 describes a dosage form having enteric coated NSAID (piroxicam, diclofenac, or a salt of diclofenac) combined with misoprostol.¹⁰ EP '867 does not disclose a dosage form comprising esomeprazole in an amount effective to raise the gastric pH of a patient to at least 3.5. Further, EP '867 does not disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH.

C. The Claims of the '285 Patent Are Valid and Would Not Have Been Obvious

DRL contends that the Asserted Claims are obvious in view of the following combinations of references:

- WO '064 and WO '320 in light of Daneshmend and Chandramouli (claims 1-4)
- WO '064 and WO '320 in light of Daneshmend and Hawkey (claims 1-4)
- WO '368 and WO '320 in light of Daneshmend or Hawkey and Chandramouli (claims 1-4)
- The '843 Patent in light of WO '064, Daneshmend, and Hawkey (claims 1-4)
- WO '064 in view of Hawkey, Daneshmend, Chandramouli, and Dent (claims 1-4)
- The '843 Patent, WO '368, and/or EP '867 in Combination With Ramage, Wilson, Sangiah, the '118 Patent, the '354 patent, Brown, Trondstad, Nefesoglu and/or the '974 Patent (claims 1-4)
- The '118 Patent and/or the '354 Patent in view of the '843 Patent, WO '368, EP '867, Ramage, Wilson, Sangiah, Brown, Trondstad, Nefesoglu, Okabe, Konturek, Takeuchi, and/or the '974 patent (claims 1-4)
- The '843 Patent, WO '368 and/or EP '867 in view of Sangiah, Hawkey III, Nefesoglu, Wolfe, Brown and/or the '974 Patent (claims 1-4)
- The '118 Patent and/or the '354 Patent in view of the '843 Patent, WO '368, EP '867, Trondstad, Hawkey III, Nefesoglu, Wolfe, Brown and the '974 Patent (claims 1-4).

¹⁰ EP '867, ¶¶ 14, 16.

The asserted combinations of references do not render any claims of the '285 patent obvious.

1. The Law of Obviousness

A patent claim is invalid “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.”¹¹ Obviousness is a legal determination, but it turns on factual inquiries into the level of ordinary skill in the art, the scope and content of the prior art, and the differences between the prior art and the claims at issue.¹²

Since the Supreme Court’s decision in *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), the Federal Circuit has reiterated that all the claim limitations of the invention at issue must be found to exist in the prior art references before proceeding with an obviousness analysis.¹³ Furthermore, even if all the claim limitations of the invention at issue are found in the prior art references, a claimed invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.”¹⁴ Rather, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an “apparent reason” to combine the elements in the manner claimed¹⁵ and “a reasonable expectation of success.”¹⁶ Any assertion of a “reasonable expectation of success” must find a basis in the factual record.¹⁷

¹¹ 35 U.S.C. § 103(a).

¹² *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

¹³ *Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2009).

¹⁴ *KSR*, 550 U.S. at 418; *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1351–52 (Fed. Cir. 2010).

¹⁵ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may not be employed to identify relevant prior art and relevant teachings therewithin: *Heidelberger Druckmaschinen AG*

Obviousness is not likely to exist where one of ordinary skill in the art is faced with multiple paths,¹⁸ especially where those paths lead away from the claimed invention.¹⁹ The challenges associated with the inventive process that “would have prevented one of ordinary skill in this art from traversing the multiple obstacles to easily produce the invention” weigh against a finding of obviousness.²⁰ Where the teachings in the art discourage one from doing what is claimed, the art establishes “the very antithesis of obviousness.”²¹ “A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would . . . be led in a direction divergent from the path that was taken by the applicant.”²² “An inference of nonobviousness is especially strong where the prior art’s teachings undermine the very reason

v. Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

¹⁶ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”); *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a combination of elements “must do more than yield a predictable result;” combining elements that work together “in an unexpected and fruitful manner” would not have been obvious).

¹⁷ See, e.g., *Sanofi-Synthelabo*, 550 F.3d at 1089 (“Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

¹⁸ See *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1380 (Fed. Cir. 2008) (affirming a finding that the patents were not obvious when “[t]he district court gave lengthy consideration to the multiple paths that would have faced a person of ordinary skill in the art who recognized” the problem solved by the patents).

¹⁹ See, e.g., *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (citing *United States v. Adams*, 383 U.S. 39, 52 (1966) (“The opposite conclusion [of obviousness] would follow, however, if the prior art indicated that the invention would not have worked for its intended purpose or otherwise taught away from the invention.”)).

²⁰ *Ortho-McNeil Pharm. Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008).

²¹ *In re Buehler* 185 USPQ 781 (CCPA 1975); *In re Rosenberger and Brandt*, 156 USPQ 24, 26 (CCPA 1967).

²² *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)).

being proffered as to why a person of ordinary skill would have combined the known elements.”²³

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.²⁴ An objective indicium is any “event[] proved to have actually happened in the real world” that evidences the nonobvious nature of the invention.²⁵ The existence of an enduring, unmet need; difficulties encountered by those skilled in the field; expressions of skepticism; and copying are classical indicia of nonobviousness.²⁶ These factual inquiries “guard against slipping into use of hindsight,”²⁷ and “may often be the most probative and cogent evidence of nonobviousness.”²⁸

2. The Art Taught Away from the Invention

At the time of the invention, the art taught away from releasing proton pump inhibitors (PPIs), such as esomeprazole, directly into stomach acid conditions as claimed in the ’285 patent. Instead, the art taught that the release of PPIs should be delayed to prevent them from coming into contact with stomach acid. The universal approach for preventing PPIs from immediately releasing upon ingestion was to coat them with a barrier, such as an enteric coating. The protective barrier allows the PPIs to safely pass through an acidic environment (such as the stomach) and release when at a safe, pre-determined pH.

²³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009).

²⁴ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

²⁵ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

²⁶ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Panduit*, 810 F.2d at 1569; *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janssen*, 456 F.Supp.2d at 669–72.

²⁷ *Graham*, 383 U.S. at 36.

²⁸ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

The literature is replete with examples teaching that PPIs should be enteric coated and not immediately released into the stomach acid regardless of pH. A number of examples are provided below.

[PPIs] are all acid-labile, so when administered orally *they must be formulated in an enteric coating to protect them from rapid degradation in the stomach*. They are rapidly absorbed in the duodenum.²⁹

* * * * *

All the proton pump inhibitors have a similar core structure, a substituted pyridyl methylsulfinyl benzimidazole. . . As a class, these drugs are therefore *acid-unstable, requiring protection against gastric acidity for oral formulation* and requiring reconstitution for i.v. administration.³⁰

* * * * *

These proton pump inhibitors are, however, susceptible to degradation/transformation in acidic reacting and neutral media. . . . [I]t is obvious that a proton pump inhibitor in an oral solid dosage form must be protected from contact with the acidic reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is less acidic, neutral or alkaline and where rapid absorption of the pharmaceutically active substance, i.e. the proton pump inhibitor, can occur. A pharmaceutical dosage form of these proton pump inhibitors is best protected from contact with acidic gastric juice by an enteric coating layer.³¹

* * * * *

It is well known that omeprazole is sensitive to acidic conditions and the after contact with an acid, omeprazole will degrade and will not function in its intended manner. Initially, alkaline

²⁹ Stedman & Barclay (AZV00293753 - AZV00293765), *Review Article: Comparison of the Pharmacokinetics, and Acid Suppression and Efficacy of Proton Pump Inhibitors*, AILMENT PHARMACOL. THER., 14:963-978, 963 (2000) (emphasis added).

³⁰ Sachs *et al.* (AZV00293734 - AZV00293752), *Review Article: The Control of Gastric Acid and Helicobacter Pylori Eradication*, ALIMENT PHARMACOL. THER. 14:1383-1401, 1387 (2000) (emphasis added).

³¹ U.S. Patent No. 6,013,281 (Lundberg *et al.*), Col. 4, line 58 through Col. 5, line 7 (PZV0000000070 - PZV0000000082).

materials were added to a core of omeprazole and later an enteric coating was applied over the core to prevent the omeprazole from contacting the acidic pH conditions of the stomach.³²

* * * * *

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of omeprazole can occur. A pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastric juice by an enteric coating.³³

* * * * *

PPIs are highly acid labile and hence oral formulations are enteric coated.³⁴

* * * * *

Due to the acidic gastric condition, a pharmaceutical dosage form of omeprazole must be coated with an enteric coating to prevent omeprazole from premature contact with gastric juice.³⁵

* * * * *

It is well known that some of the gastric acid suppressing agents, such as proton pump inhibitors are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that the one of the active substances being an acid susceptible proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the prior art, see for example U.S. Pat No. 4,786,505 (AB Hassle) describing a preparation comprising omeprazole.³⁶

³² U.S. Patent No. 6,077,541 (Chen et al.), Col. 1, lines 8-14 (PZV0000000083 -PZV0000000087).

³³ U.S. Patent No. 5,690,960 (Bengtsson et al.), Col. 1, lines 38-47 (PZV0000000059 -PZV0000000065).

³⁴ U.S. Patent No. 5,708,017 (Dave et al.), Col. 1, lines 28-29 (PZV0000000066 -PZV0000000069).

³⁵ Int'l Patent Publication No. WO 01/52816 (Carlsbad Technology, Inc.), page 2, lines 14-16 PZV0000000195 - PZV0000000219).

³⁶ U.S. Patent No. 6,132,771 (Depui et al.), Col. 2, lines 47-57 (PZV0000000148 -PZV0000000162).

* * * * *

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating.³⁷

* * * * *

With respect to the stability properties of omeprazole, it is obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and that omeprazole must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur. A pharmaceutical oral dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer.³⁸

* * * * *

Chemical substances that are easily destroyed in an acid medium (which is expressed herein by the term "acid-labile, and meaning chemical substances that are labile in an acid medium), such as benzimidazoles and, in particular, omeprazole, lansoprazole and pantoprazole, create a special problem for formulators when it is required to provide a pharmaceutical form designed for oral administration. The product does indeed come into contact with the stomach content, which is a highly acid medium, leading to breakdown of these chemical substances. In order to avoid contact between the substances and the acid gastric juice following oral administration of the substance, a pharmaceutical formulation is conventionally used, such as a capsule or tablet which contains a core (tablet, microgranule, pellet, etc . . .) containing the acid-labile active substance and an outer layer that surrounds this core and which consists of a gastro-resistant composition that is enterosoluble. Generally, the coating agent is a compound that is particularly insoluble in an acid medium, but which is soluble in a neutral or alkaline medium.³⁹

* * * * *

³⁷ U.S. Patent No. 4,853,230 (Lovgren et al.), Col. 1, lines 14-19 (PZV0000000050 -PZV0000000058).

³⁸ U.S. Patent No. 6,090,827 (Erickson et al.), Col. 1, line 65 through Col. 2, line 6 PZV0000000088 - PZV0000000095).

³⁹ U.S. Patent No. 6,159,499 (Seth), Col. 1, lines 32-52 (PZV0000000168 - PZV0000000185).

It is also known that omeprazole readily degrades in acidic medium and in neutral medium. The degradation half-life of omeprazole is ten minutes at a pH of less than 4, eighteen hours at a pH equal to 6.5 and approximately 300 days at a pH equal to 11. For this reason, pharmaceutical dosage forms of omeprazole for oral administration are gastroprotected so that the active principle reaches the small intestine without being degraded.⁴⁰

* * * * *

As shown in FIG. 1, the presence of acid is a prerequisite to the conversion of omeprazole to its chemically active sulfenamide. However, the resulting sulfenamide is a labile molecule which transforms further to a number of other compounds that are unreactive to nucleophilic attack by the H⁺ /K⁺ -ATPase thiol(s) and are therefore incapable of inhibiting the enzyme. These transformations are acid catalyzed. Accordingly, in a strict chemical sense, while acid is a prerequisite for the conversion of omeprazole to its active form, it also acts to its detriment. As a partial solution to this problem, omeprazole drug products are formulated to resist the acidic medium of the stomach by enteric coating. The coating is dissolved in the relatively neutral environment of the duodenum and omeprazole is absorbed into the blood stream which carries the prodrug to the proton pump. It should be emphasized however, that the conversion of the prodrug to the active enzyme inhibitor can only be achieved in acidic media which also results in substantial degradation of the active sulfenamide. In summary, the instability of omeprazole in acidic environments, which is a prerequisite to its activation into a proton pump inhibitor, is the major shortcoming of this drug.⁴¹

* * * * *

The presently used proton pump inhibitors are pyridyl methyl sulfinyl benzimidazoles (or compounds of closely related structure) with a pKa of 4.0 to 5.0. Their mechanism of action requires accumulation in the acidic space of the parietal cell (secretory canaliculus, pH ca. 1.0) and subsequently hydrogen ion catalyzed conversion to the reactive thiophilic species that is capable of inhibiting the gastric ATPase, enzyme resulting in effective inhibition of gastric secretion. Because of this mechanism the presently used PPI type drugs require specialized gastro

⁴⁰ U.S. Patent No. 6,551,621 (Debregeas et al.), Col. 1, lines 17-25 (PZV0000000186 -PZV0000000194).

