United States District Court,
S.D. New York.

In re OMEPRAZOLE PATENT LITIGATION.

Astrazeneca AB, et al,
Plaintiffs.
v.
Mylan Laboratories Inc., et al,
Defendants.
Astrazeneca AB, et al,
Plaintiffs.
v.
Laboratorios Dr. Esteve, S.A., et al,
Defendants.
Astrazeneca AB, et al,
Plaintiffs.
v.
Lek Pharmaceutical and Chemical Co., D.D., et al,
Defendants.
Astrazeneca AB, et al,
Plaintiffs.
v.
Apotex Corp., et al,
Defendants.
Astrazeneca AB, et al,
Plaintiffs.
v.
Impax Laboratories, Inc,
Defendant.

No. M-21-81 (BSJ)

May 31, 2007.

Background: Owner of patents for pioneer drug to treat gastrointestinal disorders brought action against pharmaceutical companies, alleging infringement.

Holdings: Following bench trial, the District Court, Jones, J., held that:
(1) two companies did not infringe asserted claims of patents;
(2) two companies literally infringed asserted claims of patents in part;
(3) patents were not invalid for failing to satisfy written description, enablement or best mode requirements;
(4) patents were not invalid for being in public use or lack of novelty; and
(5) patents were not invalid for obviousness.

Judgment for plaintiffs in part and defendants in part.

4,786,505, 4,853,230. Infringed in Part.

Errol B. Taylor, Fred Zullow, Jack Griem, Milbank, Tweed, Hadley & McCloy for Astrazaneca.

Robert S. Silver, Allan H. Fried, William C. Youngblood, Marc Bassler, Alan H. Bernstein, Lynne Terrebonne, Bruce J. Chasan, Ceasar, Rivise, Bernstein, Cohen & Pokotilow, Karen J. Bernstein, Pryor, Cashman, Sherman & Flynn, LLP, for Apotex.

Jeffrey J. Toney, John North, Sutherland, Asbill & Brennan, LLP, Steven J. Lee, Thomas J. Meloro, Anthony Giaccio, Kenyon & Kenyon, for Impax.

Douglass C. Hochstetler, Beth D. Jacob, Joanne Kokoski, Schiff, Hardin & Waite, Michael Muczynski, Marshall Gerstein & Borum, Joseph Angland, Heller Ehrmann LLP, for Lek.

Mark A. Pacella, James H. Wallace, Jr., Wiley, Rein & Fielding, for Mylan & Esteve.

Opinion & Order

BARBARA S. JONES, District Judge.

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INTRODUCTION FN1

FN1. The following citation forms are used:

Trial Testimony:	"[Witness Name] Tr. [Page:Line]"
Trial Exhibits:	Astra: "PSWTX ___"
	Mylan/Esteve: "M/EX ___"
	Lek: "LEKTX ___"
	Apotex: "APO ___"
	Impax: "ITX ___"
Deposition Testimony:	"[Witness Name] Dep. Tr. [Page:Line]"
Patents:	"[Exhibit Number] [Column:Line]"

These patent cases relate to the drug Prilosec(R), one of the most widely prescribed medicines in history. Plaintiffs AstraZeneca AB, Aktiebolaget Hassle, KBI-E, Inc., KBI Inc., and AstraZeneca, LP (collectively "Plaintiffs") assert certain claims of two patents which cover the Prilosec(R) formulation, U.S. Patent Numbers 4,786,505 and 4,853,230 (the "'505 Patent" and the "'230 Patent"), as being infringed by the following defendant pharmaceutical corporations: Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (together "Mylan"), Esteve Quimica, S.A. and Laboratorios Dr. Esteve, S.A. (together "Esteve"), Apotex Corp., Apotex Inc., and Torpharm Inc. (together "Apotex"), Lek Pharmaceutical and Chemical Company D.D. and Lek USA, Inc. (together "Lek"), and Impax Laboratories, Inc. ("Impax") (collectively "Second Wave Defendants"). FN2 Pursuant to 28 U.S.C. s. 1407 (2000), the Judicial Panel on Multidistrict Litigation consolidated the patent infringement suits for pre-trial purposes before this court. The actions against

Apotex and Impax were remanded to their original courts upon completion of pre-trial matters, and were subsequently transferred back to this Court for a consolidated trial with the other Second Wave Defendants.

