

Filed: July 2, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

DR. REDDY'S LABORATORIES INC.,

Petitioner

v.

POZEN INC. and HORIZON PHARMA USA, INC.,

Patent Owners

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U.S. Patent No. 9,393,208 to Ault *et al.*

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*Inter Partes* Review IPR2018-001341

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Petition for *Inter Partes* Review of U.S. Patent No. 9,393,208

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## **LISTING OF EXHIBITS**

<b>Exhibit</b>	<b>Description</b>
1001	U.S. Patent No. 9,393,208, <i>Method for Delivering a Pharmaceutical Composition to Patient in need thereof</i> (filed Dec. 28, 2015) (issued Jul. 19, 2016) (“the ’208 patent”)
1002	Declaration of David C. Metz, M.D. (“Metz Decl.”)
1003	Declaration of Michael Mayersohn, Ph.D. (“Mayersohn Decl.”)
1004	U.S. Patent No. 6,926,907, <i>Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS</i> (filed May 31, 2002) (issued Aug. 9, 2005)
1005	U.S. Patent No. 8,557,285, <i>Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS</i> (filed Aug. 23, 2011) (issued Oct. 15, 2013)
1006	Howden, <i>Review Article: Immediate-Release Proton-Pump Inhibitor Therapy – Potential Advantages</i> , 22 (Suppl. 3) ALIMENT. PHARMACOL. THER. 25 (2005)
1007	U.S. Patent No. 5,877,192, <i>Method for the Treatment of Gastric Acid-Related Diseases and Production of Medication using (-) Enantiomer of Omeprazole</i> (filed Apr. 11, 1997) (issued Mar. 2, 1999)
1008	<i>Products on NDA 020067 (EC-Naprosyn)</i> , FDA.GOV, <a href="https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&amp;ApplNo=020067">https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&amp;ApplNo=020067</a> (last visited Aug. 23, 2017)
1009	EC-Naprosyn prescribing information (Jan. 2007)
1010	Zegerid approval letter and prescribing information (2004)
1011	Goldstein et al., 116 <i>A Single Tablet Multilayer Formulation of Enteric-Coated Naproxen Coupled with Non-Enteric Coated OMEPRAZOLE is Associated with a Significantly Reduced Incidence of Gastric Ulcers vs. Enteric-Coated Naproxen: A Prospective, Randomized, Double-Blind Study</i> , 134(4) GASTROENTEROLOGY A19 (2008)

Exhibit	Description
1012	Hochberg et al., <i>A Novel, Single-Tablet Formulation that Delivers Immediate-Release Omeprazole Followed by Enteric-Coated (EC) Naproxen Significantly Reduces the Incidence of Gastric Ulcers Compared with EC Naproxen Alone: Results of a Prospective, Randomised, Double-Blind, 6-Month Study including Patients with OA and RA</i> , EULAR (2008)
1013	U.S. Patent No. 9,220,698 Prosecution History Excerpt: Amendment C and Response to Final Office Action (Jan. 30, 2013)
1014	Wolfe et al., <i>Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome</i> , 118 GASTROENTEROLOGY S9 (2000)
1015	Bell et al., <i>Appropriate Acid Suppression for the Management of Gastro-Oesophageal Reflux Disease</i> , 51(suppl. 1) DIGESTION 59 (1992)
1016	Hassan-Alin et al., <i>Lack of Pharmacokinetic Interaction between Esomeprazole and the Nonsteroidal Anti-Inflammatory Drugs Naproxen and Rofecoxib in Healthy Subjects</i> , 25(11) CLIN. DRUG INVEST. 731 (2006)
1017	Khosravan et al., <i>Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs</i> , 46 J. CLIN. PHARMA. 855 (2006)
1018	Jung et al., <i>Steady-State Pharmacokinetics of Enteric-Coated Naproxen Tablets Compared with Standard Naproxen Tablets</i> , 16(6) CLIN. THER. 923 (1994)
1019	Davies et al., <i>Clinical Pharmacokinetics of Naproxen</i> , 32(4) CLIN. PHARMACOKINET. 268 (1997)
1020	Naprosyn/EC-Naprosyn/Anaprox DS Prescribing Information (Mar. 2017)

Exhibit	Description
1021	Dan M. Roden, <i>Principles of Clinical Pharmacology</i> , in HARRISON’S PRINCIPLES OF INTERNAL MEDICINE 13 (Dennis L. Kasper et al. eds., 16th ed. 2005)
1022	Malcolm Rowland & Thomas N. Tozer, CLINICAL PHARMACOKINETICS (3d ed. 1995)
1023	Clissold et al., <i>Omeprazole A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Peptic Ulcer Disease and Zollinger-Ellison Syndrome</i> , 32 DRUGS 15 (1986)
1024	U.S. Patent No. 7,411,070, <i>Form of S-Omeprazole</i> (filed Sept. 25, 2003) (issued Aug. 12, 2008)
1025	U.S. Patent No. 5,714,504, <i>Compositions</i> (filed Jan. 23, 1995) (issued Feb. 3, 1998)
1026	Michael Mayersohn, <i>Principles of Drug Absorption</i> , in MODERN PHARMACEUTICS 21 (3d ed. 1996)
1027	Howden, <i>Clinical Pharmacology of Omeprazole</i> , 20(1) CLIN. PHARMACOKINET. 38 (1991)
1028	Lind et al., <i>Esomeprazole Provides Improved Acid Control vs. Omeprazole in Patients with Symptoms of Gastro-Oesophageal Reflux Disease</i> , 14 ALIMENT. PHARMACOL. THER. 861 (2000)
1029	Regårdh et al., <i>Pharmacokinetics and Metabolism of Omeprazole in Animals and Man – An Overview</i> , 20(suppl. 108) SCAND. J. GASTROENTEROL 79 (1985)
1030	Vimovo prescribing information (Dec. 2014)
1031	<i>Target</i> , WEBSTER’S NEW WORLD COLLEGE DICTIONARY (4th ed. 2005)
1032	<i>Target</i> , THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (4th ed. 2006)
1033	<i>Target</i> , MERRIAM-WEBSTER’S CONCISE DICTIONARY (Large print ed. 2006)
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1042	Goldlust et al., <i>Nighttime Dosing of Omeprazole Immediate-Release Oral Suspension Rapidly Decreases Nocturnal Gastric Acidity</i> , 99(10) AM. J. GASTROENTEROLOGY S39 (2004)
1043	Nexium Prescribing Information (Feb. 2001), available at <a href="https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21153lbl.pdf">https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21153lbl.pdf</a> (last visited Nov. 22, 2017)
1044	Prilosec Prescribing Information (June 2002), available at <a href="https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19810s074lbl.pdf">https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19810s074lbl.pdf</a> (last visited Nov. 22, 2017)
1045	Opinion & Order, <i>Horizon Pharma, Inc. v. Dr. Reddy's Labs, Inc.</i> , No. 15-cv-3324-SRC-CLW (consolidated) (D.N.J. Nov. 14, 2017), ECF No. 82
1046	U.S. Patent No. 9,393,208 Prosecution History Excerpts

## **I. INTRODUCTION**

Dr. Reddy's Laboratories Inc. ("Petitioner") petitions for *Inter Partes* Review of claims 1-7 of U.S. Patent No. 9,393,208 ("the '208 patent") (Ex. 1001), which is assigned to Pozen Inc. ("Pozen") and Horizon Pharma USA, Inc. ("Horizon") (collectively, "Patent Owners"), under 35 U.S.C. §§ 311-319 and 37 C.F.R. Part 42 and seeks a determination that all claims (1-7) of the '208 patent be canceled as unpatentable.

This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith is a power of attorney and exhibit list per § 42.10(b) and § 42.63(e). Pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a) accompanies this Petition.

## **II. MANDATORY NOTICES**

Petitioner provides the following mandatory notices.

### **A. Real Parties-In-Interest Under 37 C.F.R. § 42.8(b)(1)**

The real parties-in-interest for Petitioner are Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd.

### **B. Related Matters Under 37 C.F.R. § 42.8(b)(2)**

The following litigations or instituted *inter partes* reviews related to the '208 patent are pending:

- *Inter Partes* Review IPR2017-01995 of Mylan Pharmaceuticals Inc.;

- *Inter Partes* Review IPR2018-00272 of Mylan Pharmaceuticals Inc.;
  - *Inter Partes* Review IPR2018-00894 of Dr. Reddy's Laboratories, Inc.;
  - *Horizon Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, No. 15-3324 (D.N.J.);
  - *Horizon Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, No. 16-4918 (D.N.J.);
  - *Horizon Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, No. 16-9035 (D.N.J.);
  - *Horizon Pharma, Inc. v. Mylan Pharms. Inc.*, No. 15-3327 (D.N.J.);
  - *Horizon Pharma, Inc. v. Mylan Pharms. Inc.*, No. 16-4921 (D.N.J.);
- and
- *Horizon Pharma, Inc. v. Lupin Ltd.*, No. 16-4920 (D.N.J.).

**C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)**

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**D. Service Information Under 37 C.F.R. § 42.8(b)(4)**

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Petitioner consents to electronic service by e-mail at the following email addresses: apollack@buddlarner.com; dshelhoff@buddlarner.com; ssender@buddlarner.com; lweinstein@buddlarner.com

**III. GROUNDS FOR STANDING (37 C.F.R. §§ 42.101 and 42.104)**

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '208 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified herein. The Petition is timely because Petitioner has filed it no later than one month after June 14, 2018, the institution date of an *inter partes* review of *Mylan Pharmaceuticals Inc. v. Pozen Inc. and Horizon Pharma USA, Inc.*, IPR2018-00272 (“the Mylan IPR”) to which joinder is requested. Mylan consents to joinder of DRL’s petition and had consented to joinder of DRL’s related petition *Dr. Reddy’s Laboratories Inc. v. Pozen Inc. and Horizon Pharma USA, Inc.*, IPR2018-00894, concerning U.S. Patent No. 9,220,698. (See Paper 9 at p. 1).

**IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. § 42.22(a) and 37 C.F.R. § 42.104(b))**

Petitioner respectfully requests *inter partes* review and cancellation of claims 1-7 on the grounds set forth below.

**Ground 1:** Claims 1-7 are unpatentable as anticipated under 35 U.S.C. § 102 by U.S. Patent No. 8,557,285 (“’285 patent”).

**Ground 2:** Claims 1-7 are unpatentable as obvious under 35 U.S.C. § 103 over the ’285 patent.

**Ground 3:** Claims 1-7 are unpatentable as obvious under 35 U.S.C. § 103 over the ’285 patent in view of the EC-Naprosyn<sup>®</sup> label and Howden 2005.

Petitioner’s full statement of the reasons for the relief requested is set forth below. In support of these grounds for unpatentability, Petitioner submits the expert declarations of Dr. David Metz (Ex. 1002 (“Metz Decl.”)) and Dr. Michael Mayersohn (Ex. 1003 (“Mayersohn Decl.”))<sup>1</sup> and relies on other Exhibits set forth in the concurrently-filed Listing of Exhibits.

## **V. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW**

A petition for *inter partes* review must demonstrate “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). This Petition clears that threshold. There is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

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<sup>1</sup> The Metz and Mayersohn declarations used in this petition are the same as in the Mylan’s IPR2018-00272 because Mylan has agreed to share its experts with DRL.



## **VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED**

### **A. Summary of the Argument**

The claims of the '208 patent recite a method of administering a drug formulation to target certain pharmacokinetic (PK) and pharmacodynamic (PD) parameters. But the drug formulation and method of administration were both known—Patent Owners previously disclosed them in two prior art patents: U.S. Patent Nos. 6,926,907 (Ex. 1004) and 8,557,285 (Ex. 1005). And there is nothing novel about the PK/PD elements—they are the natural result of administering the known formulation according to the known method. To extend patent protection eight years beyond the '907 patent's expiration, the inventors of the '208 patent simply ran a routine clinical trial using a known drug and known method to document an inherent property of the drug. They then claimed the expected and unsurprising results. “Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). The '208 patent's claims are unpatentable as anticipated by, or obvious over, the '285 patent.

Specifically, the '208 patent claims a method of treating arthritis by administering a combination tablet of naproxen 500mg (EC-Naprosyn<sup>®</sup>) and esomeprazole 20mg (Nexium<sup>®</sup>) twice daily. Naproxen relieves arthritis pain and

inflammation, but long-term administration was known to cause gastric injury. To solve this problem, proton pump inhibitors (PPIs)—esomeprazole for example—were prescribed to raise gastric pH, preventing naproxen-induced injury.