⁴¹ U.S. Patent No. 6,093,738 (Karimian et al.), Col. 1, line 56 through Col. 2, line 11 PZV0000000112 - PZV0000000147).

protection to remain active for duodenal absorption. For this reason, and due to sensitivity to degradation in the acid milieu of the stomach, oral formulations of the PPI drugs are usually enteric coated. The need for enteric coating is a shortcoming because enteric coating is expensive and moisture sensitive.⁴²

* * * * *

The pharmaceutical effects of omeprazole on the organism has been extensively researched and are widely known. On the other hand, the longer-term stability of pharmaceutical formulations containing omeprazole has so far proved troublesome. Because the stability of omeprazole is influenced by organic solvents and moisture and its conversion is promoted by reagents giving an acid reaction or hindered by reagents giving an alkaline reaction, an oral omeprazole formulation must be protected with an enteric coating against the action of stomach acid so that it can develop its effect in the small intestine.⁴³

* * * * *

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.⁴⁴

* * * * *

Omeprazole degrades very rapidly in water solutions at low pH values....Preformulation studies have shown that moisture, solvents and acidic substances have a deleterious effect on the stability of omeprazole and should be avoided in pharmaceutical formulations...For a substance which is very slightly soluble in water and which rapidly degrades in the acid environment of the stomach, there is a limited number of options as far as pharmaceutical development is concerned.⁴⁵

* * * * *

⁴² U.S. Patent No. 6,093,734 (Garst et al.), Col. 1, line 58 through Col. 2, line 5 (PZV0000000096 - PZV0000000111).

⁴³ U.S. Patent No. 6,149,942 (Scheiwe et al.), Col. 1, lines 9-19 (PZV0000000163 -PZV0000000167).

⁴⁴ European Patent No. 0567201 (Astra AB), page 2, lines 14-16 (PZV0000000001 -PZV0000000020).

⁴⁵ Pilbrant and Cederberg "Development of an oral formulation of omeprazole." Scand. J. Gastroenterol. 1985:20 (suppl. 108):113-120 (PZV0000000030 - PZV0000000037).

[I]t is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.⁴⁶

* * * * *

PRILOSEC Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach.⁴⁷

* * * * *

Omeprazole is acid labile and is administered orally as enteric coated granules in capsules.⁴⁸

* * * * *

The stability of the PPIs in water solution is highly dependent on pH. The positively charged ion present at low pH values degrades rapidly. The half-life of degradation of the PPIs in dilute solutions at pH is in the range of a few minutes.⁴⁹

* * * * *

The susceptibility for degradation in acid media, such as the contents of the stomach, precludes the use of conventional oral dosage forms.⁵⁰

* * * * *

There are two main options for getting around the risk of acid-catalyzed degradation of the PPI in the stomach after oral administration.

1. To secure a neutral/alkaline gastric pH by coadministration of pH buffering substances. This was done in early human

⁴⁶ U.S. Patent No. 4,786,505 (Lovegren et al.) Col. 1, lines 36-39 (PZV0000000038 -PZV0000000049).

⁴⁷ Physicians' Desk Reference, Edition 46 (1992), page 1530 (PZV0000000025 -PZV0000000029).

⁴⁸ MIMS Annual 1992, MIMS Australia, at 1-8, column 1 (16th ed. 1992) (PZV0000000021 -PZV0000000024).

⁴⁹ Ake G. Pilbrant, *Pharmaceutical Considerations*, in Proton Pump Inhibitors 161, 162 (Lars Olbe ed., 1999).

⁵⁰ *Id.* at 163.

pharmacological studies with omeprazole [6] but can hardly be applied to a marketable pharmaceutical formulation for longer use.

2. To ensure that the active drug is not released in the stomach by using an enteric coating which dissolves only in solutions with a pH of 5.5 or higher, such as is the case in the small intestine.⁵¹

In addition to the examples provided above, the references relied upon by DRL in its invalidity contentions also teach that PPIs should not be immediately released into the stomach regardless of pH. For example, WO '064 explains that “it is obvious that the[*sic*] one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer.”⁵² WO '320 similarly explains that “it is necessary in this case for oral preparations to protect the active compounds from the action of acids.”⁵³ Instead of using an enteric coating of pH dependent polymers to protect the PPI, WO '320 uses another form of enteric coating composed of mixture of at least one sterol and at least one polymer.⁵⁴ Such coating allows the PPI to pass safely through the stomach and not to be released until the surrounding pH is sufficiently high, *e.g.*, at the intestine level. The '974 patent, another reference relied upon by DRL, explains that because PPIs are susceptible to acid degradation, they need to be protected from being released into the stomach, preferably by an enteric coating.⁵⁵ Similarly, Wolfe emphasizes that PPIs require an enteric coating to prevent them from immediately releasing upon ingestion.⁵⁶ In addition, WO'293, which is also relied upon by DRL, describes an oral dosage form in which the active ingredient, such as omeprazole, is not released

⁵¹ *Id.*

⁵² WO '064, p. 3, lines 26-28 (emphasis added).

⁵³ WO '320, p. 1.

⁵⁴ *Id.* at p. 3, last paragraph.

⁵⁵ The '974 patent, col. 4, lines 24-30.

⁵⁶ Wolfe, p. S25.

until the dosage form passes the stomach and gets into the small intestine.⁵⁷ WO '293 is directed to dosage forms for omeprazole.⁵⁸ The dosage forms are surrounded by a semipermeable membrane that prevents the release of omeprazole until a pre-determined amount of time.⁵⁹ Again this still prevents PPIs from being released until such time when the surrounding pH is sufficiently high, e.g., at the intestine level. Thus, the WO '293 does not describe an immediate-release of at least a portion of PPI regardless of pH.

Further, DRL's and Lupin's expert, Dr. John R. Horn, testified during his deposition on June 14, 2012, that a person having ordinary skill in the art would understand that the reason PPIs are enteric coated is because they are acid labile molecules that break down in the stomach.⁶⁰ In articles written by Dr. Horn, he states that proton pump inhibitors require an enteric coating when given orally to protect them from degradation in the stomach. If they degrade in the stomach they will not be absorbed.⁶¹ Dr. Horn also testified that in 2001, a person having ordinary skill in the art would have known that proton pump inhibitors require an enteric coating to protect them from degrading in the stomach.⁶² According to Dr. Horn, a person having ordinary skill in the art in 2001 would have realized that proton pump inhibitors are acid labile

⁵⁷ WO '293, p. 4, lines 11-22.

⁵⁸ WO '293, Abstract.

⁵⁹ *See, e.g.*, WO '293, p. 1, first paragraph, and p. 4, lines 19-22 ("The time interval [for disruption and release of the omeprazole] is to be determined so that the pellets have had time to pass the stomach at that very moment, and have reached the small intestines. The entire dose of the active ingredient will then start to be released into the small intestine where absorption can occur.")

⁶⁰ *See* Horn Dep. Tr. at 10:12-15; 63:7-12; 64:22-65:1.

⁶¹ *See* Horn Dep. Tr. at 96:4-8; 107:4-108:2.

⁶² *See* Horn Dep. Tr. at 97:4-13

and they need to be protected from the destructive effects of gastric acid when administered orally.⁶³

Dr. Horn is also the author of numerous articles on the subject of PPIs. In “Therapeutic Benefits of PPIs,” published online at www.pharmacytimes.com in 2008, Dr. Horn wrote that “[b]ecause the PPIs are weak bases, exposure to stomach acid will greatly reduce their absorption. Therefore, most PPIs are protected from stomach acid by a pH-sensitive enteric coating that prevents dissolution until the more neutral pH of the small intestine is encountered.”⁶⁴ Thus, according to Dr. Horn, it is desirable to enteric coat PPIs so as to protect them from stomach acid.

With respect to immediate release formulations of omeprazole, Dr. Horn wrote that “[i]mmediate-release omeprazole (IR OME) formulations (suspension and capsule) use sodium bicarbonate to protect the [omeprazole] from gastric acid, thus eliminating the need for enteric coating...IR OME is absorbed more quickly than [delayed release omeprazole]...”⁶⁵ Thus, according to Dr. Horn, the purpose of sodium bicarbonate in immediate release formulations of omeprazole is to protect the omeprazole from gastric acid so that it can be absorbed. Dr. Horn also says that “[t]he removal of the enteric coating and use of antacids to protect [omeprazole] as it passes through the stomach has proven to be an elegant modification that enhances pH control. By eliminating the enteric coating, IR OME is more rapidly absorbed and suppresses gastric secretion...”⁶⁶ Thus, according to Dr. Horn, formulations of omeprazole that contain antacids such as sodium bicarbonate allow the omeprazole to pass through the stomach. Dr. Horn is

⁶³ See Horn Dep. Tr. at 97:14-24.

⁶⁴ Therapeutic Benefits of PPIs at pgs. 1-2.

⁶⁵ Therapeutic Benefits of PPIs at pg. 2.

⁶⁶ Therapeutic Benefits of PPIs at pg. 3.

completely silent as to any “local effect” when omeprazole is formulated with an antacid such as sodium bicarbonate. On the contrary, Dr. Horn says that formulations of omeprazole buffered with sodium bicarbonate allow the omeprazole to pass through the stomach.

Dr. Horn, has also given presentations on the subject of PPIs. One such presentation was entitled “New Perspectives in the Management of Acid-Related Disorders: The Latest Advances in PPI Therapy” [New Perspectives] available online at www.medscape.org/viewarticle/503473. In that presentation, Dr. Horn was again completely silent as to any “local effect” when omeprazole is formulated with an antacid such as sodium bicarbonate.

Dr. Horn stated the following regarding PPIs: “This prodrug has to be absorbed in the systemic circulation, find its way to the parietal cell, and get into the canalicular space, where it then is activated, and only then is it able to bind to the proton pumps and shut the pumps down...”⁶⁷ “If you take a PPI in its raw form and expose it to the acid in your stomach, it will protonate in your stomach and not be absorbed; it will be degraded in the stomach...you don’t want these drugs to protonate until they get to the site of action, which is at the secretory canalicular space.”⁶⁸ Thus, according to Dr. Horn, PPIs must be absorbed in order to be later protonated and it is undesirable to allow PPIs to protonate in the stomach. If they are protonated in the stomach, they will be degraded.

Thus, contrary to DRL’s assertions, a person having ordinary skill in the art would not have been motivated to formulate omeprazole, or any other PPI, for at least a portion thereof for immediate release regardless of pH in combination with a delayed release NSAID coating. In fact, presented with extensive data for clinically and commercially proven enteric coated PPIs at

⁶⁷ New Perspectives at pg. 2.

⁶⁸ *Id.*

the time of the invention⁶⁹ contradicts the assertion that one skilled in the art would have been motivated to use non-enteric coated PPI in combination with another active, e.g., NSAID.

3. A Person of Ordinary Skill Could Not Have Had a “Reasonable Expectation” of Success

For an invention to be obvious, there must be a “reasonable expectation of success.” For a particular combination, there must be a “reasonable expectation” that it will function for its intended purpose.

DRL provides no evidence that a person of ordinary skill would have had a reasonable expectation of success in reducing the side effects of NSAIDs by combining an NSAID with an immediate-release of at least a portion of esomeprazole regardless of pH in a unit dosage form. In fact, as mentioned above, the art widely taught that PPIs, such as esomeprazole, should not be immediately released into the stomach because they were known to be susceptible to acid degradation.⁷⁰ Thus, the art at the time of the invention actually provides evidence that one of ordinary skill in the art would have expected failure, not success in the use of an immediate-release of at least a portion of esomeprazole regardless of pH. As such, the prior art teaches away from the invention as claimed.

4. Objective Indicia of Nonobviousness

In an obviousness determination, any objective indicia of nonobviousness must be taken into account. With respect to objective indicia of nonobviousness including secondary considerations, Plaintiffs reserve the right to amend or supplement these contentions as discovery proceeds in this case.

⁶⁹ Ake G. Pilbrant, *Pharmaceutical Considerations*, in Proton Pump Inhibitors 161, 164 (Lars Olbe ed., 1999).

⁷⁰ See e.g., *supra*, notes 33-67, incorporated herein by reference in their entirety.

Notwithstanding the foregoing, Plaintiffs assert that it was completely unexpected by persons having ordinary skill in the art at the time of the invention that a PPI could or even should be formulated such that it was “not surrounded by an enteric coating” and that “is released regardless of the pH of the medium.” as required by all of the asserted claims of the ’285 patent. This is because PPIs, such as esomeprazole, were well known by those having skill in the art to be acid labile and to rapidly degrade when exposed to the acidic environment of the stomach, thus rendering them ineffective.⁷¹

The skepticism of those having skill in the art was such that it was not contemplated that PPIs could be formulated into a unit dosage form without the protection of an enteric coating. Indeed, persons having skill in the art at the time of the invention tried and failed to formulate PPIs without the use of an enteric coating and abandoned these efforts.⁷² Thus, the prior art, taken as a whole, would not have led a person to the claimed invention. It was contrary to the prevailing wisdom at the time of the invention that a PPI could be formulated without an enteric coating and be immediately released into acidic gastric juice. According to the prevailing wisdom, a person having ordinary skill in the art would have been led away from the invention claimed in the ’285 patent because the prior art taught away from formulating acid labile PPIs without enteric coatings. Neither was there any expectation that a non-enterically coated PPI could or even should be formulated into a single dosage unit with an NSAID such that the dosage unit would provide for coordinated release.