FN2. A trial of the first wave of defendants accused of infringement under the Hatch-Waxman Act was held from December through June of 2003. *See* Astra Aktiebolag v. Andrx Pharm., Inc., 222 F.Supp.2d 423 (2002), *aff'd,* 84 Fed.Appx. 76 (2003). The defendants in that litigation are referred to as the "First Wave Defendants," and the action itself is referred to as the "First Wave Litigation."

The case was tried to the Court sitting without a jury for 42 trial days, starting April 3, 2006 and ending June 14, 2006. The court has considered weeks of trial testimony, volumes of depositions, thousands of exhibits, pre-trial briefings, and post-trial findings of fact and conclusions of law submitted by all parties. The Court has made determinations as to the relevance and materiality of the evidence and assessed the credibility of each witness. Upon the record before the Court, pursuant to Federal Rule of Civil Procedure 52(a), the Court finds the following facts to have been proven and sets forth its conclusions of law.

For the reasons stated below, the Court finds the following: Defendants Mylan and Esteve do not infringe the asserted claims of the '505 and '230 Patents. Defendant Lek does not infringe the asserted claims of the '505 and ' 230 Patents. Defendant Apotex literally infringes claims 1, 5, 6, and 10 of the '505 Patent, and claims 1, 6, 7, and 13 of the '230 Patent. Defendant Impax literally infringes claims 1, 5, 6, 8, and 10 of the '505 Patent, and claims 1, 6, 7, 10, and 13 of the '230 Patent. The asserted claims of the '505 and '230 Patents are valid.

I. *The Parties*

Plaintiff AstraZeneca AB ("Astra") is a company organized and existing under the laws of Sweden, having its principal place of business at Sodertalje, Sweden. Plaintiff Aktiebolaget Hassle ("Hassle") is a company organized and existing under the laws of Sweden, having its principal place of business at Molndal, Sweden. Plaintiff KBI-E Inc. ("KBI-E") is a Delaware corporation, having its principal place of business at Wilmington, Delaware. Plaintiff KBI Inc. ("KBI") is a Delaware corporation having its principal place of business at Whitehouse Station, New Jersey. KBI and KBI-E have exclusive rights in the United States under the patents-in-suit. Plaintiff Astra Pharmaceuticals, L.P. is a limited partnership organized under the laws of Delaware, having its principal place of business at Wayne, Pennsylvania. Plaintiff AstraZeneca, LP is a limited partnership organized under the laws of Delaware having its principal place of business at Wayne Pennsylvania. AstraZeneca, LP holds an approved New Drug Application from the United States Food and Drug Administration ("FDA") for an omeprazole formulation which it sells under the name Prilosec(R). (Second Am. Compl. Against Mylan para.para. 2-7; Compl. Against Esteve para.para. 2-7; Second Am. Compl. Against Lek para.para. 2-7; Second Am. Compl. Against Apotex para.para. 2-7; Second Am. Compl. Against Impax para.para. 2-6.) Plaintiffs are referred to collectively as "Astra."

Defendant Mylan Laboratories Inc. is a corporation organized under the laws of Pennsylvania having its principal place of business at Pittsburgh, Pennsylvania. Defendant Mylan Pharmaceuticals Inc. is a corporation organized under the laws of West Virginia having its principal place of business in Morgantown, West Virginia, and is registered as a foreign business in the State of New York. Mylan Pharmaceuticals is a wholly-owned subsidiary of Mylan Laboratories. (Second Am. Compl. Against Mylan para.para. 8-11; Mylan's Answer, Affirmative Defenses, and Countercls. to Pls.' Second Am. Compl. ("Mylan's Answer & Countercls. to Second Am. Compl.") para.para. 8-11.)