As a result, skilled artisans designed tablets combining naproxen and PPIs. In 2001, the '285 and '907 patents disclosed and claimed the “PN formulation,” a specific tablet structure combining naproxen and esomeprazole. The PN formulation purportedly features “coordinated release,” whereby esomeprazole is immediately released and the naproxen releases only once the esomeprazole has raised gastric pH. Dr. John Plachetka, one of the four inventors of the '208 patent, is the named inventor of the '285 and '907 patents.

The '208 patent claims the precise formulation and method of administration disclosed in Dr. Plachetka's '285 and '907 patents seven years prior. The only other elements it recites are certain PK/PD values for naproxen and esomeprazole. But these PK/PD values result from administering the prior art PN formulation per the prior art method. The '208 patent concedes this point, referring to the '907 patent as a formulation that “can be effective in improving NSAID tolerability through dosages of esomeprazole and naproxen that produce the desired pharmacodynamic response and pharmacokinetic values.” Ex. 1001, 1:30-37.

The law does not permit Patent Owners to extend their monopoly nearly a decade by simply claiming an inherent characteristic of their previously-disclosed

formulation and method of administration. Indeed, the '208 patent is exactly why the inherency doctrine exists: “one of the principles underlying the doctrine of inherent anticipation is to ensure that the public remains free to make, use or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate.” *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1345-46 (Fed. Cir. 2005) (quotation and alteration omitted).

The Federal Circuit previously held that “an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations.” *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). Yet, that is exactly what Patent Owners did here— they gave a known formulation to patients and claimed the resulting serum concentrations. “The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation.” *Id.* All claims of the '208 patent are anticipated by or obvious over at least the '285 patent.

Alternatively, all claims of the '208 patent are obvious over the '285 patent in view of the EC-Naprosyn<sup>®</sup> label (Ex. 1009) and Howden 2005 (Ex. 1006). Even if not inherent, a skilled artisan would have known to target the claimed PK/PD values because they were known to be produced by effective drugs already on the market: EC-Naprosyn<sup>®</sup> for naproxen and Zegerid<sup>®</sup> for esomeprazole. Skilled

artisans would understand from the EC-Naprosyn<sup>®</sup> label and Howden 2005 that EC-Naprosyn<sup>®</sup> and Zegerid<sup>®</sup> produced PK/PD values at which delayed-release naproxen and immediate-release esomeprazole were effective. When developing the claimed PN formulation, skilled artisans would target PK/PD values known to provide efficacy. As the '208 patent's claims require only that the prior art teach a skilled artisan to "target" the claimed PK/PD values, all claims are obvious over the '285 patent in view of the EC-Naprosyn<sup>®</sup> label and Howden 2005.

#### **B. Level of Ordinary Skill in the Art**

A person of ordinary skill in the art ("POSA") is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. The field of art involves the knowledge of a medical doctor and that of a pharmacologist or pharmacokineticist with experience in dosage form design and evaluation. Thus, the hypothetical POSA is a collaboration between a pharmacologist or pharmacokineticist having a Ph.D. degree or equivalent training, or a M.S. degree with at least 2 years of some experience in dosage form design and in in vitro and in vivo evaluation of dosage form performance, and a medical doctor having at least 2 years of practical experience treating patients in the gastroenterology field. Ex. 1002 ¶¶23-24; Ex. 1003 ¶¶19-20.

#### **C. The '208 Patent and Its Prosecution**

## **1. NSAID Gastropathy**

The '208 patent relates to formulations and methods of treatment to prevent injury caused by chronic use of non-steroidal anti-inflammatory drugs ("NSAIDs"). NSAIDs are a class of drugs used to treat pain and inflammation. Ex. 1002 ¶25. The class includes, e.g., aspirin, naproxen, ibuprofen, and diclofenac. *Id.* NSAIDs are among the most commonly prescribed medications in the world and have been used for decades. *Id.* The NSAID naproxen was first approved by the FDA in 1976 under the trade name Naprosyn. Ex 1020, 1.

NSAIDs can cause a variety of side effects over chronic administration. Ex. 1002 ¶26. These NSAID-induced side effects are commonly called "NSAID-related injury" or "gastropathy." *Id.* This injury, however, can be reduced by controlling acid in the stomach through concomitant administration of an acid inhibitor with the NSAID. *Id.*, ¶27.

## **2. Specification of the '208 Patent**

The '208 patent claims priority to a provisional application filed on September 9, 2008. It relates to methods of administering to a patient delayed-release naproxen 500mg and immediate-release esomeprazole 20mg in a single tablet. Ex. 1001, 24:7-11; Ex. 1002 ¶¶29, 33-36; Ex. 1003 ¶¶40-45, 48-62. The specification calls this formulation "PN400/E20." Ex. 1001, 26:1-2; Ex. 1002 ¶¶34-35; Ex. 1003 ¶43. The '208 patent recites in its claims certain PK/PD results

for patients administered PN400/E20. *See, e.g.*, Ex. 1001, col. 35, Tbls. 6, 11; Ex. 1003 ¶¶43-44. As explained in more detail *infra*, Section VI.E.1, when a patient intakes a drug, it has a particular effect, *i.e.*, it reduces pain and/or increases stomach pH. Ex. 1003 ¶¶25-28. Scientists measure these effects by determining PK/PD values. Ex. 1003 ¶¶27-29. PK measures the body's absorption of the drug; PD describes the drug's effect on the body. Ex. 1003 ¶¶25-28.

The '208 patent describes certain PK parameters: " $C_{\max}$ ," " $T_{\max}$ ," and "area under the curve" or "AUC." *Id.* ¶44. To a skilled artisan,  $C_{\max}$  is the maximum concentration the drug achieves in the patient's blood plasma. *Id.* ¶31.  $T_{\max}$  refers to the time after administration at which the patient's  $C_{\max}$  is reached. *Id.* Finally, "area under the curve" or AUC measures the total amount of drug delivered over a certain period after administration, for example after ten hours ( $AUC_{0-10}$ ) or after twenty-four hours ( $AUC_{0-24}$ ). Ex. 1003 ¶¶31, 37-38. Because there is natural intra- and inter-patient variation, pharmacokinetic parameters are generally recited as average (mean) values plus or minus a variation, as in the '208 patent. Ex. 1003 ¶32, 44.

The background of the '208 patent notes that NSAIDs were understood to induce gastrointestinal injury, such as ulcers, when used frequently. Ex. 1001, 1:19-24; Ex. 1002 ¶30; Ex. 1003 ¶45. Skilled artisans knew that stomach acid was "[a] major factor contributing to the development of gastrointestinal lesions." Ex.

1001, 1:24-25; Ex. 1003 ¶45. The specification next refers to several strategies previously taken “to reduce the gastrointestinal risk associated with taking NSAIDs by administering agents that inhibit stomach acid secretion, such as, for example, proton pump inhibitors with the NSAID.” Ex. 1001, 1:27-30; Ex. 1002 ¶¶31-32; Ex. 1003 ¶45. The specification identifies the ’907 patent as an example of a formulation that is “effective in improving NSAID tolerability through dosages of esomeprazole and naproxen that produce the desired pharmacodynamic response and pharmacokinetic values.” Ex. 1001, 1:34-37; Ex. 1003 ¶46. Notably, the specification of the ’907 patent made similar statements and then also disclosed, among others, the same formulation claimed in the ’208 patent: a unit dose form containing 500mg of delayed-release naproxen and 20mg of immediate-release esomeprazole. Ex. 1004, 1:11-44, 5:1-19, claims 1, 5, 51-52; Ex. 1002 ¶¶51-54; Ex. 1003 ¶¶46-47; *see* Ex. 1001, 1:19-41. The prior art ’285 patent, which shares a specification with the ’907 patent, again claims the same immediate-release esomeprazole with coated naproxen formulation with the added specificity of disclosing naproxen doses from 200-600mg and esomeprazole doses from 5-100mg. Ex. 1005, claim 4; Ex. 1002 ¶¶49-50; Ex. 1003 ¶47.<sup>2</sup>

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<sup>2</sup> As discussed *infra*, Section VI.E.2.a, the ’285 patent was not filed until after the earliest possible priority date for the ’208 patent (Sept. 9, 2008), but the ’285 patent is nevertheless prior art to the ’208 patent because the ’285 patent claims

The '208 patent's specification sets forth several abbreviations and definitions. Ex. 1001, 3:15-6:10, Table 1; Ex. 1003 ¶48. "About" is defined as indicating that "a given number may vary by at least 5%, with variations of 10%, 15% or 20% being possible." Ex. 1001, 5:31-33. However, "[w]ith regard to time periods referred to herein, the term 'about' is intended to reflect variations from the specifically identified time periods that are acceptable within the art." *Id.*, 5:51-53. After the definitions section, the specification lists several pages of largely repetitive statements of claim language, noting that they are embodiments of the claimed invention. *Id.*, 6:17-23:49.

Finally, the specification disclosed an exemplary clinical trial. Ex. 1001, 24:5-46:30; Ex. 1002 ¶¶33-34; Ex. 1003 ¶49. Example 1 is a single-center, randomized, crossover, open-label study in 28 healthy adults. Ex. 1001, 24:5-9, 35. All patients crossed over between four treatments: twice-daily delayed-release naproxen 500mg combined with each of three doses of immediate-release esomeprazole (10, 20, or 30mg), and twice-daily immediate-release naproxen 500mg administered separately with once-daily delayed-release esomeprazole 20mg. Ex. 1001, 25:62-26:8; Ex. 1002 ¶34; Ex. 1003 ¶49. On days 1 and 9, various PK and PD measurements were taken throughout the day. Ex. 1001, 24:52-54, 26:22-34, 26:48-62.

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priority to 2001.



The primary pharmacodynamics metric was the mean percent of time in a 24-hour period during which gastric pH was greater than 4.0 and the results were set forth in Table 4. For the claimed formulation (PN400/E20), the mean was 71.35%. Ex. 1001, Tbl. 4; Ex. 1003 ¶50. For PN400/E30 (500mg naproxen and 30mg esomeprazole twice daily) and PN400/E10 (500mg naproxen and 10mg esomeprazole twice daily), the results were 76.5% and 40.85%, respectively. Ex. 1001, Tbl. 4. Separate administration of equivalent daily esomeprazole doses as PN400/E10 resulted in an improved percentage of 56.85%. *Id.*

Key pharmacokinetic measurements included mean  $C_{\max}$  and median  $T_{\max}$  for naproxen, and mean AUC for esomeprazole. Naproxen PK results are summarized in Table 11 and Figure 6. *Id.*, Tbl. 11, Fig. 6. At Day 9, mean  $C_{\max}$  for the AM naproxen dose in the claimed PN400/E20 formulation was 86.2  $\mu\text{g/mL}$  and median  $T_{\max}$  was 3.00. *Id.*, Tbl. 11, Tbl. 13; Ex. 1003 ¶52. For the PM naproxen dose, mean  $C_{\max}$  was 76.8  $\mu\text{g/mL}$  and median  $T_{\max}$  was 10.0. Ex. 1001, Tbl. 11, Tbl. 13; Ex. 1003 ¶52.

Esomeprazole PK data are illustrated in Table 6. At Day 9, the mean AUC for esomeprazole in the claimed PN400/E20 formulation was 1216  $\text{hr} \cdot \text{ng/mL}$  for the AM dose and 919  $\text{hr} \cdot \text{ng/mL}$  for the PM dose. Ex. 1001, Tbl. 6, Tbl. 8; Ex. 1003 ¶53. Table 6 also reports coefficients of variation of 69% for the AM dose mean AUC and 84% for the PM dose mean AUC. Ex. 1001, Tbl. 6, Tbl. 8; Ex.

### **3. The '208 Patent Prosecution**

The application leading to the '208 patent was filed on December 28, 2015, claiming priority to a provisional application filed September 9, 2008. The '208 patent issued on July 19, 2016, just seven months after the application was filed.

During prosecution, the Examiner issued a single rejection, for double patenting over the parent patent, U.S. Patent No. 9,220,698. Ex. 1046 at 2-5. The applicant responded by filing a terminal disclaimer, and the patent subsequently issued. *Id.* at 11.