Another indicium of non-obviousness is that unexpected results were obtained with the claimed invention. Administration of Vimovo[®], an embodiment of the claimed invention,

⁷¹ See e.g., *supra*, notes 33-52, incorporated herein by reference in their entirety.

⁷² Pilbrant & Cederberg, Development of an oral formulation of omeprazole, 20 Scand. J. Gastroenterol, at 113-120 (suppl. 108, 1985) (PZV0000000030-PZV0000000037).

resulted in unexpectedly greater reductions in gastric ulcers as compared to other NSAID combination treatments intended to reduce NSAID-induced gastric ulceration. For example, in denying the opposition to European Patent No. 1411900—which corresponds to United States Patent No. 6,926,907 (the '907 patent) and the '285 patent — the European Patent Office noted that the reduction rate of gastric ulcers with Vimovo® administration was significantly and unexpectedly greater than that achieved in a comparable test system with Arthrotec™, which contains the NSAID diclofenac and misoprostol.⁷³ In addition, those skilled in the art, such as Anchen's formulator Dr. Grant Heinicke, recognized that the effectiveness of the uncoated esomeprazole in Vimovo® was unexpected and contrary to the teachings of the published literature.⁷⁴ As another example, despite the acknowledged increase in gastric ulcers for those taking low-dose aspirin with NSAID as compared to those taking NSAID alone, patients taking Vimovo® with low-dose aspirin do not have increased gastric ulcers compared to those taking Vimovo® alone.⁷⁵

Another indicium of non-obviousness is the fact that AstraZeneca licensed the '907 and '285 patents from Pozen.⁷⁶ And, finally, another indicium of non-obviousness is copying of the Vimovo® product as evidenced by the ANDAs directed to a combination naproxen/esomeprazole formulation submitted to the United States Food and Drug Administration by Anchen, Lupin, Dr. Reddy's Laboratories, Mylan, and Watson.

⁷³ See EP 1411900, Grounds for the decision (Annex) – opposition at 12 (March 5, 2013).

⁷⁴ See AnchenPharma102175.

⁷⁵ Angiolillo, *et al.*, “Impact of concomitant low-dose aspirin on the safety and tolerability of naproxen and esomeprazole magnesium delayed-release tablets in patients requiring chronic nonsteroidal anti-inflammatory drug therapy: an analysis from 5 Phase III studies.” *J. Thromb Thrombolysis*. Dec. 2013.

⁷⁶ AstraZeneca/Pozen Collaboration and License Agreement (August 1, 2006) (AZV00312892-AZV00312996).

D. The Claims of the '285 Patent Would Not Have Been Obvious over WO '064 and WO '320 in Light of Daneshmend and Chandramouli

WO '064⁷⁷ and WO '320, optionally in view of Daneshmend and Chandramouli, do not render claims 1-4 obvious as DRL asserts. While there is no motivation or reason to combine the references as DRL suggests—the two primary references themselves teach away from doing so—even if combined, the references do not disclose compositions that provide for the coordinated release of the '285 Patent, *i.e.*, they do not disclose esomeprazole at least a portion of which is not enteric coated and is immediately released regardless of pH and naproxen that is enteric coated. Further, all of the references cited by DRL were before the United States Patent and Trademark Office (“USPTO”) during the examination of the '285 Patent,⁷⁸ and most of the references cited by DRL were either before the USPTO during the examination of the related '907 Patent or are cumulative of references that were before the USPTO during that examination.⁷⁹

WO '064, which was assessed by the USPTO during examination of the '285 Patent, is directed to dosage forms combining a PPI and an NSAID. However, DRL admits that WO '064 fails to disclose an acid inhibitor that is not surrounded by an enteric coating.⁸⁰ Indeed, WO '064 requires an enteric coating around the PPI.⁸¹ The enteric coating prevents the PPI from immediately releasing upon ingestion. Moreover, during prosecution of the '285 Patent and the related '907 Patent, applicants specifically distinguished the claims of the '285 Patent and the

⁷⁷ The USPTO reviewed the disclosure of WO '064 during prosecution, because U.S. Pat. Nos. 6,365,184 and 6,613,354 were considered during prosecution. Both are continuations of the PCT application published as WO '064, PCT/SE96/01735.

⁷⁸ The '285 patent file history.

⁷⁹ The '907 patent file history (AZV001359954-55).

⁸⁰ See DRL Invalidity Contentions at 14.

⁸¹ *See, e.g.*, WO '064, p. 4, lines 15-17.

related '907 Patent over the disclosure of WO '064 by relying on the immediate-release characteristics of at least a portion of the PPI regardless of pH. Applicants explained that because the compositions in WO '064 were enteric coated, the “release of acid inhibitor in Depui’s compositions would be delayed whereas acid inhibitor release from Applicant’s compositions is immediate.”⁸² Therefore, DRL’s burden to prove otherwise is particularly difficult.⁸³ WO '064 also fails to disclose the coordinated release of the two active ingredients required in the claims of the '285 Patent.

WO '320, which was before the USPTO during examination of the '285 Patent and was not considered as relevant by the USPTO, is the reference DRL seeks to combine with WO '064. WO '320 does not cure these deficiencies. WO '320 is directed to coated particles of acid labile active compounds, such as PPIs. Instead of protecting the acid-labile compounds with a typical enteric coating of pH dependent polymers, WO '320 uses another form of enteric coating comprising “a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.”⁸⁴ The protective coating allows the PPIs to pass safely through the stomach and prevents release of PPIs until its surrounding pH is sufficiently high, e.g., at the intestine level. WO '320 fails to disclose naproxen surrounded by an enteric coating, the immediate release of at least a portion of esomeprazole regardless of pH and/or the coordinated release of esomeprazole with another active ingredient. Thus, even in combination, WO '320 and WO '064 fail to disclose esomeprazole at least a portion of which is immediately released regardless of pH or the claimed

⁸² The '907 patent file history (AZV001359954-55) 11/19/2004 Response.

⁸³ *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447 (Fed. Cir. 1986).

⁸⁴ WO '320, p. 3, last paragraph.

coordinated release of the '285 Patent, *i.e.*, esomeprazole at least a portion of which is not enteric coated and is immediately released regardless of pH and naproxen that is enteric coated.

DRL also incorrectly suggests that one of skill in the art would be motivated to modify the enteric coated PPI in WO '064 with the sterol, polymer and fatty acid coated particles of acid-labile compounds of WO '320, to yield the claimed pharmaceutical composition, and that the motivation to do so can be found in either the disclosure of WO '320 itself or from the disclosure of Daneshmend and Chandramoli.

First, DRL's assertion ignores that WO '320 itself expressly teaches away from using an immediate-release PPI regardless of pH by explaining that it is "necessary . . . for oral preparations to protect the active compounds from the action of acids."⁸⁵ WO '064 similarly teaches away from using an immediate-release PPI regardless of pH, stating "it is obvious that the[sic] one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer."⁸⁶ In other words, both of the references that DRL seeks to combine expressly teach that PPIs should not be released into the stomach. That WO '320 and WO '064 teach away from the claimed invention is also consistent with the understanding of those of skill in the art at the time of invention. As discussed above, in Section I.C.2, and incorporated herein by reference, at the time of filing, the art specifically taught away from the use of a PPI that was not enteric coated and immediately released regardless of pH, because it was widely believed that PPIs must be enteric coated to survive the acidic environment of the stomach. Thus, one of ordinary skill in the art would have had no reasonable expectation of success in modifying the PPI of WO '064 such that at least a portion of the PPI would not be enteric coated and would be immediately released regardless of pH.

⁸⁵ WO '320 at 1 (emphasis added).

⁸⁶ WO '064, p. 3, lines 26-28 (emphasis added).

Neither of the two other references cited by DRL, Daneshmend and Chandramouli, teaches otherwise. Daneshmend and Chandramouli disclose the concomitant, separate administration of PPIs and NSAIDs to prevent NSAID-related gastric injury.^{87, 88} And both are cumulative to numerous other references that were before the USPTO during prosecution of the '285 Patent and were not considered as relevant by the USPTO, and that similarly disclose the concomitant, separate administration of acid inhibitors and NSAIDs.⁸⁹ Neither suggests that esomeprazole and naproxen should be administered in a single unit dosage form, much less one that provides for the coordinated release of the two active ingredients. And significantly, neither suggests that at least a portion of esomeprazole should be immediately released upon ingestion regardless of pH or otherwise contradicts the widespread belief in the art that PPIs should be enteric coated and not immediately released regardless of pH. For at least these reasons, neither Daneschmend nor Chandramouli would to motivate one of skill in the art to modify the enteric coated PPI in WO '064 with the sterol, polymer and fatty acid coated particles of acid-labile compounds of WO '320, to produce the claimed pharmaceutical composition, or give one of skill in the art any reasonable expectation of success in doing so.

Consequently, the asserted references fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the

⁸⁷ Daneshmend, p. 514, Abstract.

⁸⁸ Chandramouli, Title.

⁸⁹ See, e.g., Brown et al. "Prevention of Gastrointestinal Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs" *Pract. Drug Safety* 21:503-12 (1999); Hawkey, et al., "Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Anti-Inflammaotry Drugs" *N. Engl. J. Med.* 338:727-734 (1998).

coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

E. The Claims of the '285 Patent Would Not Have Been Obvious over WO '064 and WO '320 in Light of Daneshmend and Hawkey

WO '064 and WO '320, optionally in view of Daneshmend and Hawkey, do not render claims 1-4 obvious as DRL asserts. As discussed above, in Section I.D, and incorporated herein by reference, WO '064 and WO '320 do not render the asserted claims obvious. In this combination of references, however, DRL substitutes the disclosure of Hawkey for Chandramouli. Hawkey, which is like Daneshmend and Chandramouli and other references and was also before the USPTO and were not considered as relevant by the USPTO during prosecution of the '285 Patent, discloses the concomitant, separate administration of acid inhibitors and NSAIDs to prevent NSAID-related gastric injury.⁹⁰ But, as with those references, Hawkey fails to disclose or suggest that esomeprazole and naproxen should be administered in a single unit dosage form or one that provides for the coordinated release of esomeprazole and naproxen. Hawkey also fails to disclose or suggest that at least a portion of a PPI could be immediately released regardless of pH, and thus fails to controvert the widespread belief in the art—and the express disclosure of WO '064 and WO '320—that PPIs should not be immediately released regardless of pH. Therefore, even in view of Daneshmend and Hawkey, one of skill in the art would not modify the PPI of WO '064, as suggested by DRL, or have any reasonable expectation of success in doing so.

Consequently, the asserted references fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is immediately released regardless of pH, while naproxen is enteric coated and is

⁹⁰ Hawkey, p. 171.

released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

F. The Claims of the '285 Patent Would Not Have Been Obvious over WO '368 and WO '320 in Light of Daneshmend or Hawkey and Chandramouli

WO '368 and WO '320, optionally in view of Daneshmend or Hawkey and Chandramouli, do not render claims 1-4 obvious as DRL asserts. As discussed above, in Section I.B.3, and incorporated herein by reference, WO '368 does not disclose, among other things, a dosage form comprising a PPI, such as esomeprazole, in an amount effective to raise the gastric pH of a patient to at least 3.5. Rather, WO '368, which was before the USPTO and was not considered as relevant by the USPTO during prosecution of the '285 Patent, describes a dosage form having enteric coated NSAID pellets combined with misoprostol which is a prostaglandin.⁹¹ DRL incorrectly suggests that one of skill in the art would substitute the sterol, polymer and fatty acid coated particles of the PPI in WO '320 for the prostaglandin of WO '368.⁹² As explained above in Section I.C.2, and incorporated herein by reference, such a modification ignores that at the time of invention, the art, as well as the express disclosure of WO '320, specifically taught that PPIs should not be immediately released into the acid environment of the stomach. And, also as explained above in Sections I.D-E, none of Daneshmend, Hawkey or Chandramouli disclose or suggest that at least a portion of a PPI could be immediately released regardless of the pH. Therefore, one of ordinary skill in the art would have had no reasonable expectation of success in the use of an immediate-release of at least a portion of PPI regardless of pH.

⁹¹ WO '368, Abstract.

⁹² See DRL Invalidity Contentions, at 18.