Defendant Esteve Quimica, S.A. is a company existing under the laws of Spain, with its principal place of business in Barcelona, Spain. Defendant Laboratorios Dr. Esteve, S.A. is a company existing under the laws of Spain, with its principal place of business at Barcelona, Spain. Esteve Quimica and Laboratorios Dr.

Esteve have entered into agreements, collaborated, and engaged in activities with Mylan Pharmaceuticals relating to the product that is the subject of Mylan Pharmaceuticals' ANDA No. 75-876. (Compl. Against Esteve para.para. 8, 10, 15; Defendants' Answer, Affirmative Defenses, and Countercls. to Pls.' Compl. ("Esteve's Answer & Countercls. to Compl.") para.para. 8, 10, 15.)

Defendant Lek Pharmaceuticals d.d., formerly known as Lek Pharmaceutical and Chemical Company d.d., is a corporation organized under the laws of Slovenia, having its principal place of business at Ljubljana, Verovskova, Slovenia. Defendant Lek Services, Inc., formerly known as Lek USA, is a corporation organized under the laws of Delaware, having its principal place of business at Wilmington, North Carolina. FN3 (Second Am. Compl. Against Lek para.para. 8-9; Lek's Am. Answer to Second Am. Compl. and Countercls. ("Lek Answer & Countercls. to Second Am. Compl.") para.para. 8-9.)

FN3. Lek was acquired during the pendency of this litigation by Novartis and became part of Sandoz, an affiliate of Novartis. (Decl. of Peter Rupprecht at para.para. 4, 6.)

Defendant Apotex Corp. is a Delaware corporation with a place of business in Vernon Hills, Illinois. Defendant Apotex, Inc. is a Canadian corporation with a place of business in Weston, Ontario, Canada. Apotex Corp. is a wholly-owned subsidiary of Apotex, Inc. Defendant TorPharm, Inc. is a Canadian corporation with its principal place of business in Etobicoke, Ontario, Canada. (Second Am. Compl Against Apotex para.para. 8-11; Apotex's Answer, Affirmative Defenses and Countercls. to Pls.' Second Am. Compl. ("Apotex Answer & Countercls. to Second Am. Compl.") para.para. 8-11.) Together they comprise Defendant "Apotex".

Defendant Impax Laboratories, Inc. is a Delaware corporation, having its principal place of business in Hayward, California. (Second Am. Compl. Against Impax para. 7; Impax's Answer and Countercls. to Second Am. Compl. para. 7.)

II. *The Patents-In-Suit*

Omeprazole is a compound that inhibits gastric acid secretion and can be used for the treatment of gastric and duodenal ulcers. (PSWTX 1A 1:17-1:20.) It belongs to a class of medicines called "proton pump inhibitors." (Langer Tr. 6969:1.) Omeprazole is very difficult to formulate. In particular, it is exceptionally acid labile, which means it is susceptible to degradation and/or transformation in acid-reacting and neutral media. (PSWTX 1A 1:21-1:24.) It is also sensitive to heat, moisture, organic solvents, and light. (Langer Tr. 6970:19-25; PSWTX 2821-4.) An oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in the stomach, in order to reach the proximal part of the small intestine, where it is effective, without degradation. (PSWTX 11:35-1:39.) Due to the stability properties of omeprazole, developing a formula or dosage form that would remain stable both in the body and on the shelf, and deliver the compound to the proper site of the body, proved to be formidable.

A group of Astra scientists set out to develop an oral dosage form of omeprazole and its related compounds, and their work ultimately culminated in the patents at issue in this case. (PSWTX 1A; PSWTX 2A.) Drs. Ake Pilbrant and Kurt Lovgren were a part of that team, and they are two of the named inventors on Astra's '505 and '230 Patents. (PSWTX 1A; PSWTX 2A.) Astra made and tested many different formulations before creating an oral formulation that included omeprazole with an alkaline reacting compound ("ARC") in the core, a water soluble subcoat, and an enteric coating. (Langer Tr. 6971:1-6975:4; PSWTX 2821-4.) After clinical trials of this formulation, Plaintiffs filed patent applications for their omeprazole formulation.