#### **D. Claim Construction (37 C.F.R. §§ 42.100(b), 42.104(b)(3))**

Pursuant to 37 C.F.R. § 42.100(b), a claim in an unexpired patent is given its broadest reasonable interpretation in light of the specification. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). Petitioner submits for purposes of this petition only that all terms in the claims of the '208 patent besides “target” do not require construction and take on their plain meaning.<sup>3</sup>

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<sup>3</sup> Because the claim construction standard in an *inter partes* review is different than that used in litigation, Petitioner reserves the right to present different constructions of terms in litigation under the applicable claim construction standards. *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004).

## 1. “Target” Means “With The Goal of Obtaining”

All claims of the '208 patent recite certain PK/PD properties of the claimed naproxen-esomeprazole combination. Specifically, the claims recite PK values for both naproxen and esomeprazole, and the PD result of administering esomeprazole (*i.e.*, raising the stomach pH). Ex. 1001, 46:33-47:9. The claims state that “the AM and PM unit dose forms *target*” these PK properties and “further *target*” the PD property.

The broadest reasonable construction of “target” is “with the goal of obtaining.”<sup>4</sup> This interpretation follows directly from “target’s” plain meaning. Ex.

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<sup>4</sup> In parallel district court proceedings, Petitioner has contended that “target” is indefinite. Petitioner also presented the construction proposed here. In a detailed decision dated November 14, 2017, the District Court agreed with Petitioner, concluding that “target” means “set as a goal.” Ex. 1045 at 11. The Court found that “Plaintiffs’ proposed construction makes no sense, and Defendants’ proposed construction makes sense,” and that Petitioner’s construction “fits with the Court’s understanding of what ‘target’ ordinarily means.” *Id.* The court further discredited Patent Owner’s expert, Dr. Taft. *Id.* at 8-9. The Court deferred Petitioner’s indefiniteness argument to summary judgment. *Id.* at 10. In proposing its construction for “target”—which the District Court adopted—in this IPR, Petitioner does not relinquish its position that “target” is indefinite, and Petitioner

1003 ¶¶66, 74-78. The intrinsic evidence does not expressly ascribe any particular meaning to the term “target.” *Id.* ¶¶67-68, 75-76. Nor is “target” a term of art in the patent’s field. *Id.* ¶76. “Target” must thus carry its ordinary meaning. *Id.*

“Target’s” ordinary meaning is “with the goal of obtaining.” Ex. 1003 ¶77. “Dictionaries or comparable sources are often useful to assist in understanding the commonly understood meaning of words and have been used both by our court and the Supreme Court in claim interpretation.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1322 (Fed. Cir. 2005). The Merriam-Webster’s Concise Dictionary defines “target” as to “establish as a goal.” Ex. 1033. Similarly, the American Heritage Dictionary defines “target” as “to establish as a target or goal,” Ex. 1032, and Webster’s New World College Dictionary defines “target” as “to establish as a target, goal, etc.,” Ex 1031. And they are right—“targeting” a bullseye, for example, tells no one where an arrow actually strikes.

The intrinsic evidence supplies no reason to diverge from “target’s” ordinary meaning. “Target” appears in the specification only in repetition of claim language. Ex. 1003 ¶¶67-68. Likewise, the prosecution history does not mention “target” or its meaning. *Id.* ¶75.

If anything, the intrinsic evidence further supports Petitioner’s construction. The skilled artisan would understand from the data disclosed in the specification

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intends to continue to press its indefiniteness arguments before the District Court.

that the patentee intended “target” to allow for wider variation of the PK values than the  $\pm 20\%$  recited in the claims. *Id.* ¶¶70-74.

To elaborate, the claims state that certain PK/PD values are “targeted.” Ex. 1001, 46:32-47:9. These targeted PK values are copied from experimental results disclosed in the specification. *Id.*, Tbl. 6; Ex. 1003 ¶71. In Example 1, the claimed formulation was given to 28 patients according to the claimed method, and the resulting PK values were measured. Ex. 1001, 24:35, 25:62-26:8, 26:23-34; Ex. 1003 ¶71. In addition to disclosing mean PK values, the specification also disclosed the variation associated with those mean values. Ex. 1003 ¶71. For example, for esomeprazole, Table 6 of the specification disclosed a mean AUC for the AM esomeprazole dose of 1216 hr\*ng/mL, with variation of  $\pm 69\%$ . Ex. 1001, Tbl. 6 (Treatment B). For the PM esomeprazole dose, Table 6 reports a mean AUC of 919 hr\*ng/mL, with even greater variation of  $\pm 84\%$ . *Id.*

However, while the claims recite these same mean AUC values, they recite a much narrower range of variation,  $\pm 20\%$ . *Id.*, 46:56-47:5; Ex. 1003 ¶72. The claims therefore require much more precision than is supported by the specification. Ex. 1003 ¶¶72-74. Rather than create a written description or enablement problem, the patent drafters wrote the claims so that the recited PK values need only be “targeted,” not necessarily achieved. The broadest reasonable interpretation of “target” is therefore “with the goal of obtaining.” Ex. 1003 ¶¶66-

78.

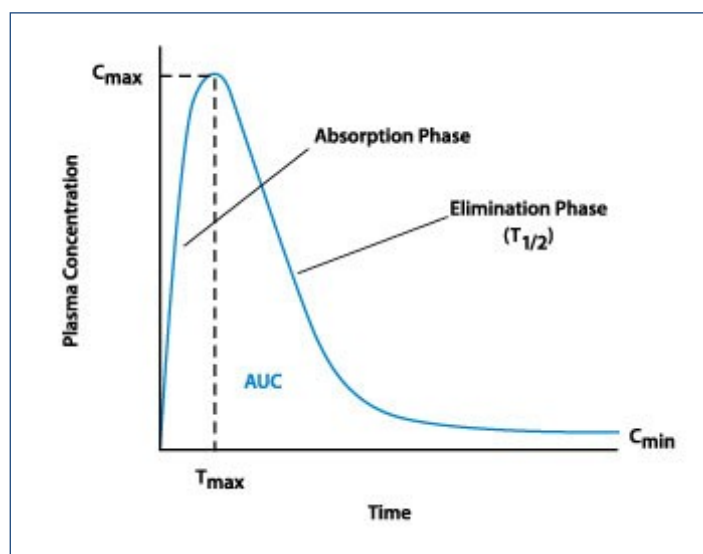
## **E. Scope and Content of the Prior Art**

### **1. PK/PD Overview**

Pharmacokinetics (PK) involve body processes affecting drug movement into (absorption), within (distribution), and out of (metabolism and excretion) the body. Ex. 1003 ¶25. Generally, a drug's PK properties and dosage form control the drug's plasma concentration, which drives the drug's PD (clinical or toxic) effect and time course. *Id.* ¶¶25-29. The PK and PD properties of a drug are typically studied together. *Id.* ¶¶27-29. A basic skill for a pharmacokineticist is the ability to test a drug and gather PK/PD data to describe the drug's behavior. *Id.* ¶27.

It is often worthwhile to describe and model the plasma concentration-time profile of a drug after administering it to a patient to monitor PK/PD effects. *Id.*

¶29. After drug administration, blood samples are obtained over time, and a blood or blood-derived fluid sample is analyzed to determine the drug concentration at each time point. *Id.* ¶30. The concentration-time profile is then analyzed to estimate the drug's pharmacokinetic parameters. *Id.* Below is a hypothetical concentration-time profile following single oral dosing of an immediate-release dosage form.



The concentration-time profile can be used to estimate values such as  $C_{max}$  (maximum drug concentration),  $T_{max}$  (time of  $C_{max}$ ),  $t_{1/2}$  (drug half-life in the body), and AUC (total systemic absorption or exposure to the drug, measured by the area under the concentration-time curve). *Id.* ¶31.

Some single-unit dosage forms, like Vimovo<sup>®</sup>, provide pulsatile or repeat dosing, with multiple drug releases occurring at different post-ingestion times, which was well-known in the art. *Id.* ¶¶33-34. Repeat action is often achieved by covering a delayed-release core of one drug with an immediate-release layer of another (or the same) drug. *Id.* ¶34. In a repeat-dosing tablet, assuming no drug-drug interaction, the individual concentration-time curves will contribute additively to a total drug concentration-time curve. *Id.* ¶¶35-36.

It is often useful to characterize a dosage form's pharmacokinetics after

multiple oral doses, where the drug accumulates in the body to a maximum plasma concentration. *Id.* ¶37. In this “fluctuating steady state,” often after 4 or 5 half-lives, the concentration-time profile repeats after each dose. *Id.* In a “constant steady state,” the drug concentration is constant because the rate of drug entering the body equals the rate of drug being eliminated from the body. *Id.* At steady state,  $C_{\max}$  and  $T_{\max}$  will have the same meaning as for single dosing, but the AUC is measured over an interval (often the dosing interval). *Id.* ¶¶38-39. Further, a POSA will often monitor and plot the average plasma concentration over all subjects at each time to create an average plasma concentration-time profile. *Id.* ¶32. This indicates the pharmacokinetic behavior of the dosage form across multiple subjects. *Id.*

## **2. References Disclosing Combined Naproxen-Esomeprazole Formulations**

### **a. '285 Patent**

The '285 patent described the formulation claimed in the '208 patent. The '285 patent claims priority to Provisional Application No. 60/294,588, which was filed on June 1, 2001. The '285 patent therefore has a priority date of June 1, 2001, and is prior art to the '208 patent under § 102(e)(2).<sup>5</sup>

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<sup>5</sup> This holds true even though the application leading to the '285 patent was filed on August 23, 2011, and did not issue until October 15, 2013, both after the



The '285 patent explained that “[a]lthough non-steroidal anti-inflammatory drugs are widely accepted as effective agents for controlling pain, their administration can lead to the development of gastroduodenal lesions, e.g., ulcers

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priority date of the '208 patent. Section 102(e)(2) states that a patent is prior art if it was “granted on an application for patent by another filed in the United States before the invention by the application for patent ....” “By another” refers to a different inventive entity, which exists if not all inventors are the same. *Ex parte DesOrmeaux*, 25 U.S.P.Q. 2d 2040 (Bd. Pat. App. & Inter. 1992). Therefore, even though both the '285 and '208 patents list John Plachetka as an inventor, the '285 patent has a different inventive entity because the '208 patent lists three other inventors in addition to John Plachetka. Ex. 1001, [72]; Ex. 1005, [75]. In addition, the Federal Circuit has held that, under § 102(e), “the effective date of a reference United States patent as prior art is its filing date in the United States.” *Sun Studs, Inc. v. ATA Equip. Leasing, Inc.*, 872 F.2d 978, 983 (Fed. Cir. 1989); *see* MPEP § 2136.03. “In other words, the claims of a patent are invalid if they read on the invention disclosed in a different U.S. patent application that was filed before, but issued after, the filing date of the inventor's patent.” *Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1322 (Fed. Cir. 2013). That is the case here.

and erosions, in susceptible individuals.” Ex. 1005, 1:30-33; Ex. 1002 ¶39; Ex. 1003 ¶82. Stomach acid is “a major factor contributing to the development of these lesions,” and acid inhibitors had been shown to improve NSAID tolerability. Ex. 1005, 1:34-39; Ex. 1002 ¶¶40-41. The ’285 patent disclosed that “more potent and longer lasting acid inhibitors, such as proton pump inhibitors, are thought to be more protective during chronic administration of NSAIDs than shorter acting agents, e.g., histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub> blockers).” Ex. 1005, 1:48-52; Ex. 1002 ¶40; Ex. 1003 ¶82.

The ’285 patent taught a combination NSAID-PPI formulation to prevent NSAID-induced gastric injury. Specifically, the ’285 patent disclosed “a single, coordinated, unit-dose product” combining an immediate-release PPI and a delayed-release (enteric-coated) NSAID. Ex. 1005, 3:14-20; Ex. 1002 ¶¶43-46; Ex. 1003 ¶¶79-81, 83. This formulation “provides for coordinated drug release in a way that elevates gastric pH and reduces the deleterious effects of the NSAID on the gastroduodenal mucosa, *i.e.*, the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen.” Ex. 1005, 4:46-51; Ex. 1002 ¶¶43-46; Ex. 1003 ¶81. The ’285 patent also taught methods of administering this formulation. *See, e.g.*, Ex. 1005, 3:11-26; Ex. 1002 ¶47; Ex. 1003 ¶84.