Consequently, the asserted references, i.e., WO '368 and WO '320, optionally in combination with Daneshmend or Hawkey and Chandramouli, fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

G. The Claims of the '285 Patent Would Not Have Been Obvious over the '843 Patent in View of WO '064, Daneshmend, and Hawkey

The '843 Patent, in view of WO '064, Daneshmend and Hawkey, does not render claims 1-4 obvious as DRL asserts. As discussed above, in Section I.B.2, and incorporated herein by reference, the '843 Patent does not disclose, among other things, a dosage form comprising esomeprazole in an amount effective to raise the gastric pH of a patient to at least 3.5. Rather, the '843 patent, which was before the USPTO and was not considered as relevant by the USPTO during prosecution of the '285 Patent, describes a dosage form having an enteric coated NSAID core (diclofenac or piroxicam) surrounded by mantle coating comprising a prostaglandin, such as misoprostol.⁹³ The prostaglandins in the '843 patent are not esomeprazole nor are they PPIs. Consequently, the '843 patent does not disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH.

One of skill in the art would not have altered the dosage forms disclosed in the '843 Patent to include at least a portion of an immediate release PPI regardless of pH. As explained above in Section I.C.2, and incorporated herein by reference, such a modification ignores that at the time of invention, the art specifically taught that PPIs should not be immediately released

⁹³ The '843 Patent, Abstract.

into the acid environment of the stomach. And also as explained above in Sections I.D-E, none of WO '064, Daneshmend or Hawkey discloses or suggests that at least a portion of a PPI could be immediately released regardless of pH. Indeed, WO '064 expressly teaches away from using an immediate-release PPI regardless of pH by explaining that “it is obvious that the[*sic*] one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer.”⁹⁴ Therefore, one of ordinary skill in the art would have had no reasonable expectation of success in the use of an immediate-release of at least a portion of PPI regardless of pH.

Consequently, the asserted references fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

H. The Claims of the '285 Patent Would Not Have Been Obvious Over WO '064 in View of Hawkey, Daneshmend, Chandramouli, and Dent

WO '064, in view of Hawkey, Daneshmend, Chandramouli, and Dent, does not render the claims of the '285 Patent obvious, as DRL asserts. As discussed above, in Section I.D, and incorporated herein by reference, WO '064 does not disclose a PPI at least a portion of which is not enteric coated and is immediately released regardless of pH and also does not disclose the coordinated release of the two active ingredients as required in the claims of the '285 Patent. Indeed, WO '064 requires an enteric coating around the PPI, which prevents the PPI from

⁹⁴ WO '064, p. 3, lines 26-28 (emphasis added).

immediately releasing upon ingestion.⁹⁵ And, during prosecution of the '285 Patent and the related '907 Patent, the applicants distinguished the claims of the '285 Patent and the '907 Patent over the disclosure of WO '064.

Yet, DRL incorrectly asserts that one of skill in the art simply would have “understood” that the enteric coated PPI of WO '064 could be modified to provide for the coordinated release of the claims of the '285 Patent.⁹⁶ First, none of the secondary references cited by DRL, Hawkey, Daneshmend, Chandramouli or Dent,⁹⁷ which were all before the USPTO and were not considered as relevant by the USPTO during prosecution of the '285 Patent, discloses a PPI at least a portion of which is not enteric coated or is immediately released regardless of pH.⁹⁸ In addition, one of skill in the art would not have “understood” that the dosage forms of WO '064 could be modified to provide the coordinated release of the '285 Patent, because, as explained above in Section I.C.2, and incorporated herein by reference, at the time of invention, the art specifically taught that PPIs should be enteric coated and should not be immediately released into the acid environment of the stomach. Not only did the art teach away from the claimed invention, WO '064 itself expressly teaches away from using an immediate-release PPI regardless of pH that is not enteric coated by explaining that “it is obvious that the[sic] one of the active substances being a proton pump inhibitor must be protected from contact with acidic

⁹⁵ *Id.* at p. 4, lines 15-17.

⁹⁶ DRL Invalidity Contentions, at 18-20.

⁹⁷ Dent was considered by the USPTO during examination of the related '907 Patent. Dent, like the other secondary references DRL cites here (Hawkey, Daneshmend and Chandramouli) discloses the concomitant, separate administration of acid inhibitors and NSAIDs to prevent NSAID-related gastric injury. Indeed, Dent is a review article that discusses Daneshmend and similar references.

⁹⁸ The discussion of Hawkey, Daneshmend and Chandramouli in Section II.D-E is incorporated herein by reference.

gastric juice by an enteric coating layer.”⁹⁹ Therefore, one of ordinary skill in the art would not have been motivated to modify the dosage forms of WO '064 as asserted by DRL, nor would one of skill in the art have had any reasonable expectation of success in the use of a PPI at least a portion of which was not enteric coated and was immediately released regardless of pH to provide the coordinated release required in the '285 Patent. None of Daneshmend, Hawkey, Chandramouli, or Dent cure the deficiencies of WO '064, or controvert the understanding in the art, or the express disclosure of the WO '064 itself, that PPIs should be enteric coated and should not be immediately released regardless of pH. Those references do not disclose or suggest that at least a portion of a PPI need not be enteric coated or could be immediately released regardless of pH.

Consequently, WO '064, even in view of Hawkey, Daneshmend, Chandramouli, and Dent, fails to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is not enteric coated and is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents. Accordingly, the claims of the '285 Patent would not have been obvious at the time of the invention.

I. The Claims of the '285 Patent Would Not Have Been Obvious over the '843 Patent, WO '368, and/or EP '867 in Combination with Ramage, Wilson, Sangiah, the '118 Patent, the '354 Patent, Brown, Trondstad, Nefesoglu and/or the '974 Patent

The '843 Patent, WO '368 and/or EP '867, either alone or in combination with Ramage, Wilson, Sangiah, the '118 Patent, the '354 Patent, Brown, Trondstad, Nefesoglu and/or the '974 Patent, do not render claims 1-4 obvious, as DRL asserts. The references, alone or in

⁹⁹ WO '064, p. 3, lines 26-28 (emphasis added).

combination, fail to account for an immediate-release of at least a portion of esomeprazole regardless of pH and also fail to account for the coordinated release of esomeprazole and naproxen, *i.e.*, the immediate-release of at least a portion of esomeprazole regardless of pH and the pH-dependent release of naproxen.

As discussed above, in Sections I.B.2-4, and incorporated herein by reference, the '843 Patent, WO '368, and EP '867, which were all before the USPTO and were not considered as relevant by the USPTO during prosecution of the '285 Patent, fail to disclose esomeprazole at least a portion of which is not enteric coated and is immediately released regardless of pH and also fail to disclose the coordinated release of the two active ingredients as required in the claims of the '285 Patent. Rather, those references are directed to dosage forms comprising a prostaglandin.

None of Ramage, Wilson, Sangiah, the '118 Patent, the '354 Patent, Brown, Trondstad, Nefesoglu, or the '974 patent, which were all before the USPTO and were not considered as relevant by the USPTO during prosecution of the '285 Patent, cure the deficiencies of the '843 Patent, WO '368, and EP '867, because they also fail to describe esomeprazole at least a portion of which is not enteric coated and is immediately released regardless of pH. As with the '843 Patent, WO '368, and EP '867, Ramage, Wilson, and Sangiah are directed to the study of misoprostol, which is not a PPI let alone esomeprazole. Ramage investigates misoprostol's ability to inhibit food stimulated secretion.¹⁰⁰ Wilson looks at the effects of misoprostol on gastric acid and mucus secretion.¹⁰¹ Sangiah compares the effects of misoprostol with omeprazole on basal gastric pH in horses.¹⁰² Although Sangiah mentions omeprazole, it does not

¹⁰⁰ Ramage, p. 9, first column under the heading "Introduction."

¹⁰¹ Wilson, Title.

¹⁰² See, e.g., Sangiah, Title, Abstract.

suggest that at least a portion of omeprazole should be immediately released upon ingestion regardless of pH, nor does it suggest that omeprazole might be substituted for misoprostol in the dosage forms of the '843 Patent, WO '368, and EP '867. Further, Sangiah discloses the intravenous injection of omeprazole to horses and, as such, one of skill in the art would not combine it with the '843 Patent, WO '368, and EP '867, which are directed to oral pharmaceutical compositions for use in humans.

The majority of the remaining secondary references are related to PPIs. While these references, even in combination, also fail to disclose a PPI at least a portion of which is immediately released regardless of pH and the coordinated release of the active ingredients required in the claims of the '285 Patent, there also would have been no reason or motivation to combine the references to substitute the PPI of the secondary references for the prostaglandin of '843 Patent, WO '368, and EP '867.

The '118 Patent and the '354 Patent are directed to combining NSAIDs with PPIs in a single dosage form.^{103, 104} Both were considered by the USPTO during examination of the '285 Patent and were not considered as relevant by the USPTO. The '118 Patent does not describe the construction of the dosage form, nor does it suggest that at least a portion of PPIs should be immediately released upon ingestion regardless of pH. The USPTO also came to this same conclusion when it allowed the claims of the related '907 Patent over the '118 Patent.¹⁰⁵ Therefore, DRL's burden to overcome the presumption of validity is particularly difficult to meet.¹⁰⁶ Further, one of skill in the art would not combine the '118 patent with the '843 patent,

¹⁰³ The '118 patent, Abstract.

¹⁰⁴ The '354 patent, Abstract.

¹⁰⁵ The '907 patent file history (AZV00135970) 3/29/2005 Notice of Allowance.

¹⁰⁶ *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447 (Fed. Cir. 1986).

WO '368, and EP '867 as the '118 patent is directed to treating the symptoms of overindulgence while the '843 patent, WO '368, and EP '867 are directed to reducing the gastric damage associate with taking NSAIDs. The '354 Patent teaches away from using an immediate-release PPI form by indicating that an enteric coating must be used to protect the PPI from acidic gastric juice. The '354 Patent states that “it is obvious that the[sic] one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer.”¹⁰⁷ As with the '118 Patent, the USPTO expressly allowed the claims of the related '907 Patent over the '354 Patent.¹⁰⁸

Brown looks at using acid suppression as therapy in the prevention and treatment of the gastrointestinal adverse effects caused by NSAIDs.¹⁰⁹ Brown reports that PPIs can be effective in the prevention of the adverse gastrointestinal effects caused by NSAIDs,¹¹⁰ but does not describe or suggest using an immediate-release of at least a portion of PPI regardless of pH.

Trondstad is not concerned with PPIs. It compares the gastric mucosal damage caused by enteric coated naproxen with the gastric mucosal damage caused by non-enteric coated naproxen.¹¹¹

Nefesoglu investigates whether an increase in gastric pH due to omeprazole treatment alters the release rate of a drug from an enteric-coated formulation.¹¹² The omeprazole used in

¹⁰⁷ The '354 Patent, p. 3, lines 26-28.

¹⁰⁸ The '907 Patent file history (AZV00135970) 3/29/2005 Notice of Allowance.

¹⁰⁹ Brown, Abstract.

¹¹⁰ *Id.* at p. 510, second column, under the heading “Conclusions”.

¹¹¹ Trondstad, Abstract.

¹¹² Nefesoglu, Abstract.

Nefesoglu was enteric coated and therefore did not immediately release upon ingestion regardless of pH.¹¹³

The '974 Patent describes base addition salts of omeprazole.¹¹⁴ It does not describe or suggest that at least a portion of PPIs should be immediately released upon ingestion regardless of pH. Instead, it teaches away from using an immediate-release PPI regardless of pH. The '974 Patent explains that because PPIs are susceptible to acid degradation, they need to be protected from release in the stomach, preferably by an enteric coating.¹¹⁵

In addition to the express teaching away found in a number of the secondary references themselves, the art specifically taught away from use of an immediate-release PPI regardless of pH and toward other, more promising solutions. As explained above in Section I.C.2, and incorporated herein by reference, at the time of invention, the art specifically taught that PPIs should be enteric coated and should not be immediately released into the acid environment of the stomach. Thus, one of ordinary skill in the art would have had no reasonable expectation of success in proceeding as claimed.

Consequently, the asserted references, i.e., the '843 Patent, WO '368 and/or EP '867, either alone or in combination with Ramage, Wilson, Sangiah, the '118 Patent, the '354 Patent, Brown, Trondstad, Nefesoglu and/or the '974 Patent, fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is not enteric coated and is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or

¹¹³ *Id.* at second column, second paragraph.

¹¹⁴ The '974 Patent, Title, Abstract.

¹¹⁵ *Id.* at col. 4, lines 24-30.

higher, thereby providing for the coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

J. The Claims of the '285 Patent Would Not Have Been Obvious In View of the '118 Patent and/or the '354 Patent in view of the '843 Patent, WO '368, EP '867, Ramage, Wilson, Sangiah, Brown, Trondstad, Nefesoglu, Okabe, Konturek, Takeuchi, and/or the '974 Patent

The '118 Patent and/or the '354 Patent, in view of the '843 Patent, WO '368, EP '867, Ramage, Wilson, Sangiah, Brown, Trondstad, Nefesoglu, Okabe, Konturek, Takeuchi, and/or the '974 Patent do not render claims 1-4 obvious, as DRL asserts.