On April 20, 1987, Plaintiffs filed the patent application that led to the ' 505 Patent with the United States Patent and Trademark Office ("USPTO"). FN4 This application claims priority on a U.K. patent application

filed April 30, 1986. (PSWTX 1A.)

FN4. The '505 Patent expired on April 20, 2007. Astra received a six-month period of market exclusivity pursuant to 21 U.S.C. s. 355a(c)(e)(B) for conducting pediatric testing of its drug upon the FDA's request. This six-month period of "pediatric exclusivity" is set to expire on October 20, 2007. (*See* Order Denying Motion to Dismiss for Lack of Subject Matter Jurisdiction, May 25, 2007.)

The '505 Patent discloses particular oral pharmaceutical formulations for the omeprazole compound,FN5 processes for making those formulations, and methods of treating gastrointestinal disease using those formulations. (PSWTX 1A 1:5-11.) The ' 505 Patent also describes some of the previously mentioned difficulties with making an oral omeprazole formulation. (PSWTX 1A 1:21-34.) For example, omeprazole degrades rapidly in the stomach, unless it is protected from contact with the acidic gastric juice. (PSWTX 1A 1:17-56.) The omeprazole compound is also sensitive to moisture and organic solvents. (PSWTX 1A 1:33-34.) Despite this sensitivity,omeprazole is not very soluble in the water found in bodily fluids. Consequently, the drug is difficult to handle and formulate. (Langer Tr. 6970:19-25; PSWTX 2821-4.) Thus, the ' 505 Patent inventors were faced with the problems of developing an oral pharmaceutical formulation of omeprazole that had "good resistance towards gastric juice as well as good stability during long-term storage." (PSWTX 1A 1:40-2:13; 14:64-16:40.)

FN5. The term of Plaintiffs' basic omeprazole patent covering the chemical formula for omeprazole and its administration for gastric acid inhibition, U.S. Patent No. 4,255,431 (the "'431 patent") expired on October 5, 2001.

The '505 Patent claims a new formulation that, among other things, permits the omeprazole drug molecule to pass unharmed through the stomach's acidic environment and to dissolve rapidly in the upper portion of the small intestine. (PSWTX 1A 3:14-18; 5:19-58.) The inventors' solution to omeprazole's multiple stability problems was a formulation that comprises (1) a core region containing omeprazole and an alkaline reacting compound ("ARC") or an alkaline salt of omeprazole optionally mixed with an ARC; (2) an inert subcoating that is water soluble or rapidly disintegrating in water and disposed on the core region; and (3) an outer enteric layer disposed on the subcoating. (*See, e.g.,* PSWTX 1A 3:42-54.) As a result, the omeprazole in the patented formulation is available for absorption into the bloodstream, while possessing superior stability. (PSWTX 1A 3:14-20.)

Claim 1 of the '505 Patent specifies a pharmaceutical product that includes three elements:

1. An oral pharmaceutical preparation comprising

(a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;

(b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds; and

(c) an outer layer disposed on said subcoating comprising an enteric coating.

(PSWTX 1A 16:42-54.)

Claims 2 through 9, and 11 through 13, are product claims that depend on claim 1, but then add other features, such as the reference to microenvironment and pH in claim 5:

5. A preparation according to claim 1 wherein the alkaline core comprises omeprazole and pH-buffering alkaline compound rendering to the micro-environment of omeprazole a pH of 7-12.

(PSWTX 1A 16:65-68.)

In contrast to product claims like claim 1, claim 14 is a process claim. Claim 14 specifies:

14. A process for the preparation of an oral pharmaceutical preparation containing omeprazole, comprising

(a) preparing a core comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;

(b) coating the core with one or more layers of an inert subcoating material selected from among tablet excipients and polymeric film-forming compounds to form a subcoated core; and

(c) coating the subcoated core with an enteric coating.

(PSWTX 1A 18:13-25.)