The ’285 patent further provided that the NSAID can be naproxen and the

acid inhibitor can be esomeprazole. Ex. 1005, 3:46, 4:6; Ex. 1002 ¶¶49-50; Ex. 1003 ¶83. The '285 patent contained several examples providing formulation recipes and setting out the coordinated release tablet structure. *See* Ex. 1005, Examples 6-8; Ex. 1003 ¶¶84-85. This included formulations where naproxen is present in an amount of between 200-600mg and esomeprazole in an amount of from 5-100mg per unit dosage form. Ex. 1005, claim 4; Ex. 1003 ¶¶86-87. The '285 patent further taught that “[n]aproxen is particularly useful when contained in tablets or capsules in an amount of from 250 to 500 mg,” Ex. 1005 at 7:9-10, and that “about 40 mg” of esomeprazole is “preferred,” *id.* at 8:10. Ex. 1003 ¶84.

#### **b. '907 Patent**

The '907 patent is the first patent that issued from a provisional application filed June 1, 2001. It therefore has a priority date of June 1, 2001, and is prior art to the '208 patent. The '907 patent is the parent to several other patents, including the '285 patent, and it largely shares a specification with the '285 patent. Ex. 1002 ¶¶51-52. The '907 patent thus has a substantively identical disclosure to the '285 patent, but for the claims. *Id.* In general, the '907 patent's claims were directed to an oral unit dose pharmaceutical composition comprising an immediate-release acid inhibitor and a delayed-release NSAID. Ex. 1004, 20:9-32; Ex. 1002 ¶¶53-54; Ex. 1003 ¶¶88-89. However, the '907 patent also claimed various methods of administering that pharmaceutical composition. Ex. 1004, 21:41-23:13; Ex. 1002

¶55; Ex. 1003 ¶¶90-91. For example, claim 47 of the '907 patent recited a method of treating a patient for pain or inflammation comprising administering immediate-release esomeprazole and 200-600mg of delayed-release naproxen. Ex. 1004, 22:62-63.

### **c. Hochberg 2008**

Hochberg (Ex. 1012) is a poster entitled “A novel, single-tablet formulation that delivers immediate-release omeprazole followed by enteric-coated (EC) naproxen significantly reduces the incidence of gastric ulcers compared with EC naproxen alone: results of a prospective, randomised, double-blind, 6-month study including patients with OA and RA.” Hochberg was presented in Paris, France between June 11 and June 14, 2008, and is prior art to the '208 patent. Ex. 1012. Hochberg was not considered by the examiner in prosecution.

Hochberg disclosed that the PN tablet structure (immediate-release PPI, delayed-release naproxen) successfully delivers the PPI before absorption of the naproxen and that a PN formulation may be effective for reducing the risk of NSAID-induced gastric ulcers. *Id.*, Introduction; Ex. 1003 ¶¶96-97. Specifically, Figure 1 of Hochberg presented the pharmacokinetic profile of PN200, the same formulation claimed in the '208 patent, but with omeprazole instead of the closely-related PPI esomeprazole.<sup>6</sup> Ex. 1012, Introduction; Ex. 1003 ¶96.

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<sup>6</sup> Omeprazole is a racemic mixture, having equal parts S- and (less active) R-

Hochberg also disclosed that the PN formulation was effective in reducing the risk of NSAID-induced gastric ulcers. Ex. 1012, Results, Conclusions; Ex. 1002 ¶¶64-65; Ex. 1003 ¶97. Hochberg reported on a 6-month study of chronic NSAID users. Ex. 1012, Methods. Patients were randomized to either the PN formulation twice daily, or just delayed-release naproxen 500mg twice daily. *Id.* After six months, “[t]he incidence of gastric ulcers during the course of the study was significantly lower in the PN200 group compared with the EC naproxen group (8.3% vs. 29.4% for PN200 and EC naproxen, respectively).” *Id.*, Results; Ex. 1002 ¶¶64-65; Ex. 1003 ¶97. According to Hochberg, “[t]he PN formulation may offer a potential treatment option for patients at risk of NSAID-associated gastric ulcers or duodenal ulcers and may help address issues of persistence of use and compliance with gastroprotective agents.” Ex. 1012, Results.

**d. Goldstein 2008**

Goldstein (Ex. 1011) is an abstract entitled “A Single Tablet Multilayer Formulation of Enteric-Coated Naproxen Coupled with Non-Enteric-Coated OMEPRAZOLE Is Associated with a Significantly Reduced Incidence of Gastric Ulcers vs. Enteric-Coated Naproxen: A Prospective, Randomized, Double-Blind

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enantiomers. Ex. 1003 ¶119. Esomeprazole is the “S-” enantiomer of omeprazole. *Id.* at ¶120. Esomeprazole, like omeprazole, was long known as an effective inhibitor of gastric acid secretion. *Id.* ¶¶119-20; *see* Ex. 1007, 2:38-45.

Study.” Goldstein was published in the April 2008 edition of the journal Gastroenterology, and is prior art to the ’208 patent. Goldstein reported on the same clinical trial as Hochberg. Ex. 1011; Ex. 1002 ¶¶62-63; Ex. 1003 ¶94. Goldstein concluded that the PN formulation “may add to the treatment armamentarium for patients at risk of NSAID-associated GU, and address adherence to [NSAID-PPI] co-therapy.” Ex. 1011; Ex. 1002 ¶¶62-63, 65; Ex. 1003 ¶94.

**e. Hassan-Alin 2005**

Hassan-Alin (Ex. 1016) is an article entitled “Lack of Pharmacokinetic Interaction between Esomeprazole and the Nonsteroidal Anti-Inflammatory Drugs Naproxen and Rofecoxib in Healthy Subjects.” It was published in the Clinical Drug Investigation journal in 2005, and is prior art to the ’208 patent.

Hassan-Alin explained that NSAIDS “are widely used for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and a wide variety of other acute and chronic painful musculoskeletal disorders.” Ex. 1016, 2; Ex. 1003 ¶99. However, Hassan-Alin also noted that NSAIDs are associated with adverse events. Ex. 1016, 2; Ex. 1003 ¶99. Hassan-Alin further reported that “[e]someprazole, which confers a longer time with intragastric pH >4 than all other PPIs, is expected to be effective for the prevention of NSAID-associated ulcers.” Ex. 1016, 3; Ex. 1003 ¶100. Thus, Hassan-Alin disclosed that esomeprazole is expected to be widely used in

conjunction with NSAIDs. Ex. 1016, 7; Ex. 1003 ¶100. Hassan-Alin investigated whether esomeprazole's and naproxen's pharmacokinetics are affected by administration of esomeprazole and naproxen in combination. Hassan-Alin reported results of a randomized, three-way crossover trial. Ex. 1016, 3; Ex. 1003 ¶101. Subjects received naproxen 250mg twice daily, esomeprazole 40mg once daily, and the two together. Ex. 1016, 3; Ex. 1003 ¶101. PK measurements were taken on day seven. Ex. 1016, 3; Ex. 1003 ¶101.

Trial results demonstrated that naproxen has no “effect on the pharmacokinetics of esomeprazole, and esomeprazole does not have any effect on the pharmacokinetics of naproxen,” and thus the two could be taken together to prevent NSAID injury. Ex. 1016, 9; Ex. 1003 ¶102. These results were “in agreement with previous studies involving omeprazole, which showed no drug-drug interactions between omeprazole and three different NSAIDs,” including naproxen. Ex. 1016, 9; Ex. 1003 ¶102.

### **3. References Disclosing the PK/PD of Immediate-Release PPIs**

#### **a. Howden 2005**

Howden, C.W., “Review article: immediate-release proton-pump inhibitor therapy—potential advantages,” *Aliment Pharmacol. Ther.* 22(3):25-30 (2005) (Ex. 1006) (“Howden 2005”), is a review article published in 2005. Ex. 1003 ¶111. Howden 2005 was not considered by the examiner in prosecution. Howden

2005 summarized the PK/PD values of immediate-release omeprazole in the form of Zegerid<sup>®</sup> powder for oral suspension and the potential advantages over delayed-release PPIs. Ex. 1006, 1; Ex. 1003 ¶112. Howden 2005 reported that Zegerid<sup>®</sup> is available in two strengths, 40mg or 20mg. Ex. 1006, 2; Ex. 1003 ¶112; Ex. 1002 ¶57. Howden 2005 disclosed the PK data of  $T_{max}$ ,  $C_{max}$ , and AUC on day one and day seven of administration for Zegerid<sup>®</sup>. Ex. 1006, 2-3; Ex. 1003 ¶112. Howden 2005 also disclosed the results of PD studies with Zegerid<sup>®</sup>. Ex. 1006, 3-4; Ex. 1002 ¶57; Ex. 1003 ¶112. Howden 2005 disclosed that the mean AUC for immediate-release omeprazole after once-daily dosing of 20mg for one and seven days is 825 and 1446 ng\*hr/mL, respectively. Ex. 1006, 2; Ex. 1003 ¶112. For 40mg dosing, Howden 2005 reported that the corresponding values are 2228 and 4640 ng\*hr/mL, respectively. *Id.* Howden 2005 further disclosed that after seven days of once-daily dosing of 40mg of omeprazole, gastric pH remained above four for 77% of a 24-hour period. Ex. 1006, 3, Fig. 2; Ex. 1003 ¶112. Figure 2 of Howden 2005 showed that gastric pH drops significantly after about 15 hours with once-daily dosing. Ex. 1006, 3; Ex. 1003 ¶112. Finally, Howden 2005 showed that pH could be maintained over 4 for more than 80% of a 24-hour period at steady state. Ex. 1006, 4 Fig. 3; Ex. 1003 ¶112; Ex. 1002 ¶57.

**b. Zegerid<sup>®</sup> Label**

The Zegerid<sup>®</sup> (omeprazole) Powder for Oral Suspension Prescribing



Information (2004) (“Zegerid<sup>®</sup> Label”) (Ex. 1010) was published in 2004. The examiner did not consider the Zegerid<sup>®</sup> label in prosecution. A POSA would have been familiar with Zegerid<sup>®</sup> as an effective treatment available on the market as of the ’208 patent’s priority date. Ex. 1002 ¶60. According to the label, Zegerid<sup>®</sup> is indicated for treatment of duodenal ulcer, gastroesophageal reflux disease, and treatment and maintenance of erosive esophagitis. Ex. 1010, 10; Ex. 1002 ¶60; Ex. 1003 ¶114.

The Zegerid<sup>®</sup> label disclosed a powder for oral suspension that contains omeprazole as its active ingredient. Ex. 1010, 4; Ex. 1002 ¶61; Ex. 1003 ¶115. It also reported PK values following oral 20mg once-daily dosing for one and seven days. Ex. 1010, 5. In particular, the  $AUC_{(0-inf)}$ <sup>7</sup> for the dose on day one is 825 ng\*hr/mL, with a 72% coefficient of variation; the  $AUC_{(0-inf)}$  for the dose on day

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<sup>7</sup> “ $AUC_{(0-inf)}$ ” is the total amount of drug delivered by the dose in question. Ex. 1003 ¶116 n.3. A skilled artisan would understand that Zegerid<sup>®</sup>’s  $AUC_{(0-inf)}$  is useful to understand the AUC produced from hours zero to ten, and ten to twenty-four, because “absorption of omeprazole is rapid, with mean peak plasma levels of omeprazole occurring at around 30 minutes (range 10 to 90 minutes) after a single dose or repeated once-daily administration.” Ex. 1010, 4, Figures (showing little absorption by hour eight); Ex. 1003 ¶116 n.3.

seven is 1446 ng\*hr/mL, with a 61% coefficient of variation. *Id.*; Ex. 1003 ¶116. The label also reported clinical results of the effect of Zegerid® 20mg on intragastric pH on day seven, *i.e.*, PD values. Ex. 1010, 6-7; Ex. 1003 ¶117. Finally, the label further noted that “[r]epeated single daily oral doses of Zegerid 20 mg have produced nearly 100% inhibition of 24-hour integrated intragastric acidity in some subjects.” Ex. 1010, 7; Ex. 1003 ¶118.