As discussed above, in Section I.I, and incorporated herein by reference, the '118 Patent and the '354 Patent, which were both before the USPTO during prosecution of the '285 Patent, are directed to dosage forms combining a PPI and an NSAID. These references, however, do not disclose compositions that provide for the coordinated release of the '285 Patent, *i.e.*, they do not disclose esomeprazole at least a portion of which is not enteric coated and is immediately released regardless of pH and naproxen that is enteric coated. Similarly, the USPTO expressly allowed the claims of the related '907 Patent over both the '118 Patent and the '354 Patent.¹¹⁶

The cited secondary references, the '843 Patent, WO '368, EP '867, Ramage, Wilson, Sangiah, Brown, Trondstad, Nefesoglu, and the '974 Patent, which were all before the USPTO during prosecution of the '285 Patent, fail to cure the deficiencies of the '843 Patent and WO '368 because they also do not describe esomeprazole at least a portion of which is not enteric coated or is immediately released regardless of pH. The '843 Patent, WO '368, and EP '867 describe dosage forms that combine an NSAID with misoprostol, which is not a PPI.^{117, 118, 119}

¹¹⁶ The '907 Patent file history (AZV00135970) 3/29/2005 Notice of Allowance.

¹¹⁷ The '843 Patent, Abstract.

¹¹⁸ WO '368, Abstract.

¹¹⁹ EP '867, p. 2, para. [0014].

Ramage, Wilson, and Sangiah are also directed to the study of misoprostol, which is not a PPI. Ramage investigates misoprostol's ability to inhibit food stimulated secretion.¹²⁰ Wilson looks at the effects of misoprostol on gastric acid and mucus secretion.¹²¹ Sangiah compares the effects of misoprostol with omeprazole on basal gastric pH in horses.¹²² Although Sangiah mentions omeprazole, it does not suggest that at least a portion of it should be immediately released upon ingestion regardless of pH. Further, Sangiah discloses the intravenous injection of omeprazole to horses and, as such, one of skill in the art would not combine it with the '843 patent, WO '368, and EP '867, which are directed to oral pharmaceutical compositions for use in humans.

Brown looks into the use of acid suppression as therapy in the prevention and treatment of the gastrointestinal adverse effects of NSAIDs but does not describe the use of immediate-release of at least a portion of PPIs regardless of pH.¹²³ Trondstad is not concerned with PPIs. It compares the gastric mucosal damage caused by enteric coated naproxen with the gastric mucosal damage caused by non-enteric coated naproxen.¹²⁴ Nefesoglu investigates whether an increase in gastric pH due to omeprazole treatment alters the release rate of a drug from an enteric-coated formulation.¹²⁵ The omeprazole used in Nefesoglu was enteric coated and therefore not capable of immediately releasing upon ingestion.¹²⁶ The '974 Patent describes base

¹²⁰ Ramage, p. 9, first column under the heading "Introduction."

¹²¹ Wilson, Title.

¹²² See, e.g., Sangiah, Title, Abstract.

¹²³ Brown, Abstract.

¹²⁴ Trondstad, Abstract.

¹²⁵ Nefesoglu, Abstract.

¹²⁶ *Id.* at p. 549, second column, second paragraph.

addition salts of omeprazole.¹²⁷ The '974 Patent teaches away from using an immediate-release PPI regardless of pH by explaining that PPIs are susceptible to acid degradation and need to be protected from release in the stomach, preferably by an enteric coating.¹²⁸

Konturek, which was before the USPTO during prosecution of the '285 Patent, reports the results of a very small study involving eight mongrel dogs that were given omeprazole intravenously or intraduodenally. This was not a clinical study but an experiment using an artificial, in vivo, environment. The authors state that the omeprazole stock solution was “diluted in 10 mM NaHCO₃ [sodium bicarbonate], because the drug is unstable at low pH...”¹²⁹ The authors speculate that “the effect of topical omeprazole may depend, at least in part, upon its absorption from the gastric lumen and accumulation in the mucosa without entering the circulation.”¹³⁰ The authors state, however, that “[b]ecause the drug is not stable at an acid pH, it is unlikely that its local action should be responsible for a very potent and prolonged suppression of gastric secretion observed after its oral administration.” A person having ordinary skill in the art, reading Konturek, would not have been motivated to formulate omeprazole with at least a portion of an immediate release coating because Konturek acknowledges that omeprazole is unstable at low pH and it is unlikely that a potent or prolonged suppression of gastric secretion will be obtained when administered locally. Konturek expressly formulated the omeprazole by diluting it in sodium bicarbonate, which is basic, in order to protect the omeprazole from acid degradation upon exposure to the stomach. This is completely different from formulating omeprazole with at least a portion of an immediate release coating. A person having ordinary

¹²⁷ The '974 patent, Title, Abstract.

¹²⁸ *Id.* at col. 4, lines 24-30.

¹²⁹ Konturek at pg. 72.

¹³⁰ Konturek at pg. 76.

skill in the art would not have been motivated to formulate omeprazole, or any other PPI, using at least a portion of an immediate release coating based on Konturek's aqueous formulation of omeprazole diluted in 10 mM NaHCO₃ because the two formulations are completely different. Furthermore, Konturek's results could not be confirmed in a study conducted eleven years later, as discussed below.

Okabe, which was before the USPTO during prosecution of the '285 Patent, reports the results of a study involving fourteen beagles, which was not a clinical study but an experiment using an artificial, in vivo, environment. Importantly, Okabe states that they "could not confirm [Konturek's] results despite applying a much higher dose [of omeprazole]..."¹³¹ In other words, locally applied omeprazole in the Okabe study did not inhibit gastric acid secretion even though it was applied at a much higher dose than that used in the Konturek study.¹³² Okabe notes that their formulations were administered together with 1% NaHCO₃ (pH 8.3) (sodium bicarbonate) in the case of local application.¹³³ In spite of this, they noted that the color of the omeprazole solution changed to brown after a 5 minute application suggesting extensive degradation of the drug.¹³⁴ The authors speculate as to the reason why they could not confirm the results obtained by Konturek and state that a possible reason might be due to the different methods of administration or different vehicles used in the formulations. Konturek continuously perfused the lumen with omeprazole suspended in polyethylene glycol, while Okabe applied it only once for 30 minutes after suspending it in 0.5% carboxymethylcellulose. A person having ordinary skill in the art, reading Okabe, would not have been motivated to formulate omeprazole with an

¹³¹ Okabe at pg. 98.

¹³² *Id.*

¹³³ Okabe at pg. 92.

¹³⁴ Okabe at pg. 99.

immediate release coating for at least a portion thereof because locally applied omeprazole in the Okabe study did not inhibit gastric acid secretion. In fact quite to the contrary, Okabe acknowledges that omeprazole is unstable at low pH and Okabe's results were thus contrary to those Konturek reported 10 years earlier. Similarly, the results obtained using leminoprazole, which was administered together with 1% NaHCO₃ (pH 8.3) in the case of local application, would not have motivated a person having ordinary skill in the art to formulate at least a portion of a PPI with an immediate release coating because an immediate release coating is completely different from administering a PPI with an aqueous solution of 1% NaHCO₃ (pH 8.3). Further, results by Okabe and Konturek demonstrated to one skilled in the art that the so-called "local effects" were highly unpredictable and irreproducible depending on many unknown factors such as methods of administration and compositions of the formulation, etc. Therefore, one skilled in the art would have considered the so called "local effects" not proven, controversial, and highly speculative at most. Such uncertain finding would not have motivated one skilled in the art at the time of the invention to forego a tried and true approach of using enteric coated PPIs and instead chasing some effects that may or may not exist. In addition, even assuming such local effects exist they would have been considered by one skilled in the art as mostly relevant only with respect to fast onset or short term effect. He or she would not have considered the so called "local effects" relevant in terms of treating long term side effects of NSAID. Given the fact that the so called "local effect" was not reproducible and highly depended on factors not fully understood at the time, one skilled in the art would have also been concerned whether any deviation from the tested setting reported by Konturek or others would have caused the "disappearance" of the local effect as demonstrated by Okabe. Therefore, even if there was sufficient motivation one skilled in the art would not have had a reasonable expectation of

obtaining the so called “local effect” by formulating at least a portion of a PPI as a solid immediate release coating since a solid immediate release formulation is drastically different from the method of administration and compositions of formulation used by Konturek.

Takeuchi, which was before the USPTO during prosecution of the '285 Patent, describes studies involving topically applied omeprazole to anesthetized rats. The purpose of the study was to identify criteria to be used for screening potential H⁺/K⁺ ATPase inhibitors under in vivo conditions, which is completely different from identifying the effects of PPIs under clinical conditions.¹³⁵ The Takeuchi study was not a clinical study but an experiment using an artificial, in vivo, environment. Anesthetized rat stomachs were exposed for 10 minutes to 1 mL solutions of omeprazole either suspended in 1% carboxymethylcellulose adjusted to pH 9.0 with the addition of NaHCO₃ (sodium bicarbonate) or dissolved in 0.1 N HCl (pH 1.0).¹³⁶ Takeuchi purports to interpret its results as evidence for a local effect upon administration of omeprazole. As stated above, however, all of the studies reported by Takeuchi were conducted under nonclinical conditions. Moreover, Takeuchi teaches that the effects of acidified omeprazole disappeared when applied at more than 30 minutes after dissolution and further suggests that the observed transient inhibition of acid secretion by acidified omeprazole may be partly due to the action afforded by the degradation products of omeprazole. That is, Takeuchi confirms the acid-labile nature of omeprazole. Nothing in Takeuchi would have motivated a person having ordinary skill in the art to formulate at least a portion of a PPI with an immediate release coating because an immediate release coating not only would subject a PPI to the acidic gastric juice, but also is completely different from administering a PPI in an aqueous solution of NaHCO₃ (sodium bicarbonate) or dissolved in 0.1 N HCl (pH 1.0). Takeuchi even discounts the applicability or

¹³⁵ Takeuchi at pg. 407.

¹³⁶ Takeuchi at pg. 398.

relevance of any perceived “local effect” stating that “omeprazole is given as an enteric coated capsule in humans, and thus the compound is released in the intestine, its local effect can be ignored under clinical conditions.”¹³⁷ At the time of the invention, one skilled in the art would have also considered the results disclosed by Takeuchi in the context of conflicting results reported by Okabe and Konturek. Therefore, one skilled in the art would have still considered these results controversial and speculative at most.

Furthermore, it is important to note that Konturek, Okabe, and Takeuchi, alone or in combination, only describe liquid PPI formulations (either in NaHCO₃ or HCl) for topical administration. Inasmuch as DRL contends the rapid onset of acid inhibitory through local effect of the immediate release PPI formulation, one skilled in the art would not be motivated to attempt to modify the liquid formulations of Konturek, Okabe, and Takeuchi to a coating as claimed in the '285 patent because one of skill in the art would have known that the liquid formulation bypasses the necessary dissolution step prior to absorption and thereby can be absorbed much faster than the solid dosage form. To the extent one of ordinary skill in the art would have used a PPI and a bicarbonate salt, one would have formulated them in a liquid dosage form that is incompatible and cannot be combined with an enteric coated NSAID.¹³⁸ For example, sodium bicarbonate in solution would erode the enteric coating surrounding the NSAID. Even if, for the sake of argument, the sodium bicarbonate is used as a solid, which contradicts the teachings of the cited references and DRL's contentions of rapid onset PPI, it is

¹³⁷ Takeuchi at pg. 407.

¹³⁸ See, e.g., Pashankar *et al.*, Omeprazole Maintenance Therapy for Gastroesophageal Reflux Disease After Failure of Fundoplication, J. PEDIATRIC GASTROENTEROLOGY AND NUTRITION 32: 145-149 (Feb. 2001); Sharma *et al.*, Oral Pharmacokinetics of Omeprazole and Lansoprazole After Single and Repeated Doses as Intact Capsules or as Suspensions in Sodium Bicarbonate, AILMENT. PHARMACOL. THER. 14: 887-892 (2000); Sharma *et al.*, The Effects on Intragastric Acidity of Per-Gastrostomy Administration of an Alkaline Suspension of Omeprazole, AILMENT. PHARMACOL. THER. 13:1091-1095 (1999).

not feasible to combine such a solid formulation with an enteric coated NSAID to construct a single dosage form due to the incompatibilities of ingredients, difficulties in manufacture, restrictions to the size, shape, and/or other physical attributes of the dosage form, and other reasons.¹³⁹

In addition to the express teaching away found in a number of the secondary references themselves, the state of the art at the time of the invention specifically and universally taught away from use of an immediate-release PPI regardless of pH and toward other, more promising solutions. As explained above in Section I.C.2, and incorporated herein by reference, at the time of invention, the art universally teaches that PPIs must be enteric coated and should not be immediately released into the acid environment of the stomach. *See id.* Thus, one of ordinary skill in the art would have had no reasonable expectation of success in proceeding as claimed. DRL has not produced a single reference that teaches otherwise.

Consequently, the asserted references fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is not enteric coated and is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

¹³⁹ *See, e.g.*, U.S. Patent No. 4,786,505; U.S. Patent Application Publication No. 2003/0039691; Remington: The Science and Practice of Pharmacy, Edition 20 (2000), Chapters 45 and 46; and FDA Guidance for Size, Shape, and Other Physical Attributes of Tablets and Capsules (2013).