Like the '505 Patent, the '230 Patent relates to particular oral pharmaceutical formulations of omeprazole, processes for making formulations, and methods of treating gastrointestinal disease using those formulations.FN6 (PSWTX 2A 1:5-12.) The ' 230 Patent differs from the ' 505 Patent in that the ' 230 Patent covers not just omeprazole but acid-labile pharmaceutically active substances such as a certain class of benzimidazole compounds including omeprazole, and their salts. (PSWTX 2A 1:28-2:33.)

FN6. The '230 Patent also expired on April 20, 2007. But like the '505 Patent, Astra also received a six-month period of market exclusivity for the '230 patent for conducting FDA-requested pediatric studies. The '230 Patent's period of "pediatric exclusivity" is set to expire on October 20, 2007. (*See* Order Denying Motion to Dismiss for Lack of Subject Matter Jurisdiction, May 25, 2007.)

The '230 Patent also includes claims directed to products and claims directed to processes. Claim 1, a product claim, specifies:

"1. A pharmaceutical preparation comprising:

(a) an alkaline reacting core comprising an acid-labile pharmaceutically active substance and an alkaline reacting compound different from said active substance, an alkaline salt of an acid labile pharmaceutically active substance, or an alkaline salt of an acid labile pharmaceutically active substance and an alkaline reacting compound different from said active substance;

(b) an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds; and

(c) an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced"

(PSWTX 2A 13:1-20.)

Dependent product claims add features to claim 1. For example, claim 6 refers to a pH-buffering alkaline reacting compound which renders the microenvironment a specified pH.

6. A preparation according to claim 1, wherein an alkaline core comprises the acid labile compound and a pH-buffering alkaline reacting compound which renders to the micro-environment of the acid labile compound a pH of 7-12.

(PSWTX 2A 14:4-8.)

Claim 12 of '230 Patent, an independent process claim, provides:

12. Process for the preparation of an oral pharmaceutical formulation containing an acid labile compound in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers where after the subcoated cores are further coated with an enteric coating layer.

(PSWTX 2A 14:33-41.)

A. *Patent Ownership*

In the First Wave litigation, the Court found that Astra owns both the '505 and the '230 Patents. Astra v. Andrx, 222 F.Supp.2d at 514. Astra has again established ownership in the patents-in-suit.

Astra is the owner of the '505 and '230 Patents by virtue of assignment from the inventors. The inventors, Kurt Lovgren, Ake Pilbrant, Mitsuru Yasumura, Satoshi Morigaki, Minoru Oda, and Naohiro Ohishi, assigned all their rights in the '505 and '230 Patents to Aktiebolaget Hassle. The assignments were executed between March 19, 1987 and April 2, 1987, before the filing of the U.S. applications leading to the patents-in-suit. (PSWTX 1266.) The '505 and '230 Patents were issued to Aktiebolaget Hassle as the assignee (PSWTX 1A; PSWTX 2A), and "[t]he issuance of [a] patent by the Patent Office to the plaintiff establishe[s] prima facie ownership," Electric Auto-Lite Co. v. P. & D. Mfg. Co., 78 F.2d 700, 704 (2d Cir.1935) (citation omitted).

Plaintiffs also own the '505 and '230 Patents as a result of agreements between Aktiebolaget Hassle and Fujisawa Pharmaceutical Co., Ltd. and Mitsubishi Pharma Corporation, successor to Yoshitomi Pharmaceutical Co., Ltd., that grant Astra all of Fujisawa and Yoshitomi's interest in omeprazole-related patents outside of Japan. Aktiebolaget Hassle's ownership of the '505 and ' 230 Patents was affirmed by Fujisawa Pharmaceutical Co., Ltd. and by Mitsubishi Pharma Corporation in October of 2003. Fujisawa and Mitsubishi confirmed that all rights they had in the '505 and '230 Patents through their employees, Mitsuru Yasumura, Satoshi Morigaki, Minoru Oda, and Naohiro Ohishi, were assigned to Aktiebolaget Hassle pursuant to an agreement between Fujisawa, Mitsubishi, and Aktiebolaget Hassle. (PSWTX 1266.)