#### **4. References Disclosing the Pharmacokinetics of Naproxen**

##### **a. EC-Naprosyn® Label**

The delayed-release naproxen 500mg in the formulation claimed in the '208 patent was sold publicly before the priority date as EC-Naprosyn®. The EC-Naprosyn® label (Ex. 1009), last revised before the priority date in January 2007,<sup>8</sup> disclosed various pharmacokinetic information about delayed-release naproxen 500mg. Specifically, the EC-Naprosyn® label reported that delayed-release naproxen 500mg twice daily provided a mean  $C_{\max}$  of 94.9 µg/mL and mean  $T_{\max}$  of 4 hours, with 18% and 39% coefficients of variation, respectively. Ex. 1009, 43. Thus, the  $C_{\max}$  range is 77.8 µg/mL to 112.0 µg/mL. Ex. 1003 ¶104. The label further stated that “[w]hen EC-NAPROSYN was given to fasted subjects,

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<sup>8</sup> The examiner did not consider any version of the EC-Naprosyn® label in prosecution.

peak plasma levels were attained about 4 to 6 hours following the first dose (range: 2 to 12 hours).” Ex. 1009, 3. Moreover, EC-Naprosyn® “dissolves primarily in the small intestine rather than in the stomach, so the absorption of the drug is delayed until the stomach is emptied.” *Id.*; Ex. 1003 ¶104. Finally, the label disclosed that different dosage forms of naproxen are “bioequivalent in terms of extent of absorption (AUC) and peak concentration ( $C_{\max}$ ),” although the products differ in their “pattern[s] of absorption.” Ex. 1009, 3; Ex. 1003 ¶104.

**b. Khosravan 2006**

Khosravan (Ex. 1017) is an article entitled “Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs.” It was published in the Journal of Clinical Pharmacology in 2006, two years before the ’208 patent’s priority date. The examiner did not consider Khosravan in prosecution. Khosravan studied whether febuxostat, a treatment for gout, has pharmacokinetic interactions with indomethacin and naproxen. Ex. 1017; Ex. 1003 ¶105. One arm of Khosravan’s randomized study involved administering naproxen 500mg twice daily at 8 am and 8 pm for seven days. Ex. 1017, 3; Ex. 1003 ¶105. On day seven, blood samples were taken to create a PK profile. Ex. 1017, 3-4; Ex. 1003 ¶105. Results showed that the naproxen 500mg AM dose had a  $C_{\max}$  of 93.7  $\mu\text{g/mL}$  ( $\pm 7.1$ ) and  $T_{\max}$  of 1.5 (range from 1.0 - 4.0). Ex. 1017, 9; Ex. 1003 ¶105. The PM dose had a  $C_{\max}$  of 86.9 ( $\pm 8.9$ ) and  $T_{\max}$  of 2.5 (range from 1.5 - 6.0). Ex. 1017, 9;

Ex. 1003 ¶105.

**c. Jung 1994**

Jung (Ex. 1018) is an article entitled “Steady-State Pharmacokinetics of Enteric-Coated Naproxen Tablets Compared with Standard Naproxen Tablets.” Jung was published in Clinical Therapeutics in 1994, prior to the earliest priority date for the ’208 patent. Ex. 1003 ¶106. The examiner did not consider Jung in prosecution. Jung reported the results of a clinical study involving dosing enteric-coated or standard naproxen tablets, 500mg, twice daily for seven days. Ex. 1018, 3; Ex. 1003 ¶107. Jung compared steady-state pharmacokinetics of the two naproxen formulations. Ex. 1018, 3. Jung reported that the “[m]ean time to maximum plasma concentration ( $T_{\max}$ ) was greater for EC naproxen than for standard naproxen (4.0 vs 1.9 hours),” while the “maximum observed plasma concentration ( $C_{\max}$ )” was 94.9  $\mu\text{g/mL}$ . *Id.*; Ex. 1003 ¶107. Jung further reported that “[a]n enteric-coated (EC) formulation of naproxen was developed to release naproxen at the pH level of the small intestine, where dissolution takes place.” Ex. 1018, 4; Ex. 1003 ¶107. The standard deviation for the  $T_{\max}$  of EC naproxen was  $\pm 1.6$ , and for  $C_{\max}$  was  $\pm 17.5$ . Ex. 1018, 8; Ex. 1003 ¶107.

**d. Davies 1997**

Davies (Ex. 1019) is an article entitled “Clinical Pharmacokinetics of Naproxen,” which was published in the journal Clinical Pharmacokinetics in 1997.

Davies was therefore published before the earliest priority date for the '208 patent. Ex. 1003 ¶108. The examiner did not consider Davies in prosecution. Davies compiled data on the clinical pharmacokinetics of naproxen and its metabolism. Ex. 1019, 1, 3-6 (Tbl. 1); Ex. 1003 ¶109. Davies reported that “[t]he area under the plasma concentration-time curve (AUC) of naproxen is linearly proportional to the dose for oral doses up to a total dose of 500mg.” Ex. 1019, 1; Ex. 1003 ¶109. Davies noted that “[m]ultiple dose administration yields absorption characteristics similar to those seen after single doses.” *Id.*, 2; Ex. 1003 ¶109.

**F. Ground 1: All Claims of the '208 Patent Are Anticipated by the '285 Patent**

**1. The Method of Claim 1 Is Anticipated by the '285 Patent**

**a. The '285 patent disclosed the drug formulation in claim 1**

The '285 patent disclosed all elements of the drug formulation recited in claim 1. The preamble of claim 1 of the '208 patent recites “[a] method for delivering a pharmaceutical composition to a patient in need thereof.”<sup>9</sup> Ex. 1001,

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<sup>9</sup> Petitioner previously filed an IPR petition seeking review of the related '698 patent, IPR2018-00894. The claims of the two patents are virtually identical, but for the preambles to independent claim 1. The '698 patent preamble recites “[a] method for treating osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis,” whereas the '208 patent recites “[a] method for delivering a pharmaceutical

46:33-34. The '285 patent taught administering a drug to treat osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; *i.e.*, to a patient in need thereof. Ex. 1005, claim 1, 5:20-29; Ex. 1002 ¶66; Ex. 1003 ¶¶84, 126; *see* Ex. 1004, claims 23, 52. Claim 1 of the '208 patent next recites “orally administering to the patient an AM unit dose form and, 10 hours ( $\pm 20\%$ ) later, a PM unit dose form.” Ex. 1001, 46:35-36. The '285 patent disclosed twice-daily oral administration of a unit dose form. Ex. 1005, Examples 9, 10; Ex. 1002 ¶67; Ex. 1003 ¶127. Any skilled artisan reading the '285 patent would understand that twice-daily administration means giving AM and PM doses, and that the PM dose could be 8-12 hours later than the AM dose. Ex. 1002 ¶67. Any argument by Patent Owner to the contrary would mean that Vimovo<sup>®</sup>, Patent Owners' product related to the '208 patent, would not be a commercial embodiment of the '208 patent. Vimovo<sup>®</sup>'s label, like the '285 patent, states that Vimovo<sup>®</sup> is administered “twice daily,” without reference to time of day. Ex. 1030, 1.

Claim 1 of the '208 patent further requires that the AM and PM unit dose forms each comprise 500mg of naproxen and 20mg of esomeprazole. Ex. 1001, 46:38-44. The '285 patent disclosed these elements as well, claiming a unit dose form combining naproxen and esomeprazole, wherein the amount of naproxen is between 200mg and 600mg and the amount of esomeprazole is between 5mg and composition to a patient in need thereof.”

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100mg. Ex. 1005, claims 2-4; Ex. 1002 ¶¶68; Ex. 1003 ¶128. While the ranges claimed in the '285 patent anticipate the doses in claim 1 of the '208 patent, skilled artisans would have particularly used naproxen 500mg and esomeprazole 20mg. Ex. 1002 ¶¶68. The '285 patent disclosed that 250 to 500mg of naproxen is preferred. Ex. 1003 ¶¶84, 128. Naproxen 500mg twice daily and esomeprazole 40mg once daily were known approved doses for treating arthritis and preventing gastric injury, respectively. Ex. 1002 ¶¶68. Esomeprazole 20mg was also available on the market to prevent gastric injury. *Id.* The doses are therefore anticipated. *See Abbvie Inc. v. Mathilda and Terence Kennedy Institute of Rheumatology Trust*, 764 F.3d 1366, 1379 (Fed. Cir. 2014) (“[W]hen a genus is so limited that a person of ordinary skill in the art can at once envisage each member of this limited class, a reference describing the genus anticipates every species within the genus.” (alteration, internal quotations, and citations omitted)); *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344-45 (Fed. Cir. 2012) (holding a narrower range anticipated by disclosure of a broader range, particularly where there is no “considerable difference” in the way the invention operates between the prior art and claimed ranges).

Finally, claim 1 of the '208 patent states that the esomeprazole “is released from said AM and PM unit dose forms at a pH of 0 or greater.” Ex. 1001, 46:46-47. The '285 patent disclosed a naproxen-esomeprazole tablet structure “wherein

at least a portion of said esomeprazole is not surrounded by an enteric coating.” Ex. 1005, 22:10-11; Ex. 1002 ¶69; Ex. 1003 ¶129; *see* Ex. 1005, Example 6 (disclosing a tablet including immediate-release omeprazole). A skilled artisan would understand that non-enteric coated esomeprazole would release immediately, “at a pH of 0 or greater.” Ex. 1002 ¶69. The ’285 patent therefore anticipates all elements of the drug formulation recited in claim 1 of the ’208 patent. Ex. 1002 ¶¶14-15, 71; Ex. 1003 ¶¶122-30.

**b. The PK/PD elements in claim 1 are inherent in the formulation**

The remainder of claim 1 recites various PK/PD values, which the AM and PM doses “target.”<sup>10</sup> *See* Ex. 1001, 46:48-47:9. The claimed PK/PD elements are simply characteristics of a known formulation and method of administration. They are therefore unpatentable as inherent in the prior art formulation and method of administration. Ex. 1003 ¶¶131-38.

“[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Schering Corp. v. Geneva Pharms., Inc.*, 339

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<sup>10</sup> Grounds 1 and 2 of this Petition do not depend on the Board adopting Petitioner’s proposed construction of “target.” The targeted PK/PD values are inherent in the formulation taught by the ’285 patent.



F.3d 1373, 1377 (Fed. Cir. 2003). “A reference includes an inherent characteristic if that characteristic is the ‘natural result’ flowing from the reference’s explicitly explicated limitations.” *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

Importantly, “one of the principles underlying the doctrine of inherent anticipation is to ensure that the public remains free to make, use or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate.” *SmithKline*, 403 F.3d at 1345-46 (quotation and alteration omitted). Therefore, “[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.” *Bristol-Myers*, 246 F.3d at 1376.

The PK/PD elements claimed by the ’208 patent are inherent in the formulation and method of administration disclosed by the ’285 patent. Given a certain formulation and method of administration, a drug will produce a certain PK/PD profile. Ex. 1003 ¶¶133-36. This naturally results from basic biological processes—the drug is absorbed, distributed, metabolized, and excreted. Ex. 1003 ¶¶134-35. Given the prior art PN formulation, the only parameters that determine its PK/PD profile are biological, and not technological, in nature. *Id.* The skilled artisan accordingly need not manipulate the PN formulation in any way to craft a

PK/PD profile—the PK/PD profile is simply a characteristic of the formulation. Ex. 1003 ¶¶133-35. The PK/PD profile recited in claim 1 is therefore an inherent property of the PN formulation and its method of administration.

Patent Owners may argue that the PK/PD elements are novel because they were not previously known. But that is irrelevant for inherency—“[i]nherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art.” *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). Rather, “the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Id.*

Patent Owners may also assert that the pharmacokinetics and pharmacodynamics of its formulation vary within and between patients. But the existence of intra- and inter-patient variation does not change the fact that the claimed PK/PD profiles naturally result from administration of the drug. Ex. 1003 ¶136. Within an individual patient, the same biological processes are at work, even if serum concentrations vary from administration to administration. Over repeated administration, resulting PK/PD values will cluster around a mean, with an amount of natural variation that is itself a property of the drug and formulation.

The same is true of variation between patients. While a sumo wrestler and ballerina may have different serum concentrations upon administration of the same

dose, the fact remains that the PK/PD effect of the drug in each patient is an inherent characteristic of the drug. Ex. 1003 ¶¶133-36. And across a population, which includes sumo wrestlers, ballerinas, and more typical patients, the PN formulation will have an average PK/PD profile. *Id.*

The Federal Circuit agrees. In *Santarus*, as here, the patent-in-suit claimed pharmacokinetic data of a proton pump inhibitor. The Federal Circuit held in *Santarus* that “[t]he initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations.” 694 F.3d at 1354.