K. The Claims of the '285 Patent Would Not Have Been Obvious over the '843 Patent, WO '368 and/or EP '867 in View of Sangiah, Hawkey III, Nefesoglu, Wolfe, Brown and/or the '974 Patent

The '843 Patent, WO '368 and/or EP '867 in view of Sangiah, Hawkey III, Nefesoglu, Wolfe, Brown and/or the '974 Patent do not render claims 1-4 obvious, as DRL asserts. The references, even in combination, fail to disclose or render obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is not enteric coated and is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents..

As discussed above, in Sections I.B.2-4, and incorporated herein by reference, the '843 Patent, WO '368, and EP '867 do not disclose a dosage form comprising esomeprazole in an amount effective to raise the gastric pH of a patient to at least 3.5 and also do not disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH. Rather, those references are directed to dosage forms comprising a prostaglandin.

DRL's proposed combination of the '843 Patent, WO '368 and/or EP '867 with Sangiah Nefesoglu, Brown, and/or '974 Patent is repeated from a prior combination. The response to that combination, above in Section I.I, is incorporated herein by reference.

The two additional references, Hawkey III and Wolfe similarly fail to cure the deficiencies of the '843 Patent, WO '368 and/or EP '867. Hawkey III and Wolfe, like many of the other references cited by DRL and others that were before the USPTO during examination of the '285 Patent, investigate the use of acid suppression as therapy in the prevention and treatment

of the gastrointestinal adverse effects of NSAIDs.^{140, 141} These two references do not disclose or suggest the combination of esomeprazole and naproxen in a single unit dosage form. Nor do the references disclose esomeprazole wherein a portion is not enteric coated and is immediately released. Moreover, Wolfe actually teaches away from an immediate-release esomeprazole by emphasizing that PPIs require an enteric coating to prevent them from immediately releasing upon ingestion.¹⁴²

Like Wolfe, the art specifically taught away from use of an immediate-release PPI and toward other, more promising solutions. As explained above in Section I.C.2, and incorporated herein by reference, at the time of invention, the art specifically taught that PPIs such as esomeprazole should be enteric coated and should not be immediately released into the acid environment of the stomach. Thus, one of ordinary skill in the art would have had no reasonable expectation of success in proceeding as claimed. None of the secondary references cited by DRL teach otherwise.

Consequently, the asserted references fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is not enteric coated and is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

¹⁴⁰ Wolfe, Title, and S16.

¹⁴¹ Hawkey III, Abstract.

¹⁴² Wolfe, at p. S25.

L. The Claims of the '285 Patent Would Not Have Been Obvious over the '118 Patent and/or the '354 Patent in View of the '843 Patent, WO '368, EP '867, Trondstad, Hawkey III, Nefesoglu, Wolfe, Brown and the '974 Patent

The '118 Patent and/or the '354 Patent, in view of the '843 Patent, WO '368, EP '867, Brown, Trondstad, Nefesoglu and/or the '974 Patent do not render claims 1-4 obvious, as DRL asserts. DRL's proposed combination of the '118 Patent and/or the '354 Patent with the '843 Patent, WO '368, EP '867, Brown, Trondstad, Nefesoglu and/or the '974 Patent is repeated from a prior combination. The response to that combination, above in Section I.J, is incorporated herein by reference. Likewise, the two additional references, Hawkey III and Wolfe, were addressed above in Section I.K, which is incorporated herein by reference.

Consequently, the asserted references fail to disclose or make obvious a pharmaceutical composition that includes both esomeprazole and naproxen wherein at least a portion of esomeprazole is not enteric coated and is immediately released regardless of pH, while naproxen is enteric coated and is released when the pH of the surrounding medium is 3.5 or higher, thereby providing for the coordinated release of the two active agents. Accordingly, claims 1-4 would not have been obvious at the time of the invention.

M. The Claim Limitations of the '285 Patent Not Described by DRL's Asserted Prior Art (L. Pat. R. 3.4A(a))

As required by Local Patent Rule 3.4A(a), the following is a list of limitations of the asserted claims of the '285 patent that are not described within DRL's alleged prior art invalidating references:

1. "A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of: (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating;"
2. "(b) naproxen surrounded by 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;" *See, e.g., Claim 1.*

3. “wherein said unit dosage form provides for release of said esomeprazole such that 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.” *See, e.g.*, Claim 1.

N. The Claims of the ’285 Patent Are Fully Described and Enabled

The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a written description of the invention.” This requires that the specification “reasonably convey” that the applicant “invented” or “had possession” of the claimed subject matter when the application was filed.¹⁴³ Support need not be *in haec verba*,¹⁴⁴ or even express—it may be implicit¹⁴⁵ or inherent¹⁴⁶ in the disclosure. In addition, because a patent specification is written for a person of skill in the art, it is unnecessary to include information that is already known and available to persons of ordinary skill.¹⁴⁷ Thus, even if an aspect of the invention is absent from the specification, the specification may be sufficient if one of ordinary skill could “extrapolate” the missing aspect from the specification based on his or her knowledge of the art.¹⁴⁸

To support a claim to a genus, it may be “manifestly impracticable . . . to give an example of every species falling within it, or even to name every such species.”¹⁴⁹ Thus, sufficient

¹⁴³ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

¹⁴⁴ *Ariad*, 598 F.3d at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d 422, 242–25 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

¹⁴⁵ *All Dental Prodx, LLC v. Adv. Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *Wright*, 866 F.2d at 242–25.

¹⁴⁶ *Kennecott Corp. v. Kyocera Intern., Inc.*, 835 F.2d 1419, 1423 (Fed. Cir. 1987); *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

¹⁴⁷ *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Esshar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005); *Gay*, 309 F.2d at 774.

¹⁴⁸ *Waddington N. Am., Inc. v. Sabert Corp.*, 2011 WL 1098996, at *5 (D.N.J. Mar. 22, 2011); *accord Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1566–68 (Fed. Cir. 1991); *In re Eickmeyer*, 602 F.2d 974, 981 (C.C.P.A. 1981); *In re Smythe*, 480 F.2d 1376, 1384 (C.C.P.A. 1973); *Single Chip Sys. Corp. v. Intermec IP Corp.*, 2006 WL 4660129, *22 (S.D.Cal. Nov. 6, 2006).

¹⁴⁹ *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988); *Gay*, 309 F.2d at 774.

description requires only “the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members.”¹⁵⁰

With respect to enablement, a claim is not enabled if it would take undue experimentation for a person of ordinary skill to make or use the invention. Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. Enablement is an objective determination and evidence of enablement dated after the priority date is relevant to the analysis.¹⁵¹

Claims of the '285 Patent are described and enabled for a pharmaceutical composition in unit dosage form comprising therapeutically effective amount of esomeprazole and naproxen, wherein, among other things, naproxen is surrounded by 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.

The '285 Patent describes the preparation of a unit dosage form comprising therapeutically effective amount of esomeprazole and naproxen, wherein, among other things, naproxen is surrounded by a coating that inhibits its release unless the surrounding medium is at

¹⁵⁰ *Ariad*, 598 F.3d at 1351–52; *Hynix Semiconductor Inc., v. Rambus Inc.*, 2011 WL 1815978, *13 (Fed. Cir. May 13, 2011) (“[T]here is no categorical rule that a species cannot suffice to claim the genus. . . . [S]o long as disclosure of the species is sufficient to convey to one skilled in the art that the inventor possessed the subject matter of the genus, the genus will be supported by an adequate written description. Whether the genus is supported *vel non* depends upon the state of the art and the nature and breadth of the genus.”); *In re Johnson*, 558 F.2d 1008, 1018 (C.C.P.A. 1977).

¹⁵¹ *In re Armbruster*, 512 F.2d 676, 677–78 (C.C.P.A. 1975) (“The first paragraph of § 112 requires nothing more than objective enablement. . . . Assuming that sufficient reason for . . . doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . . Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct.”)(citation omitted); *In re Stephens*, 529 F.2d 1343, 1346 (C.C.P.A. 1976); *Amgen*, 314 F.3d at 1336; *Gould*, 822 F.2d at 1078.

least 3.5. For instance, the specification of the '285 Patent provides Examples 6, 7, and 8, which describe tablet or capsules containing enteric-coated naproxen or its sodium salt and immediate-release omeprazole.¹⁵² The specification also describes exemplary pharmaceutical preparations.¹⁵³ For instance, the specification explains that “[i]n a bilayer [tablet] configuration, one portion of the tablet contains the acid inhibitor in the required dose along with appropriate excipients, . . . The second portion of the tablet will contain the NSAID, preferably naproxen, in the required dose along with other excipients, . . . In the most preferred embodiment, the NSAID layer is surrounded by a polymeric coating which does not dissolve at a pH of less than 4.” It further states that “[t]he combination of an acid inhibitor and an NSAID will be in the form of a bi- or multi-layer tablet.” The specification of the '285 Patent also explains, “[d]rugs and drug combinations will typically be prepared in admixture with conventional excipients. Suitable carriers include, but are not limited to . . . hydroxymethylcellulose; polyvinyl pyrrolidone; etc.” Thus, one of ordinary skill in the art would understand that, in addition to naproxen surrounded by a coating that inhibits its release unless the surrounding medium of the unit dosage form is at least 3.5, the disclosed dosage forms may include additional naproxen outside the coating.

In agreement, the U.S. Patent & Trademark Office, whose Examiners are presumed to be one of skill in the art (*In re Sang Su Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002) (the patent examiner is presumed to act from the viewpoint of a “person having ordinary skill in the art”)), understands the specification of the '285 patent as disclosing compositions that include NSAIDs such as naproxen outside a coating that inhibits the release unless the surrounding medium of the unit dosage form is at least 3.5, as evidenced by its rejection of DRL’s design around patent application as anticipated by the '907 patent, which shares the same specification as the '285

¹⁵² The '285 patent, col. 16-20.

¹⁵³ The '285 patent, col. 8, lines 16-24.

patent. On May 19, 2010, DRL filed U.S. Patent Application No. 12/782,964, which appears to be directed to formulations encompassing the DRL II formulation. *See* Patent Application 12/782,964, Examples 1-3 and 18 (illustrating dosage forms that include Enteric coating (Part II)). Claim 1 of the application reads:

A pharmaceutical fixed unit dosage formulation for oral administration comprising a proton pump inhibitor and a nonsteroidal anti-inflammatory drug, wherein at least a portion of non-steroidal anti-inflammatory drug is released when the formulations are immersed into aqueous fluids having pH values below about 3.5.

Id. at claim 1. This claim contemplates the release of “at least a portion of” NSAID at pH levels below 3.5. *Id.* As a result, the claim would incorporate dosage forms with at least a portion of NSAID outside a coating that inhibits release unless the surrounding medium of the unit dosage form is at least 3.5. All pending claims were rejected as anticipated by the ’907 patent on July 30, 2012. The Examiner noted “[r]elease of [a] portion of non-steriodial anti-infammatory drug when the formulations are immersed into aqueous fluids having pH values below about 3.5 is [an] inherent property of the formulation” of the ’907 patent, citing the abstract, columns 3 and 4 of the specification, examples in the specification, and claim 1. Thus, Examiner, a presumptive person of ordinary skill in the art, reads the specification of the ’907 patent, which is like that of the ’285 patent, as fully disclosing compositions that include NSAID outside of an enteric coating.

Moreover, the transitional term “comprising” in a claim, which is synonymous with “including,” or “containing,” is inclusive or open-ended and does not exclude additional or unrecited elements. *See, e.g., Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) (“Comprising” is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct

within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) (“comprising” leaves “the claim open for the inclusion of unspecified ingredients even in major amounts”). Thus, the transitional term “comprising” does *not* exclude the presence of naproxen in the dosage form in addition to the naproxen that is “surrounded by a coating that inhibits its release from said unit dosage form unless said unit dosage form is in a medium with a pH of 3.5 or higher.” In addition, the claims of the ’285 Patent are not anticipated or rendered obvious by U.S. Patent Nos. 5,204,118, 5,417,980, 5,466,436, 6,365,184, and/or U.S. 5,037,815 as argued by DRL. All of these references were before the USPTO during examination of the ’285 Patent. Moreover, these references, alone or in combination, not only fail to disclose or suggest each and every element as set forth in the claims, but also do not provide the motivation to one of ordinary skill in the art to modify or combine the reference compositions in such a way to arrive at the claimed pharmaceutical composition in unit dosage form.

As to the word “inhibit”, DRL admits that it does not have exactly the same scope as “prevent.”¹⁵⁴ See also, <http://www.merriam-webster.com/dictionary/inhibit>. The specification of the ’285 Patent uses the words “inhibit” or “inhibition” many times, and those words are used in a manner consistent with the plain and ordinary meaning.¹⁵⁵ For instance, the specification explains “the value of combining acid inhibition with enteric coating of NSAID to minimize the gastrointestinal damage.”¹⁵⁶ Thus, one of ordinary skill in the art would understand the term “inhibit” as used in the claims to have its ordinary meaning.

¹⁵⁴ See DRL Invalidity Contentions at 41.