III. *The Pleadings*

These infringement actions initially arose out of Abbreviated New Drug Applications ("ANDAs") filed by Defendants. The Drug Price Competition and Patent Term Restoration Act, Pub.L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. s. 355 and 35 U.S.C. s. 271(e) (1994)), also known as the Hatch-Waxman Act, amended the Federal Food, Drug, and Cosmetic Act ("FDCA"), Pub.L. No. 52-675, 52 Stat.

1040 (1938) (codified as amended at 21 U.S.C. s.s. 301-397 (1994)) FN7, to permit filing of an ANDA to expedite FDA approval of a generic version of a drug previously approved by the FDA. *See* Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1244 (Fed.Cir.2000), *cert. denied,* 531 U.S. 993, 121 S.Ct. 484, 148 L.Ed.2d 457 (2000). Under the Hatch-Waxman Act, an applicant may file an ANDA with the FDA requesting approval to market a generic drug without undergoing the same expensive and time-consuming FDA approval process as the maker of the branded version of the drug, often called the pioneer drug, by (1) demonstrating that the generic drug is the bioequivalent of the branded drug and (2) certifying that manufacturing, marketing and selling the drug will not infringe the patent rights held by the patentee of the pioneer drug. *Id*.

FN7. There are proposed amendments to all these statutes.

The statute prescribes a precise four-step procedure for litigating patent disputes between the innovator drug company and the generic applicant. *See* 21 U.S.C. s. 355(j)(2)(A)-(B). The holder of the New Drug Application for the pioneer drug lists all of its patents that claim the drug or a use of the drug in the book entitled New Drug Products with Therapeutic Equivalence Evaluations (referred to as the "Orange Book") published by the FDA. *See* 21 U.S.C. s. 355(b)(1). In its ANDA, a generic applicant must certify one of the following four statements with respect to the patents listed under the pioneer drug in the Orange Book: no patent information has been filed ("Paragraph I" certification), the patent has expired ("Paragraph II" certification), the patent soon will expire on a specified date ("Paragraph III" certification), or the patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug" covered by the ANDA ("Paragraph IV" certification). 21 U.S.C. s. 355(j)(2)(A)(vii) (I)-(IV). Only one type of certification is pertinent here: a "Paragraph IV" certification. In a Paragraph IV certification, the generic manufacturer seeks to obtain FDA approval before a listed patent expires and asserts that the patent listed in the Orange Book is either not infringed or invalid. Following the issuance of a Paragraph IV certification, the Hatch-Waxman Act requires the generic company to give notice of the Paragraph IV certification to the innovator who listed the patent with the FDA. 21 U.S.C. s. 355(j)(2)(B). The FDA can approve an ANDA containing a Paragraph IV certification unless the patent holder files suit within forty-five days of receiving notice of a Paragraph IV certification. 21 U.S.C. s. 355(j)(5)(B)(iii); 21 C.F.R. s. 314.107(f)(2) (2006). If a patent infringement action is timely brought, final marketing approval of the ANDA cannot occur before expiration of thirty months or a decision of a court. *See* 21 U.S.C. s. 355(j)(5)(B)(iii).

Section 271(e) (2)(A) "define[s] a new (and somewhat artificial) act of infringement for a very limited and technical purpose that relates only to certain drug applications." Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676, 110 S.Ct. 2683, 110 L.Ed.2d 605 (1990). Section 271(e)(2)(A) provides a patentee with a cause of action for patent infringement based solely upon the filing of an ANDA containing a Paragraph IV certification implicating a Plaintiffs' patent rights. The artificial infringement arising by operation of law is an integral part of a statutory scheme designed to allow pharmaceutical manufacturers to market, and the public to purchase, generic drugs as soon as possible after the expiration of patents covering the pioneer drug. The infringement suit under section 271(e)(2) permits the patentee "to challenge the certification-i.e. to assert inter alia that the commercial manufacture, use or sale of the new drug *would infringe* its patent." Glaxo, Inc. v. Boehringer Ingelheim Corp., 954 F.Supp. 469, 473 (D.Conn.1996) (emphasis added). The patentee's challenge to the certification provides the court with a justiciable controversy, permitting it to efficiently resolve patent issues in advance of the generic drug's release. *See* Warner-Lambert Co. v. Apotex Corp., No. 98 Civ. 4293, 1999 WL 259946, at (N.D.Ill. Apr.8, 1999).