The facts here more strongly support unpatentability than in *Santarus*. The ’285 patent undeniably disclosed and claims the same formulation claimed in the ’208 patent. The ’208 patent’s specification even refers to the ’907 patent, which shares a specification with the ’285 patent, as a formulation that is “effective” and “that produce[s] the desired pharmacodynamic response and pharmacokinetic values.” Ex. 1001, 1:30-37. The “inventors” of the ’208 patent performed no invention. As the specification reveals, they simply administered the known formulation according to a known method and claimed the resulting PK/PD values they measured. *Santarus*, 694 F.3d at 1354. Those values are inherent in the ’285 patent’s disclosure. Ex. 1003 ¶¶131-36; Ex. 1002 ¶¶15, 70-71.

Claim 1 of the '208 patent is therefore anticipated by the '285 patent. Ex. 1002 ¶¶71; Ex. 1003 ¶¶21, 137-38.

**2. The dependent claims are anticipated by the '285 patent**

None of the dependent claims add anything inventive to claim 1. All dependent claims recite routine elements disclosed in the '285 patent and well within the skilled artisan's knowledge. Ex. 1003 ¶24.

**a. Dependent claim 2 is anticipated**

Claim 2 recites “[t]he method according to claim 1, wherein the mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period is at least about 71%.” Ex. 1001, claim 2. For the same reasons the PD element in claim 1 is inherent in the formulation disclosed in the '285 patent, claim 2's slightly heightened PD requirement is also inherent in the '285 patent's formulation. Ex. 1003 ¶¶139-41; Ex. 1002 ¶¶73-74.

**b. Dependent claims 3 and 4 are anticipated**

Dependent claims 3 and 4, which depend from claim 1 and claim 2, respectively, further recite those methods “wherein said unit dose form is administered for a period of at least about 6 days” (claim 3) and “about 9 days” (claim 4). Ex. 1001, claims 3-4. The '285 patent expressly disclosed these elements. The '285 patent taught that the PN formulation is intended for long-term administration, to address chronic conditions like arthritis. *See, e.g.*, Ex. 1005,

1:50, 3:2-3, 3:14; Ex. 1002 ¶¶75-76; Ex. 1003 ¶144. Specifically, “[t]he present invention” of the ’285 patent is “a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs ... particularly during chronic treatment.” Ex. 1005, 3:11-14. The ’285 patent and other prior art further outlined trials in which treatment is provided for multi-day periods. Ex. 1003 ¶145; *see id.* ¶166. The ’285 patent therefore disclosed that the AM and PM unit dose forms are administered for at least about 6 days and at least about 9 days. Ex. 1003 ¶¶142-46.

**c. Dependent claims 5-7 are anticipated**

Dependent claim 5 recites: The method according to claim 1, wherein said AM and PM unit dose forms are each a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

- i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;
- ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and
- iii) said second layer comprises esomeprazole or a pharmaceutically acceptable salt thereof, wherein said esomeprazole or pharmaceutically acceptable salt thereof is released at a pH of from about 0 or greater.

Ex. 1001, 47:17-48:13; Ex. 1003 ¶147.

Dependent claim 6 recites: “The method according to claim 5, wherein said esomeprazole is released at a pH of from about 0 to about 2.” Ex. 1001, 48:14-15; Ex. 1003 ¶148.

Dependent claim 7 recites: “The method according to claim 5, wherein said multi-layer tablet is substantially free of sodium bicarbonate.” Ex. 1001, 48:17-18; Ex. 1003 ¶149.

As discussed earlier, the '285 patent disclosed a multilayer tablet having at least a core and first and second layers. Ex. 1005, Figs. 1, 2; Ex. 1003 ¶150. The '285 patent further disclosed that the core is naproxen or a salt thereof, surrounded by an enteric coating, and a second layer of immediate-release esomeprazole. Ex. 1005, Figs. 1, 2, 16:1-17:47 (Example 6), claim 1; Ex. 1003 ¶150. The '285 patent therefore taught each element of claim 5 of the '208 patent. Ex. 1003 ¶150; Ex. 1002 ¶¶77, 79.

The '285 patent also disclosed a combination dosage form with a second layer of immediate-release esomeprazole, which a POSA would understand to release esomeprazole at a pH of from about 0 to about 2. Ex. 1005, Figs. 1, 2, claim 1; Ex. 1003 ¶151. The '285 patent therefore taught the element of claim 6 of the '208 patent. Ex. 1003 ¶151; Ex. 1002 ¶¶78-79.

Finally, '285 patent disclosed a combination dosage form including an

immediate-release omeprazole layer without additional sodium bicarbonate. Ex. 1005, 16:1-17:47; Ex. 1003 ¶152; Ex. 1002 ¶80. The '285 patent therefore taught this additional element of claim 7 of the '208 patent. Ex. 1003 ¶152; Ex. 1002 ¶80. Accordingly, the '285 patent disclosed each of the elements recited in claims 5-7, and those claims therefore were anticipated by the '285 patent. Ex. 1003 ¶¶147-53.

**G. Ground 2: All Claims of the '208 Patent Are Obvious Over the '285 Patent**

Alternatively, if not anticipated, all claims of the '208 patent are obvious over the '285 patent. For the reasons explained *supra*, Section VI.F.1.a, all formulation limitations are disclosed by the '285 patent. Ex. 1003 ¶154. To the extent that the 20mg esomeprazole dose was not anticipated by the '285 patent, it is obvious—the '285 patent disclosed a dose range of 5mg to 100mg, with 40mg being preferred, and 20mg and 40mg esomeprazole doses were marketed in the prior art. Ex. 1043, 1044, Ex. 1003 ¶154. Skilled artisans also understood from Goldstein and Hochberg that 20mg of omeprazole—known to be less effective than esomeprazole—was effective in the same tablet structure taught by the '285 patent. Ex. 1011, 1012, 1043, Ex. 1003 ¶154. The claimed dose is therefore obvious. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362-69 (Fed. Cir. 2007) (finding a species to be obvious and routine experimentation over disclosure of a

“small” genus of 53 species, particularly where prior art suggested use of the species); *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003) (“A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art. ... [T]he existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious.”). The ’285 patent also taught all limitations recited in the dependent claims. *See supra*, Section VI.F.2; Ex. 1003 ¶¶157-74.

Skilled artisans thus would have found any limitation not expressly disclosed by the ’285 patent, including any formulation limitation, obvious over the ’285 patent. Moreover, the PK/PD elements are obvious over the ’285 patent for two reasons: (1) they are inherent in the formulation and method of administration disclosed in the ’285 patent, and (2) they are the result of routine testing any skilled artisan could have performed on the formulation disclosed in the ’285 patent.

Petitioners’ inherency argument is the same as in the anticipation section above. But Patent Owners will likely argue, as they did during prosecution of the parent ’698 patent, that inherency is limited in the obviousness context. While application of inherency law in the obviousness context calls for more caution, inherency doctrine itself is functionally the same. In the obviousness context, to be inherent, “the limitation at issue necessarily must be present, or the natural result of



the combination of elements explicitly disclosed by the prior art.” *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). That is not substantively different than inherency’s application under § 102. In both circumstances, to be inherent, an element must be the natural result or an inherent property of what was disclosed in the prior art—whether it was disclosed in one reference (anticipation) or in a combination (obviousness).

Patent Owners may focus on statements in *Par* that “the concept of inherency must be limited when applied to obviousness” and that “[a] party must ... meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis.” *Id.* at 1195-96. But *Par* simply states that inherency is limited when supplying a teaching in the art, such as a novel tablet feature or motivation to combine. That is not the purpose of inherency law, and that is not how Petitioners apply it here. As *Par* explained, § 103 inherency focuses on whether “the limitation at issue is the ‘natural result’ of the *combination* of prior art elements.” *Id.* at 1195 (emphasis added). Here, the PK/PD elements are the natural result of administering the prior art PN formulation, and are thus an inherent property of prior art disclosures.

Consistent with inherency law and its application here, the Federal Circuit has several times determined that PK/PD data are inherent in a drug formulation or method of administering the drug. In the *Santarus* case discussed above, the

Federal Circuit held that PK data of an obvious formulation were inherent in the formulation. *Santarus*, 694 F.3d at 1354. Likewise, in *In re Huai-Hung Kao*, 639 F.3d 1057 (Fed. Cir. 2011), the Federal Circuit considered claims to a drug having a greater maximum blood serum concentration when it is administered with food. In *Kao*, the Court concluded that “the claimed ‘food effect’ is an inherent property of [the drug] itself.” *Kao*, 639 F.3d at 1070. The Federal Circuit took care to explain that “[t]his is not a case where the Board relied on an unknown property of prior art for a *teaching*. Rather, [the prior art’s] express teachings render the claimed [drug] formulation obvious, and the claimed ‘food effect’ adds nothing of patentable consequence.” *Id.*

The Federal Circuit held inherent another claim limitation to increased bioavailability with food intake in *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 616 F.3d 1267 (Fed. Cir. 2010). The Federal Circuit reasoned that “the natural result of taking [the drug] with food is an increase in the bioavailability of the drug.” *King*, 616 F.3d at 1275. Indeed, the Court found, “the only steps required to increase [the drug’s] bioavailability are (1) ingesting [the drug] (2) with food. These steps are undeniably disclosed by the prior art. An increase in [the drug’s] bioavailability is, therefore, an inherent aspect of the prior art.” *Id.* at 1276. Even simpler here, the only step required to get the claimed PK/PD values is ingesting the claimed formulation. Because the claimed formulation is “undeniably disclosed

by the prior art,” the PK/PD values are, “therefore, an inherent aspect of the prior art.” *Id.*

Patent Owners will likely rely on *Par*, where the Federal Circuit vacated and remanded a district court’s finding that a food effect was inherent in an obvious drug formulation. But *Par* does not support Patent Owners—the Federal Circuit simply determined that the district court had incorrectly recited the law, and then stated the test for inherency in the obviousness context Petitioner cites above. When it turned to considering whether the claimed food effect was inherent, the Federal Circuit demurred, vacating and remanding for the district court to apply the correct legal test. *Par*, 773 F.3d at 1196.<sup>11</sup> The case law therefore is clear that the PK/PD elements recited in claim 1 are inherent in the PN formulation, irrespective of whether claim 1 is unpatentable under §§ 102 or 103.

Finally, even if the PK/PD elements are not inherent, they are obvious over the ’285 patent because they are the product of routine testing. One of the most

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<sup>11</sup> Patent Owners may cite *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356 (Fed. Cir. 2017). But unlike *Millennium*, where “[n]o expert testified that they foresaw, or expected, or would have intended, the reaction between bortezomib and mannitol, or that the resulting ester would have the long-sought properties and advantages,” *id.* at 1367, here the ’285 and ’907 patents taught the PN formulation and its use to treat arthritis while preventing gastric injury.

basic skills for a pharmacokineticist is the ability to test a drug and gather PK/PD data. Ex 1003 ¶155. It was therefore predictable and routine for a skilled artisan to gather PK/PD data. And that is all the inventors did here—they tested a known formulation according to a known method and recorded the trial results. No undue experimentation was needed—PK/PD data were certain to result from the routine testing, and the specific values recited in claim 1 were merely the data that did in fact result. *Id.*

Moreover, while the claimed PK/PD values were entirely expected, even if they were surprising, they were still obvious. This is not a case where a new formulation was developed and was found to have unexpected results or a new application. Rather, the PN formulation was known, it was used for the same purpose, and skilled artisans knew how to determine its PK/PD profile. Ex. 1002 ¶¶14-15, 44-52, 66-70; Ex. 1003 ¶156. Thus, skilled artisans could simply apply the known solution (run a routine clinical trial on a known formulation) to solve a known problem (lack of PK/PD data) with guaranteed success (the routine trial would produce PK/PD data). Ex. 1003 ¶¶155-58; Ex. 1002 ¶¶72, 82. That is obvious. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007) (a claim is obvious if “there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent’s claims”).