¹⁵⁵ The ’285 patent, col. 1, lines 44, 59, and 64; col. 3, line 35; and col. 21, line 29.

¹⁵⁶ The ’285 patent, col. 21, line 29.

The language set forth in the specification, in addition to knowledge available to a person of ordinary skill in the art, “reasonably conveys” that the applicant “invented” or “had possession” of the claimed subject matter when the application was filed, including when the provisional application was filed. Thus, the claims are fully described for a unit dosage form comprising therapeutically effective amount of esomeprazole and naproxen, wherein, among other things, naproxen is surrounded by 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, including naproxen that is *not* surrounded by the coating.

Furthermore, one of ordinary skill in the art would be able to make and use of the claimed pharmaceutical composition in unit dosage form without undue experimentation, especially in view of the nature of the invention, the guidance in the specification, and the knowledge available to one of ordinary skill in the art. Thus, the claims are fully enabled for a unit dosage form comprising therapeutically effective amount of esomeprazole and naproxen, wherein, among other things, naproxen is surrounded by 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, including naproxen that is *not* surrounded by the coating.

Moreover, as the claims of the '285 Patent are described and enabled under 35 U.S.C. § 112, the claims are commensurate in scope with the supporting disclosures.

Plaintiffs reserve the right to amend these contentions if the relevant claim terms are construed by the Court.

Dated: April 4, 2014

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true copy of the foregoing HORIZON PHARMA, INC.'S AND POZEN INC.'S PRELIMINARY RESPONSES TO DR. REDDY'S LABORATORIES, INC. AND DR. REDDY'S LABORATORIES, LTD.'S INVALIDITY CONTENTIONS PURSUANT TO L. PAT. R. 3.6(i) was caused to be served on April 4, 2014 by electronic mail upon:

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EXHIBIT A
PLAINTIFFS' RESPONSIVE CONTENTIONS PURSUANT TO L. PAT. R. 3.4A(c) and 3.6(i)
Horizon Pharma, Inc. v. Dr Reddy's Labs., Inc., Civ. A. No. 13-cv-00091-JAP-DEA

Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
1. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:	<p>WO '064 at Abstract, pages 1, lines 8-9; 3, lines 16-22; 4, lines 11-17; Figs. 1-6; 6, lines 4-6.</p> <p>WO '320 at pages 3; 7-8.</p> <p>WO '368 at Abstract, pages 1-6 and 7 (claims 1-5).</p> <p>'843 patent at Abstract; 1:10-17; 1:65-2:60; 3:15-54; 4:8-6:65; 7:20-12:63; 1:65-2:4; 2:40-52; 2:60-64; 3:59-4:19; 6:45-7:14, 7:20 to 12:63, Figs. 1-3.</p>	<p><u>Plaintiffs Dispute DRL's Contention</u></p> <p>WO '064 relates to compositions comprising an acid inhibitor and an NSAID and does not disclose the required coordinated release of esomeprazole and naproxen. WO '064 fails to account for an immediate-release of at least a portion of esomeprazole regardless of pH and also fail to account for the coordinated release of esomeprazole and naproxen.</p> <p>WO '320 is directed to coated particles of acid labile active compounds, such as PPIs. WO '320 uses a protective coating that is described as another form of enteric coating, which prevents immediate-release of the PPI upon ingestion until the PPI passes safely through the stomach and its surrounding pH is at the intestine level. WO '320 fails to disclose naproxen surrounded by an enteric coating, the immediate release of at least a portion of esomeprazole regardless of pH, and the coordinated release of these active ingredients.</p> <p>The '843 Patent and WO '368 are directed to</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
		<p>dosage forms comprising prostaglandins which are not esomeprazole, nor are they PPIs. The '843 Patent and WO '368 fail to disclose compositions in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH, and also fail to disclose the coordinated release of the two active ingredients as required by the claim.</p> <p>The particular combinations of references identified in DRL's Invalidity Contentions would not have rendered the claims obvious for the reasons discussed in the accompanying Response to DRL's Invalidity Contentions.</p>
(a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and	<p>WO '064 at Abstract, pages 7-12; 13 lines 16-17; 24-51 (Examples 1-17).</p> <p>WO '320 at pages 3; 7-8.</p> <p>WO '368 at Abstract, pages 1-6.</p> <p>Daneshmend at pages 514-517, TABLE.</p> <p>Chandramouli at Abstract, pages 28-40.</p>	<p><u>Plaintiffs Dispute DRL's Contention</u></p> <p>WO '064 relates to compositions comprising an acid inhibitor and an NSAID and does not disclose the required coordinated release of esomeprazole and naproxen. WO '064 fails to account for an immediate-release of at least a portion of esomeprazole regardless of pH and also fail to account for the coordinated release of esomeprazole and naproxen.</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
	<p>Hawkey at Abstract, pages 170-173.</p> <p>Sangiah at pages 351-353.</p> <p>'843 patent at Abstract; 1:10-17; 1:65-2:60; 3:15-54; 4:8-6:65; 7:20-12:63; 1:65-2:4; 2:40-52; 2:60-64; 3:59-4:19; 6:45-7:14, 7:20 to 12:63, Figs. 1-3.</p> <p>EP '867, Abstract, ¶¶ 1, 4-6, 12-14, 16-18, 19-21, 27, 29, and claims 1-2.</p> <p>'118 patent, Abstract, col. 1:lines 10-16; 1:19-27; 2:61-64; 3:9-58; 5:9-44; 6:35 to 7:56, claims 1 and 8.</p> <p>Ramage, pages 10-11.</p> <p>Wilson, pages 127S-129S.</p> <p>'354 patent, Abstract, col. 1: lines 14-25, 3:18-27, 4:29-42, 4:59-65, 8:12-27, 11:46-67, 12:28-29, 15:47-60, 16:1-29:61.</p> <p>Brown, pages 504-509, Fig. 1, Tables I-II, Fig. 2.</p> <p>Nefesoglu, Abstract, pp. 552-553.</p>	<p>WO '320 is directed to coated particles of acid labile active compounds, such as PPIs. WO '320 uses a protective coating that is described as another form of enteric coating, which prevents immediate-release of the PPI upon ingestion until the PPI passes safely through the stomach and its surrounding pH is at the intestine level. WO '320 fails to disclose naproxen surrounded by an enteric coating, the immediate release of at least a portion of esomeprazole regardless of pH, and the coordinated release of these active ingredients.</p> <p>The '843 Patent, WO '368, and EP '867 are directed to dosage forms comprising prostaglandins which are not esomeprazole, nor are they PPIs. The '843 Patent, WO '368, and EP '867 fail to disclose compositions in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH, and also fail to disclose the coordinated release of the two active ingredients as required by the claim.</p> <p>Hawkey and Daneshmend disclose concomitant, separate administration of acid inhibitors and NSAIDs. These references fail</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
	'974 patent, col. 4, lines 54-59.	<p>to disclose or suggest that esomeprazole and naproxen should be administered in a single unit dosage form, or one that provides for the coordinated release of esomeprazole and naproxen.</p> <p>Chandramouli discloses the concomitant, separate administration of acid inhibitors and NSAIDs to prevent NSAID-related gastric injury. Chandramouli does not suggest that esomeprazole and naproxen should be administered in a single unit dosage form, much less one that provides for the coordinated release of the two active ingredients. Chandramouli does not suggest that at least a portion of esomeprazole should not be enterically coated and should be immediately released upon ingestion regardless of pH.</p> <p>Sangiah fails to describe a PPI at least a portion of which is not enteric coated and is immediately released regardless of pH, and also fails to disclose the coordinate release of the two active ingredients. Sangiah relates to acid inhibitor compositions and their administration and does not disclose the combination of esomeprazole with napraxen as required in the claimed unit dosage form.</p>

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		<p>While Sangiah mentions omeprazole, it does not suggest that omeprazole should be combined with naproxen, immediately released at least a portion thereof upon ingestion regardless of pH, or that omeprazole might be substituted for misoprostol in the dosage forms of the '843 Patent, WO '368, or EP '867.</p> <p>EP '867 does not disclose the use of naproxen or esomeprazole. EP '867 does not disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH. Nor does EP '867 disclose a pharmaceutical composition with the coordinated release of esomeprazole and naproxen as claimed in the '285 patent.</p> <p>The '118 Patent does not describe the construction of the dosage form claimed, nor does it suggest that at least a portion of esomeprazole should be immediately released upon ingestion regardless of pH. The '118 Patent does not describe an immediate-release esomeprazole.</p> <p>Ramage, Wilson, and Brown fail to describe esomeprazole at least a portion of which is</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
		<p>not enteric coated and is immediately released regardless of pH, and they also fail to disclose the coordinated release of esomeprazole and naproxen.</p> <p>The '354 Patent teaches away from using an immediate-release PPI form by indicating that an enteric coating must be used to protect the PPI from acidic gastric juice.</p> <p>Nefesoglu investigates whether an increase in gastric pH due to omeprazole treatment alters the release rate of a drug from an enteric-coated formulation. The omeprazole used in Nefesoglu was enteric coated and therefore did not immediately release upon ingestion regardless of pH.</p> <p>WO '064, WO '320, and the '974 Patent teach that PPIs should not be immediately released into the stomach regardless of pH, and therefore teaches away from combining esomeprazole at least a portion of which is immediately released regardless of with delayed release naproxen.</p> <p>The particular combinations of references identified in DRL's Invalidity Contentions would not have rendered the claims obvious</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
		for the reasons discussed in the accompanying Response to DRL's Invalidity Contentions.
(b) naproxen surrounded by 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>WO '064 at Abstract, pages 12-13; 16-19; 23; 24-51; 18 line 28; 23; 24-51 (Examples 1-17); Figs. 4-6; pages 58-59, 4-5 (legend).</p> <p>WO '368 at Abstract, pages 1-6 and 7 (claims 1-5) Abstract, page 1, lines 13-28; pages 2, 4, 5-6, 9-13.</p> <p>'843 patent at Abstract; 1:10-17; 1:65-2:60; 3:15-54; 4:8-6:65; 7:20-12:63; 1:65-2:4; 2:40-52; 2:60-64; 3:59-4:19; 6:45-7:14, 7:20 to 12:14, Figs. 1-3.</p> <p>EP '867, ¶¶ 13, 19-20, 22, 25-30.</p> <p>'354 patent, col. 4: lines 29-42, 4:59-65, 11:46-67, 12:28-29.</p> <p>Tronstad, Abstract, pp. 240-242.</p> <p>WO '064 at Abstract, pages 12-13; 16-19; 18 line 28; 23; 24-51 (Examples 1-17).</p> <p>WO '368 at Abstract, pages 1-6 and 7 (claims 1-5).</p>	<p><u>Plaintiffs Dispute DRL's Contention</u></p> <p>WO '064 relates to compositions comprising an acid inhibitor and an NSAID and does not disclose the required coordinated release of esomeprazole and naproxen. WO '064 fails to account for an immediate-release of at least a portion of esomeprazole regardless of pH and also fail to account for the coordinated release of esomeprazole and naproxen.</p> <p>The '843 Patent, WO '368, and EP '867 are directed to dosage forms comprising prostaglandins which are not esomeprazole, nor are they PPIs. The '843 Patent, WO '368, and EP '867 fail to disclose compositions in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH, and also fail to disclose the coordinated release of the two active ingredients as required by the claim.</p> <p>The '354 Patent teaches away from using an</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
	<p>Daneshmend at pages 514-517, TABLE.</p> <p>Chandramouli at Abstract, pages 28-40.</p> <p>Hawkey at Abstract, pages 170-173.</p> <p>Sangiah at pages 351-353.</p> <p>'843 patent at Abstract; col. 1: lines 10-17; 1:65-2:60; 3:15-54; 4:8-6:65; 7:20-12:63; 1:65-2:4; 2:40-52; 2:60-64; 3:59-4:19; 6:45-7:14, 7:20 to 12:14, Figs. 1-3.</p> <p>EP '867, ¶¶ 13, 19-20, 22, 25-30.</p> <p>'354 patent, col. 4: lines 29-42, 4:59-65, 11:46-67, 12:28-29.</p> <p>Tronstad, Abstract, pp. 240-242.</p> <p>WO '064 at Abstract, pages 12-13; 23; 24-51 (Examples 1-17).</p> <p>WO '368 at Abstract, pages 2; 9 (claims 17 and 18).</p> <p>'843 patent Abstract; Fig. 2; col. 6.</p>	<p>immediate-release PPI form by indicating that an enteric coating must be used to protect the PPI from acidic gastric juice.</p> <p>Tronstad suggests that the local side effect of naproxen may be prevented by enteric coating, but does not disclose or suggest that esomeprazole and naproxen should be administered in a single unit dosage form, or one that provides for the coordinated release of esomeprazole and naproxen.</p> <p>Hawkey and Daneshmend disclose concomitant, separate administration of acid inhibitors and NSAIDs. These references fail to disclose or suggest that esomeprazole and naproxen should be administered in a single unit dosage form, or one that provides for the coordinated release of esomeprazole and naproxen.</p> <p>Chandramouli discloses the concomitant, separate administration of acid inhibitors and NSAIDs to prevent NSAID-related gastric injury. Chandramouli does not suggest that esomeprazole and naproxen should be administered in a single unit dosage form, much less one that provides for the coordinated release of the two active</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
		<p>ingredients. Chandramouli does not suggest that at least a portion of esomeprazole should not be enterically coated and should be immediately released upon ingestion regardless of pH.</p> <p>Sangiah fails to describe a PPI at least a portion of which is not enteric coated and is immediately released regardless of pH, and also fails to disclose the coordinate release of the two active ingredients. Sangiah relates to acid inhibitor compositions and their administration and does not disclose the combination of esomeprazole with naproxen as required in the claimed unit dosage form. While Sangiah mentions omeprazole, it does not suggest that omeprazole should be combined with naproxen, immediately released at least a portion thereof upon ingestion regardless of pH, or that omeprazole might be substituted for misoprostol in the dosage forms of the '843 Patent, WO '368, or EP '867.</p> <p>EP '867 does not disclose the use of naproxen or esomeprazole. EP '867 does not disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately</p>