Defendants have each issued Paragraph IV certifications against the patents-in-suit. (PSWTX 433; PSWTX 1126; PSWTX 1127A; PSWTX 1128; PSWTX 1129.) Defendants certified in their ANDA submissions for generic omeprazole that the patents-in-suit are "invalid or will not be infringed by the manufacture, use, or sale" of their generic products. (PSWTX 433; PSWTX 1126; PSWTX 1127A; PSWTX 1128; PSWTX

1129.) Based on those ANDA filings, Plaintiffs filed a patent infringement suit pursuant to 35 U.S.C. s. 271(e)(2)(A), alleging that the generic omeprazole formulations for which Defendants seek approval will infringe or induce infringement of the asserted claims.

In addition, Defendants started selling their respective products in the United States during the pendency of this litigation. For this reason, Plaintiffs have amended the complaints to include infringement pursuant to 35 U.S.C. s. 271(a), (b) and (c). (Second Am. Compl. Against Mylan, Dec. 12, 2003; Compl. Against Esteve, Aug. 8, 2003; Second Am. Compl. Against Lek, Dec. 12, 2003; Second Am. Compl. Against Apotex, Apr. 6, 2005; Second Am. Compl. Against Impax, Mar. 2, 2005.) The issue of whether Defendants willfully infringe is not being addressed here.

A. *Complaint Against Mylan/Esteve*

Plaintiffs assert that Mylan committed an act of infringement under 35 U.S.C. s. 271(e)(2) with respect to the '505 Patent and the '230 Patent by filing an ANDA seeking FDA approval to engage in the commercial manufacture, use or sale of Mylan's product prior to the expiration of the patents-in-suit (Second Am. Compl. Against Mylan para.para. 21, 32); that Mylan has directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by selling and offering for sale Mylan's FDA-approved 10-mg and 20-mg generic omeprazole product (*Id*. para.para. 24c, 35c); and that under 35 U.S.C. s. 271(b)-(c) Mylan has induced and contributed to infringement by others who administer or use Mylan's product (*Id*. para.para. 23, 24, 34, 35). Plaintiffs further assert that Mylan had knowledge of the '505 Patent before the infringement referred to above, and such infringement has been and will continue to be willful and deliberate. (Id. para. 24d.)

Mylan's answer to the Second Amended Complaint denies infringement and asserts additional affirmative defenses of patent invalidity for failure to comply with the U.S. patent laws, including 35 U.S.C. s.s. 101, 102, 103, and/or 112, and unenforceability. Mylan asserts counterclaims for treble damages under the antitrust laws and declarations of patent invalidity and unenforceability, and requests attorneys' fees and costs. (Mylan's Answer & Countercls. to Second Am. Compl.) Mylan's antitrust counterclaims have been severed and stayed pending resolution of the allegations of the complaint.

Plaintiffs assert that Laboratorios Dr. Esteve has directly infringed the patents-in-suit by offering for sale and selling within the United States, and importing into the United States the pellets used in Mylan's product in contravention of 35 U.S.C. s. 271(a). (Compl. Against Esteve para.para. 28, 53). In addition, Plaintiffs assert that both Laboratorios Dr. Esteve and Esteve Quimica have induced infringement of the '505 and '230 Patents under 35 U.S.C. s. 271(b) by inducing infringing sales of the Mylan omeprazole products (*Id*. para.para. 35, 60), and inducing infringement by others who administer or use Mylan's product (*Id*. para.para. 36, 61). Plaintiffs assert that Esteve Quimica has further induced infringement under 35 U.S.C. s. 271(b) by Laboratorios Dr. Esteve by inducing the import, sale, and offer for sale in the U.S. of the pellets used in Mylan's product (*Id*. para.para. 38, 63); and Laboratorios Dr. Esteve has contributorily infringed the patents-in-suit under 35 U.S.C. s. 271(c) by supplying to Mylan the pellets used in Mylan's product (*Id*. para.para. 46, 71). Plaintiffs also assert that Laboratorios Dr. Esteve had knowledge of the ' 505 Patent before the infringement referred to above, and such infringement has been and will continue to be willful and deliberate. (Id. para. 29.)