**H. Ground 3: All Claims of the '208 Patent Are Obvious Over the '285 patent in View of the EC-Naprosyn<sup>®</sup> Label and Howden 2005**

**1. The Method of Claim 1 Is Obvious Over the '285 patent in View of the EC-Naprosyn<sup>®</sup> Label and Howden 2005**

As discussed *supra*, Sections VI.F.1.a and VI.G, the '285 patent disclosed the formulation elements of claim 1. Even if not inherent in the '285 patent's disclosure, the remaining PK/PD elements are disclosed by the '285 patent in view of the EC-Naprosyn<sup>®</sup> label and Howden 2005. Ex. 1003 ¶¶23-24, 175.

The claims require the AM and PM unit dose forms to “target” claimed PK/PD values. Ex. 1001, 46:48-47:9. Based on its ordinary meaning and the disclosures in the specification, “target” means “with the goal of obtaining.” *See supra*, Section VI.D.1. The skilled artisan must therefore have the goal of obtaining the recited PK and PD elements.

The skilled artisan would have been motivated to obtain the recited PK/PD values because effective, marketed drugs shared these PK/PD values. To ensure efficacy, it would have been obvious to target the PK/PD values of prior art drugs known to be effective. Ex. 1002 ¶¶83-84; Ex. 1003 ¶¶175-77. EC-Naprosyn<sup>®</sup>, a delayed-release naproxen product identical to the naproxen formulation claimed in the '208 patent, was marketed and sold for fourteen years before the priority date. Ex. 1002 ¶83; Ex. 1008, 2. The pharmacokinetics of EC-Naprosyn<sup>®</sup> were well-characterized and fell within the ranges claimed in the '208 patent. Ex. 1003 ¶178.

Based on disclosures in the EC-Naprosyn<sup>®</sup> label and other references, a skilled artisan would have been motivated to target the claimed naproxen PK values because they were known to be effective. *Id.*

References discussing the Zegerid<sup>®</sup> product, which consisted of immediate-release omeprazole, and which was marketed and sold prior to 2008, disclosed that immediate-release omeprazole produced PK/PD values within the ranges claimed by the '208 patent. Ex. 1003 ¶¶111-18, 178. Knowing that Zegerid<sup>®</sup> was effective and much like the formulation disclosed in the '285 patent, a skilled artisan would target Zegerid<sup>®</sup>'s PK/PD data in connection with the claimed formulation. Ex. 1002 ¶¶83-84; Ex. 1003 ¶178.

**a. The EC-Naprosyn<sup>®</sup> label disclosed the PK elements for naproxen**

Claim 1 recites the following PK elements for naproxen:

- i) a pharmacokinetic (pk) profile for naproxen where:
  - a) for the AM dose of naproxen, the mean  $C_{max}$  is 86.2 µg/mL (±20%) and the median  $T_{max}$  is 3.0 hours (±20%); and
  - b) for the PM dose of naproxen, the mean  $C_{max}$  is 76.8 µg/mL (±20%) and the median  $T_{max}$  is 10 hours (±20%);

Ex. 1001, 46:48-55. Delayed-release naproxen was a well-known drug before the '208 patent's priority date, and its pharmacokinetics were well-characterized. Ex.

1003 ¶¶178-84, 200. In addition to naproxen having been on the market for decades, countless studies tested and reported its pharmacokinetics. *See, e.g.*, Ex. 1019, 3-6 (Table 1); Ex. 1018; Ex. 1003 ¶¶180-83. These prior art studies consistently found PK values corresponding to those recited in claim 1. *See, e.g.*, Ex. 1018, 3 (Abstract), 7-8; Ex. 1003 ¶¶180-83, 200.

To understand the pharmacokinetics of enteric-coated naproxen, the skilled artisan would look to the EC-Naprosyn<sup>®</sup> label. Like the '285 patent, the EC-Naprosyn<sup>®</sup> label disclosed administration of delayed-release naproxen 500mg twice daily. The label taught that EC-Naprosyn<sup>®</sup> 500mg twice daily has a mean C<sub>max</sub> of 94.9 µg/mL, with a coefficient of variation of ±18% (±17.1 µg/mL), disclosing a range of 77.8 µg/mL to 112.0 µg/mL. Ex. 1009, 4; Ex. 1003 ¶180. This range for EC-Naprosyn<sup>®</sup> corresponds to the ranges claimed in the '208 patent, as shown in Table 1 below.

Table 1: Comparison of Naproxen 500mg C<sub>max</sub> Data: '208 Patent Claims and EC- Naprosyn Label

	'208 Patent	EC-Naprosyn Label	Overlap
<b>AM dose</b>	69.0 - 103.4 µg/mL	77.8 - 112.0 µg/mL	Yes
<b>PM dose</b>	61.4 - 92.2 µg/mL	77.8 - 112.0 µg/mL	Yes

Because these ranges overlap, EC-Naprosyn<sup>®</sup> label disclosed the C<sub>max</sub> values claimed for naproxen. Ex. 1003 ¶¶180-81.

The EC-Naprosyn<sup>®</sup> label provided a single  $C_{\max}$  across both doses of EC-Naprosyn<sup>®</sup> 500mg, indicating that there is no relevant difference between AM and PM doses. Ex. 1003 ¶182. Likewise, Khosravan disclosed separate  $C_{\max}$  for the AM and PM doses of naproxen 500mg and finds no statistically significant difference. Ex. 1017, 9; Ex. 1003 ¶182. The mean  $C_{\max}$  for the AM dose of naproxen 500mg in Khosravan is  $93.7 \mu\text{g/mL} \pm 7.1 \mu\text{g/mL}$ , and the mean  $C_{\max}$  for the PM dose of naproxen 500mg is  $86.9 \mu\text{g/mL} \pm 8.9 \mu\text{g/mL}$ . Ex. 1017, 9. These AM and PM mean  $C_{\max}$  ranges overlap with the AM and PM mean  $C_{\max}$  ranges claimed in the '208 patent. Ex. 1003 ¶182. And while the differences in mean  $C_{\max}$  between the AM and PM doses are not statistically significant in either Khosravan or claim 1 of the '208 patent, the mean  $C_{\max}$  in both is slightly reduced in the PM dose. *Id.*

It would therefore have been obvious to target the claimed  $C_{\max}$  ranges for naproxen—the claimed formulation uses EC-Naprosyn<sup>®</sup>, and the EC-Naprosyn<sup>®</sup> label disclosed the claimed  $C_{\max}$  values. *Id.*

It also would have been obvious to target the recited  $T_{\max}$  values. The EC-Naprosyn<sup>®</sup> label disclosed a  $T_{\max}$  of 4 hours  $\pm 39\%$ , with a range of 2 to 12 hours. Ex. 1009, 3-4. The '208 patent recites a  $T_{\max}$  for the AM dose of 3.0 hours  $\pm 20\%$ , which is taught by the EC-Naprosyn<sup>®</sup> label. Ex. 1001, 46:50-53; Ex. 1009, 3-4; Ex. 1003 ¶183. The '208 patent also recites a  $T_{\max}$  for the PM dose of 10 hours



$\pm 20\%$ , which provided a range of 8 to 12 hours, and falls within the range of 2 to 12 hours disclosed in the EC-Naprosyn<sup>®</sup> label. Ex. 1009, 3. In addition, the  $T_{\max}$  for the naproxen PM dose appears to be an artifact in the Example 1 data to which Patent Owners drafted their claims. Ex. 1003 ¶¶183-84. The '208 patent does not refer to the  $T_{\max}$  for the naproxen PM dose as unexpected, and the Vimovo label states that Vimovo is bioequivalent to enteric-coated naproxen and that “peak plasma concentrations of naproxen are reached on average 3 hours following both the morning and the evening dose.” Ex. 1003 ¶184; Ex. 1030, 26. As Patent Owners simply used EC-Naprosyn<sup>®</sup> for the delayed-release naproxen in their formulation, there is nothing new or nonobvious about the  $T_{\max}$  of the PM dose Patent Owners recorded in routine PK testing. Ex. 1003 ¶184.

A skilled artisan would therefore have been motivated to target, and had a reasonable expectation of success in targeting, the naproxen PK values recited in claim 1. Ex. 1003 ¶177.

**b. Howden 2005 disclosed the PK elements for esomeprazole**

Claim 1 recites the following PK elements for esomeprazole:

ii) a pharmacokinetic (pk) profile for esomeprazole where:

a) for the AM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the AM dose is administered to 10 hours ( $\pm 20\%$ ) after the AM dose is administered ( $AUC_{0-10,am}$ ) is 1216

hr\*ng/mL ( $\pm 20\%$ ),

b) for the PM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the PM dose is administered to 14 hours ( $\pm 20\%$ ) after the PM dose is administered (AUC<sub>0-14,pm</sub>) is 919 hr\*ng/mL ( $\pm 20\%$ ), and

c) the total mean area under the plasma concentration-time curve for esomeprazole from when the AM dose is administered to 24 hours ( $\pm 20\%$ ) after the AM dose is administered (AUC<sub>0-24</sub>) is 2000 hr\*ng/mL ( $\pm 20\%$ );

Ex. 1001, 46:56-47:5. Skilled artisans would have been motivated to target these PK values because Zegerid<sup>®</sup>, an effective immediate-release omeprazole product marketed in the prior art, produced these PK values. Ex. 1003 ¶¶185-86. To target efficacy in developing the PN formulation, skilled artisans would have looked to Zegerid<sup>®</sup>'s disclosure of PK values known to be effective. Ex. 1003 ¶186.

Howden 2005 is a study of the marketed Zegerid<sup>®</sup> product. Citing the Zegerid<sup>®</sup> label, Howden 2005 disclosed that the mean AUC at steady state of Zegerid<sup>®</sup> 20mg is 1446 hr\*ng/mL. Ex. 1006, 2. The Zegerid<sup>®</sup> label further taught that the coefficient of variation for the mean AUC figure was 61%, yielding a range of 564 hr\*ng/mL to 2328 hr\*ng/mL. Ex. 1010, 5. All three AUC figures recited in claim 1 of the '208 patent fall within Howden 2005's disclosure, as shown below in Table 2. Ex. 1003 ¶¶186-87. In addition, the total mean AUC over

24 hours is the sum of the AUCs for the AM (hours 0-10) and PM (hours 11-24) doses, so Howden 2005 also taught the total mean AUC because it disclosed the mean AUCs for the AM and PM doses. *Id.*

Table 2: Comparison of PPI AUC Data: '208 Patent Claims and Howden 2005

	'208 Patent	Howden 2005	Overlap
<b>AM dose</b>	973 - 1459 hr*ng/mL	564 - 2328 hr*ng/mL	Yes
<b>PM dose</b>	735 - 1103 hr*ng/mL	564 - 2328 hr*ng/mL	Yes
<b>24 Hours</b>	1600 - 2400 hr*ng/mL	564 - 2328 hr*ng/mL; 1128 - 4656 hr*ng/mL	Yes

Howden 2005 therefore disclosed that the PK values claimed in the '208 patent are values at which esomeprazole would be effective. Ex. 1003 ¶¶187-88. For that reason, a skilled artisan would have been motivated by Howden 2005 to target the claimed PK values. Ex. 1003 ¶186. A skilled artisan would also have had a reasonable expectation of success in targeting the claimed esomeprazole PK values. “Target” means “with the goal of obtaining,” so the claims do not require achieving the claimed PK values. Rather, a reasonable expectation of success is established if the skilled artisan reasonably expects to succeed in setting the claimed PK values as a goal. It would be routine for a skilled artisan to target pharmacokinetics of prior effective drugs. Ex. 1003 ¶¶188-90. In this endeavor, a skilled artisan would routinely note that Howden 2005 and the Zegerid® label

disclosed PK data for an effective immediate-release PPI, and set these PK values as a goal. Ex. 1003 ¶¶186-88. A skilled artisan would therefore have been motivated to target the claimed esomeprazole PK values with a reasonable expectation of success. Ex. 1003 ¶¶188-89.

First, Patent Owners may argue that Zegerid<sup>®</sup> used omeprazole, whereas the claimed formulation uses esomeprazole as the PPI. But a skilled artisan would expect any effective AUC for omeprazole to also be effective for esomeprazole. Ex. 1003 ¶¶189-90. As of the priority date, a skilled artisan would have known that omeprazole is an equal mixture of R- and S-enantiomers, which are mirror images of the same compound. Ex. 1007, 1:50-62; Ex. 1003 ¶190. The prior art also taught that omeprazole's S-enantiomer, referred to as S-omeprazole, or esomeprazole, achieves an increased AUC compared to omeprazole upon administration of the same dose. *See* Ex. 1007, Abstract (S-omeprazole is the (-)- enantiomer of omeprazole). Accordingly, targeting an AUC associated with omeprazole's efficacy would cause a skilled artisan to arrive at an effective dose of esomeprazole. Ex. 1003 ¶190.