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PLAINTIFFS' RESPONSIVE CONTENTIONS PURSUANT TO L. PAT. R. 3.4A(c) and 3.6(i)
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		<p>released regardless of pH. Nor does EP '867 disclose a pharmaceutical composition with the coordinated release of esomeprazole and naproxen as claimed in the '285 patent.</p> <p>WO '064, WO '320, and the '974 Patent teach that PPIs should not be immediately released into the stomach, and therefore teaches away from combining esomeprazole at least a portion of which is immediately released regardless of pH with delayed release naproxen.</p> <p>The particular combinations of references identified in DRL's Invalidity Contentions would not have rendered the claims obvious for the reasons discussed in the accompanying Response to DRL's Invalidity Contentions.</p>
<p>wherein said unit dosage form provides for release of said esomeprazole such that 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.</p>	<p>WO '064 at Abstract, pages 7-12; 13 lines 16-17; 16; 23; 24-51 (Examples 1-17).</p> <p>WO '320 at pages 3; 7-8.</p> <p>WO '368 at Abstract, pages 1-6 and 7 (claims 1-5).</p>	<p><u>Plaintiffs Dispute DRL's Contention</u></p> <p>WO '064 relates to compositions comprising an acid inhibitor and an NSAID and does not disclose the required coordinated release of esomeprazole and naproxen. WO '064 fails to account for an immediate-release of at least a portion of esomeprazole regardless of pH and also fail to account for the</p>

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Claim Term In U.S. Patent 8,557,285	DRL Assertion (Prior Art Where Limitation Is Allegedly Found)	Plaintiffs' Response
	<p>WO '895 at.¹</p> <p>Daneshmend at pages 514-517, TABLE.</p> <p>Chandramouli at Abstract, pages 28-40.</p> <p>Hawkey at Abstract, pages 170-173.</p> <p>Sangiah at pages 351-353.</p> <p>'843 patent at Abstract; 1:10-17; 1:65-2:60; 3:15-54; 4:8-6:65; 7:20-12:63; 1:65-2:4; 2:40-52; 2:60-64; 3:59-4:19; 6:45-7:14, 7:20 to 12:14, Figs. 1-3.</p> <p>EP '867, Abstract, ¶¶ 1, 4-6, 12-14, 16-18, 19-21, 27, 29, and claims 1-2.</p> <p>'118 patent, Abstract, col. 1: lines 10-16; 1:19-27; 2:61-64; 3:9-58; 5:9-44; 6:35 to 7:56, claims 1 and 8.</p> <p>Ramage, pages 10-11.</p> <p>Wilson pages 127S-129S.</p> <p>'354 patent, Abstract, col. 1: lines 14-25,</p>	<p>coordinated release of esomeprazole and naproxen.</p> <p>WO '320 is directed to coated particles of acid labile active compounds, such as PPIs. WO '320 uses a protective coating that is described as another form of enteric coating, which prevents immediate-release of the PPI upon ingestion until the PPI passes safely through the stomach and its surrounding pH is at the intestine level. WO '320 fails to disclose naproxen surrounded by an enteric coating, the immediate release of at least a portion of esomeprazole regardless of pH, and the coordinated release of these active ingredients.</p> <p>The '843 Patent, WO '368, and EP '867 are directed to dosage forms comprising prostaglandins which are not esomeprazole, nor are they PPIs. The '843 Patent, WO '368, and EP '867 fail to disclose compositions in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH, and also fail to disclose the</p>

¹ See DRL Invalidity Contentions, at 34.

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	<p>3:18-27, 4:29-42, 4:59-65, 8:12-27, 11:46-67, 12:28-29, 15:47-60, 16:1-29:61.</p> <p>Brown, pages 504-509, Fig. 1, Tables I-II, Fig. 2.</p> <p>Nefesoglu, Abstract, pp. 552-553.</p> <p>'974 patent, col. 4, lines 54-59.</p>	<p>coordinated release of the two active ingredients as required by the claim.</p> <p>WO '895 discloses a pharmaceutical composition comprising an NSAID and prostaglandin. It does not disclose that the prostaglandin is esomeprazole or that it raises the gastric pH to at least 3.5. Consequently, it does not disclose a dosage form comprising esomeprazole in an amount effective to raise the gastric pH of a patient to at least 3.5. It also does not disclose delayed release of naproxen until the pH is 3.5 or higher.</p> <p>Hawkey and Daneshmend disclose concomitant, separate administration of acid inhibitors and NSAIDs. These references fail to disclose or suggest that esomeprazole and naproxen should be administered in a single unit dosage form, or one that provides for the coordinated release of esomeprazole and naproxen.</p> <p>Chandramouli discloses the concomitant, separate administration of acid inhibitors and NSAIDs to prevent NSAID-related gastric injury. Chandramouli does not suggest that esomeprazole and naproxen should be</p>

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		<p>administered in a single unit dosage form, much less one that provides for the coordinated release of the two active ingredients. Chandramouli does not suggest that at least a portion of esomeprazole should not be enterically coated and should be immediately released upon ingestion regardless of pH.</p> <p>Sangiah fails to describe a PPI at least a portion of which is not enteric coated and is immediately released regardless of pH, and also fails to disclose the coordinate release of the two active ingredients. Sangiah relates to acid inhibitor compositions and their administration and does not disclose the combination of esomeprazole with naproxen as required in the claimed unit dosage form. While Sangiah mentions omeprazole, it does not suggest that omeprazole should be combined with naproxen, immediately released at least a portion thereof upon ingestion regardless of pH, or that omeprazole might be substituted for misoprostol in the dosage forms of the '843 Patent, WO '368, or EP '867.</p> <p>EP '867 does not disclose the use of naproxen or esomeprazole. EP '867 does not</p>

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		<p>disclose a composition in which at least a portion of esomeprazole should not be enteric coated and should be immediately released regardless of pH. Nor does EP '867 disclose a pharmaceutical composition with the coordinated release of esomeprazole and naproxen as claimed in the '285 patent.</p> <p>The '118 Patent does not describe the construction of the dosage form claimed, nor does it suggest that at least a portion of esomeprazole should be immediately released upon ingestion regardless of pH. The '118 Patent does not describe an immediate-release esomeprazole.</p> <p>Ramage, Wilson, and Brown fail to describe esomeprazole at least a portion of which is not enteric coated and is immediately released regardless of pH, and they also fail to disclose the coordinated release of esomeprazole and naproxen.</p> <p>The '354 Patent teaches away from using an immediate-release PPI form by indicating that an enteric coating must be used to protect the PPI from acidic gastric juice.</p> <p>Nefesoglu investigates whether an increase in</p>

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		<p>gastric pH due to omeprazole treatment alters the release rate of a drug from an enteric-coated formulation. The omeprazole used in Nefesoglu was enteric coated and therefore did not immediately release upon ingestion regardless of pH.</p> <p>WO '064, WO '320, and the '974 Patent teach that PPIs should not be immediately released into the stomach, and therefore teaches away from combining esomeprazole at least a portion of which is immediately released regardless of pH with delayed release naproxen.</p> <p>The particular combinations of references identified in DRL's Invalidity Contentions would not have rendered the claims obvious for the reasons discussed in the accompanying Response to DRL's Invalidity Contentions.</p>
2. The pharmaceutical composition of claim 1,	See Claim 1.	<p><u>Plaintiffs Dispute DRL's Contention</u></p> <p>See Plaintiffs' Response to claim 1, above.</p>
wherein naproxen is present in said unit dosage form in an amount of	WO '064 at Abstract, pages 23; 26-28 (Example 2); 31-33 (Example 4); 40 (Example 9); -51 (Examples 1-17) – discloses	<p><u>Plaintiffs Dispute DRL's Contention</u></p>

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200-600 mg.	<p>that NSAIDs can be naproxen which can be present in amount of 0.1-1000 mg, or 250 mg (12:15-13:15; 23:19-30, Example 2, 4).</p> <p>WO '368, Abstract, pages 2; 9 (claim 18) discloses that NSAID can be naproxen; usual dose is 200 mg or below (p. 2, ll. 14-19; claim 18).</p> <p>'118 patent discloses that NSAID is selected from cetaminophen, ibuprofen, ketoprofen, naproxen, indomethacin; when naproxen is present in amount of 200-500 mg (Abstract, 3:17-24, 5:9-31, claims 1, 5, 8).</p> <p>'354 patent discloses that NSAID can be naproxen; amount of NSAID is 0.1 to 1000 mg, pref. 10-800 mg, or 10-500 mg; when naproxen and PPI is omeprazole amount of naproxen is 250 mg (8:44, 8:55, 15:47-59).</p> <p>Brown discloses that therapeutically effective amount of entericcoated naproxen is 1000 mg per day when coadministered with 40 mg/day omeprazole (p. 507).</p> <p>Trondstad discloses that therapeutically effective amount of enteric-coated naproxen</p>	See Plaintiffs' Response to claim 1, above.

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	is 500 mg twice daily (p. 239).	
3. The pharmaceutical composition of claim 1,	See Claim 1.	<u>Plaintiffs Dispute DRL's Contention</u> See Plaintiffs' Response to claim 1, above.
wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.	<p>'354 patent discloses that acid inhibitor can be proton pump inhibitor, e.g., esomoprazole, present in an amount of 10-80 mg (7:1-10; 15:48-59, Example 3); (2:22-67, 6:28-40, 8:42-55, 15:38-59, 29:54-60, Examples 2 and 9, claims 5-6, 9, and 23).</p> <p>WO 97/25064 discloses that acid inhibitor can be proton pump inhibitor, e.g., pantoprazole, present in an amount of 0.1-200 mg or about 100 mg (10:5-10; 23:19-30; Example 3); (Abstract, 1:5-11; 5:25-13:25; 18:28-19:2).</p> <p>WO 99/29320 discloses that acid-labile active compounds can be omeprazole, esomeprazole or pantoprazole or salts thereof (Abstract, pp. 3-5) discloses that the amount of acid-labile active compounds is between 1 and 500 mg, or between 5 and 60 mg (p. 8).</p> <p>'118 patent discloses that acid inhibitor can be proton pump inhibitor, e.g., omeprazole (3:9-</p>	<u>Plaintiffs Dispute DRL's Contention</u> See Plaintiffs' Response to claim 1, above.

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	<p>38, 5:25-44, claims 1, 4, 14).</p> <p>Sangiah discloses that omeprazole and misoprostol are comparable in ability to inhibit acid secretion and raise gastric pH. (pp. 352-353, Figs. 2, 3).</p> <p>Hawkey II discloses that omeprazole is better tolerated and more effective in twice daily dosing than misoprostol for prophylaxis of gastric events associated with administration of NSAIDs and is associated with lower rate of relapse of ulcer and gastric erosion associated with administration of NSAIDs (Abstract, pp. 732-733).</p> <p>Nefesoglu discloses that omeprazole significantly increases the rate of absorption of enteric-coated medication due to early disruption of enteric coating and intragastric release of the drug secondary to omeprazole-mediated increase in gastric pH (Abstract, pp. 552-553).</p> <p>Wolfe discloses that proton pump inhibitors, such as omeprazole, were known to inhibit acid secretion and were known to heal gastroduodenal ulcers in patients undergoing NSAID therapy and prophylactically prevent</p>	

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	<p>ulcers when administered concomitantly. (S13-S14, S17-S18, and passim).</p> <p>Brown discloses that co-therapy with proton pump inhibitors results in less gastric acidity by elevating the luminal pH above pH 4 and reduced injuries from NSAID administration (pp. 504-505, Fig. 1).</p>	
4. The pharmaceutical composition of claim 1,	See Claim 1.	<p><u>Plaintiffs Dispute DRL's Contention</u></p> <p>See Plaintiffs' Response to claim 1, above.</p>
wherein naproxen is present in said unit dosage form in an amount of between 200-600 mg and esomeprazole in an amount of from 5 to 100 mg per unit dosage form.	See Claims 2 and 3.	<p><u>Plaintiffs Dispute DRL's Contention</u></p> <p>See Plaintiffs' Response to claims 2 and 3, above.</p>