Second, Patent Owners may argue that Zegerid<sup>®</sup> included sodium bicarbonate and the claimed formulation is substantially free of bicarbonate. As an initial matter, this argument is relevant only to claim 7—none of the other claims exclude the presence of sodium bicarbonate. Regardless, Zegerid<sup>®</sup>'s inclusion of

sodium bicarbonate is irrelevant. Skilled artisans understood from Howden 2005 that Zegerid®'s mean AUC is effective. Ex. 1006, 2; Ex. 1003 ¶191. The bicarbonate in Zegerid® served only to enhance omeprazole's stability in the stomach—it does not change omeprazole's mechanism of action or the plasma concentrations at which omeprazole is effective. Ex. 1006, 3-4; Ex. 1003 ¶191. Zegerid®'s mean AUC therefore serves as a reliable target—the skilled artisan would know that achieving that mean AUC would yield an effective drug. Ex. 1007, 2:14-36; Ex. 1003 ¶191.

Finally, Patent Owners may argue that Zegerid® was administered once daily, whereas the '208 patent claims twice-daily administration. This difference is immaterial because skilled artisans would not expect interaction between the AM and PM doses. At steady state, each successive dose has approximately the same pharmacokinetic effect as the last. Ex. 1003 ¶192. A skilled artisan would thus be able to use the AUC produced by a once-daily dose of Zegerid® as a target for both the AM and PM doses of the prior art PN formulation. Ex. 1003 ¶¶35-37, 192. Additionally, omeprazole and esomeprazole exhibit nonlinear pharmacokinetics wherein increasing the dose increases AUC disproportionately—*i.e.*, a 100% dose increase yields a more than 100% AUC increase. Ex. 1028, 6; Ex. 1003 ¶192. Therefore, a skilled artisan could routinely predict the AUC of twice-daily dosing from knowledge of the AUC produced by once-daily dosing. Ex. 1003 ¶192.

Accordingly, the esomeprazole PK elements recited in claim 1 are obvious in light of Howden 2005. Ex. 1003 ¶¶185-93.

**c. Howden 2005 disclosed the PD element**

Claim 1 of the '208 patent recites the following PD element: “the AM and PM unit dose forms further target a mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period after reaching steady state that is at least about 60%.” Ex. 1001, 47:6-9; Ex. 1003, ¶194.

Howden 2005 disclosed this element. Howden 2005 referred to a study by Goldlust in which subjects were administered AM doses of Zegerid® for seven days, and then received morning and bedtime doses of Zegerid® on the eighth day. Ex. 1006 at 4. Howden 2005 reported that “[t]he addition of the bedtime dose maintained intragastric pH above 4 for significantly longer than the morning dose alone, over both the nocturnal and entire 24-h period (Figure 3).” *Id.* Figure 3 showed that intragastric pH remained above 4.0 for about 80% of the time in a 24-hour period. *Id.*; Ex. 1003 ¶¶195-96. This disclosure of approximately 80% easily meets the “at least about 60%” requirement of claim 1. Ex. 1003 ¶196. Howden 2005 further taught that, in another study, 40mg of Zegerid® once daily—the same total daily dose as the claimed method—“kept intragastric pH above 4 for 77% (18.6 h) of the 24-h recording period.” Ex. 1006, 3. Because Zegerid® was known to be effective, skilled artisans would target the pharmacodynamic response in

patients administered Zegerid® when developing another immediate-release PPI formulation. Ex. 1003 ¶197. Howden 2005 therefore taught the PD element of claim 1. Ex. 1003 ¶198.

As the prior art disclosed all elements of claim 1, claim 1 is obvious over the '285 patent in view of the EC-Naprosyn® label and Howden 2005. Ex. 1002 ¶¶81-85; Ex. 1003 ¶¶23-24, 199-203.

**2. The dependent claims are obvious over the '285 patent in view of the EC-Naprosyn® label and Howden 2005**

**a. Dependent claim 2 is obvious**

Claim 2 recites “[t]he method according to claim 1, wherein the mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period is at least about 71%.” Ex. 1001, 47:10-12. As discussed above, Howden 2005 disclosed that twice-daily administration of Zegerid® 20mg achieves a mean % time at which intragastric pH remains at 4.0 or greater in a 24-hour period of about 80%. Ex. 1006, 4. Howden 2005 also taught that Zegerid® 40mg daily produces a figure of 77%. Ex. 1006, 3. Both of these percentages are well above the claimed percentage of “at least about 71%.” Therefore, if the PD element of claim 1 is met, claim 2 is obvious. Ex. 1003 ¶¶204-205; Ex. 1002 ¶¶86-87.

**b. Dependent claims 3 and 4 are obvious**

As explained *supra*, Section VI.F.2.b, the '285 patent taught administration of the claimed formulation for about 6 and about 9 days, as recited in claims 3 and

4 of the '208 patent. Ex. 1005, 1:50, 3:2-3, 3:14; Ex. 1002 ¶¶75-76. Further, studies described in '285 patent and other prior art also disclose administration for “about 6 days” and “about 9 days.” Ex. 1003 ¶¶206-10. Dependent claims 3 and 4 are therefore obvious. Ex. 1002 ¶88; Ex. 1003 ¶211.

**c. Dependent claims 5-7 are obvious**

For the reasons stated *supra*, Section VI.F.2.c, the '285 patent disclosed all elements recited in dependent claims 5-7. Dependent claims 5-7 are therefore obvious over the '285 patent in view of the EC-Naprosyn<sup>®</sup> label and Howden 2005. Ex. 1002 ¶¶89-90; Ex. 1003 ¶¶212-18.

**I. No Secondary Considerations Support Nonobviousness**

To counter the evidence of obviousness set forth in Grounds 2 and 3, Patent Owners may try to rely on secondary evidence. While any such evidence would be “insufficient” to overcome “such a strong showing of obviousness” here, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007), petitioner nonetheless preliminarily addresses certain expected theories, reserving the right to respond to any arguments asserted in this proceeding.

**1. There Are No Unexpected Results**

The methods claimed in the '208 patent recite administering a unit dose form comprising 500mg naproxen and 20mg immediate-release esomeprazole to “target” particular naproxen and esomeprazole PK/PD values. Ex. 1003 ¶221. As



discussed *supra*, Section VI.F.1.a, prior art such as the '285 patent, the '907 patent, Goldstein, Hochberg, and Hassan-Alin disclosed, described, and/or claimed a combination unit dose form comprising naproxen and an immediate-release PPI, including esomeprazole. The prior art also disclosed methods of administering the claimed unit dose form. *See, e.g.*, Ex. 1005, 3:11-20; Ex. 1002 ¶¶47, 55, 66-72. In addition, the prior art disclosed the PK/PD values claimed in the '208 patent as being targets for the claimed unit dose form. *See supra*, Section VI.H.1.

From these references, a POSA would have known that prior art dosage forms were effective and yielded the PK/PD values recited in the claims of the '208 patent. Ex. 1002 ¶92; *see* Ex. 1003 ¶¶103-18. A POSA would also have known how to administer the formulation recited in the claims of the '208 patent because administering a dosage form was taught in at least the '285 and '907 patents. *Id.*; *see* Ex. 1003 ¶¶84, 90-91. Thus, the PK/PD values targeted by administering the claimed formulation are not unexpected results because both the administered formulation and the results following from its dosing were disclosed and/or claimed in the prior art. Ex. 1003 ¶¶219-25.

In addition, the claimed targeted PK/PD values could not have been unexpected because they are simply the inherent result of the body's metabolic processes acting on the known dosage form administered under the known method. Ex. 1003 ¶¶133-36; Ex. 1002 ¶92.

Moreover, in prosecution of the parent '698 patent, the applicants contended that the claimed invention was superior to the combination of naproxen and famotidine (an H2-receptor blocker, which is a different drug class than PPIs, like esomeprazole). Ex. 1003 ¶¶226-27; Ex. 1002 ¶93. But, contrary to the applicants' assertion, this is not an unexpected result. As of the priority date for the '208 patent, H2-receptor blockers (like famotidine) and PPIs (like esomeprazole) were known to suppress gastric acid secretion through different mechanisms. Ex. 1014, 5-8; Ex. 1002 ¶93; Ex. 1003 ¶227. A POSA would have known, in addition, that PPIs provide greater acid suppression over a 24-hour period than H2-receptor blockers because PPIs are longer-acting, and H2-receptor blockers are shorter-acting. Ex. 1004, 1:41-58; Ex. 1014, 5, 8; *see generally* Ex. 1015; Ex. 1002 ¶93. The result claimed in the '208 patent would therefore have been expected by a POSA.

However, even if the result claimed in the '208 patent were unexpected relative to the '907 patent, it would not be sufficient to support patentability. It is well understood that unexpected results must be established relative to the closest prior art. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). The naproxen/famotidine combination is not the closest prior art to the claims of the '208 patent. Rather, as described above, the '285 and '907 patents claimed a combined dosage form of esomeprazole and naproxen and

disclosed a method of administering the dosage form. Ex. 1002 ¶¶94; Ex. 1003 ¶228. Patent Owners must therefore show that any alleged unexpected results are unexpected relative to the disclosures in the '285 and '907 patents. Ex. 1002 ¶¶93-94; Ex. 1003 ¶228.

## **2. The '208 Patent Satisfied No Long-Felt But Unmet Need**

The '208 patent satisfied no long-felt but unmet need because any long-felt but unmet need was satisfied by the naproxen-esomeprazole formulation disclosed in the '285 and '907 patents. Ex. 1002 ¶96. While NSAID-induced gastric injury was a side effect of long-term NSAID use, seven years before the '208 patent's priority date, the '285 and '907 patents disclosed administration of a naproxen-esomeprazole formulation that raised gastric pH to safe levels before release of the NSAID. *See supra*, Section VI.F.1.a. As the previously disclosed method of administration provided efficacy, the '285 and '907 patents met any long-felt but unmet need for a safer NSAID. Ex. 1002 ¶96.

## **3. There Was No Industry Skepticism**

Nor will Patent Owners be able to establish industry skepticism. As the claimed formulation and method of administration were expressly disclosed in the '285 patent, any skepticism would have to be directed to the specific PK/PD values claimed in the '208 patent. Any skepticism would further be disparaging the same invention taught by the '285 patent. Ex. 1002 ¶95. Even if Patent Owners can show

that others considered alternative formulations to be superior to the PN formulation disclosed in the '285 patent, it would not change the fact that the formulation and method of administration were known in the prior art.

#### **4. Copying by Generic Drug Makers Is Irrelevant**

Finally, the Patentees may argue that Petitioner and other generic drug companies seek to copy the invention. But “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

### **VII. CONCLUSION**

For the reasons discussed above, petitioner requests that the Board institute an *inter partes* review and determine that all claims (1-7) of the '208 patent be canceled as unpatentable.

Respectfully submitted,

Date: July 2, 2018

/s/ Alan Pollack  
Alan H. Pollack

*Counsel for Petitioner Dr. Reddy's  
Laboratories Inc.*

**CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME  
LIMITATION**

This Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1) because this Petition contains 13,952 words, as determined by the word-count function of Microsoft Word, excluding the parts of the Petition exempted by Rule (*i.e.*, a table of contents, a table of authorities, mandatory notices under 37 C.F.R. § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing).

Date: July 2, 2018

/s/ Alan Pollack  
Alan H. Pollack

*Counsel for Petitioner Dr. Reddy's  
Laboratories Inc.*

## **CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **Petition for *Inter Partes* Review of U.S. Patent No. 9,393,208** by Federal Express next business day delivery on this day on the Patent Owners' correspondence address of record for the subject patent as follows:

Steven L. Highlander  
Parker Highlander PLLC  
1120 South Capital of Texas Highway Bldg. 1, Suite 200  
Austin, TX 78746

Courtesy copies of the **Petition for *Inter Partes* Review of U.S. Patent No. 9,393,208** have been sent by Federal Express next business day delivery on this day to:

(1) Patent Owner's:

Horizon Pharma USA, Inc. 150 South Saunders Road Lake Forest, IL 60045	Pozen Inc. 8310 Bandford Way Raleigh, NC 27615
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Date: July 2, 2018

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