Esteve's Answer to the Complaint denies infringement and asserts additional affirmative defenses of patent invalidity for failure to comply with the U.S. patent laws, including 35 U.S.C. s.s. 101, 102, 103, and/or 112, and unenforceability. Mylan also asserts counterclaims for declarations of patent invalidity and unenforceability, and requests attorneys' fees and costs. (Esteve's Answer and Countercls. to Compl.)

B. *Complaints Against Lek*

Plaintiffs assert that Lek committed acts of infringement under 35 U.S.C. s. 271(e)(2) with respect to the '505 Patent and the '230 Patent by filing ANDAs seeking FDA approval to engage in the commercial manufacture, use, or sale of Lek's products prior to the expiration of the patents-in-suit (Second Am. Compl. Against Lek para.para. 21-23, 32-35; Compl. Against Lek para.para. 19-21, 28-30); that Lek has directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by manufacturing, selling, and offering for sale Lek's FDA-approved 10-mg and 20-mg generic omeprazole products (Second Am. Compl. Against Lek para.para. 24a, 24b, 24c, 35a, 35b, 35c); and that Lek has induced and contributed to infringement by others who administer or use Lek's products under 35 U.S.C. s. 271(b)-(c) (*Id*. para.para. 23, 24, 34, 35).

Lek's Answers to the Second Amended Complaint and Complaint deny infringement by their products. Lek also sues for an award of attorneys' fees and costs under 35 U.S.C. s. 285, and asserts counterclaims for treble damages under the antitrust laws. (Lek's Answer & Countercls. to Second Am. Compl.; Lek's Answer and Countercls. to Compl.) Lek's counterclaims have been severed and stayed pending resolution of the allegations of the complaints.

C. *Complaint Against Apotex*

Plaintiffs assert under 35 U.S.C. s. 271(e)(2) with respect to the '505 Patent and the '230 Patent by filing an ANDA seeking FDA approval to engage in the commercial manufacture, use or sale of Apotex's product prior to the expiration that Apotex committed an act of infringement of the patents-in-suit (Second Am. Compl. Against Apotex para.para. 21, 32); that Apotex directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by selling and offering for sale Apotex's FDA-approved 10-mg and 20-mg generic omeprazole products (*Id*. para.para. 24c, 36c, 36d); that Apotex's act was willful and deliberate (*Id*. para.para. 24e, 36e); and that Apotex has induced and contributed to infringement by others who administer or use Apotex's products under 35 U.S.C. s. 271(b)-(c) (*Id*. para.para. 23, 35). In addition, Plaintiffs claim that this case is exceptional under 35 U.S.C. s. 285 based on Apotex's lack of a meritorious defense and Apotex's litigation misconduct. (*Id*. para.para. 24e, 37.)

Apotex's Answer to the Second Amended Complaint denies infringement and asserts additional affirmative defenses of patent invalidity and unenforceability. Apotex also sues for attorneys' fees and costs and asserts counterclaims, including claims for treble damages under the antitrust laws and for declarations of patent invalidity and unenforceability. (Apotex's Answer & Countercls. to Second Am. Compl.) Apotex's antitrust counterclaims have been severed and stayed pending resolution of the allegations of the complaints.

D. *Complaints Against Impax*

Plaintiffs assert that Impax committed an act of infringement under 35 U.S.C. s. 271(e)(2) with respect to the '505 Patent and the '230 Patent by filing an ANDA seeking FDA approval to engage in the commercial manufacture, use or sale of Impax's products prior to the expiration of the patents-in-suit (Am. Compl. Against Impax para.para. 16, 28; Second Am. Compl. Against Impax para.para. 16, 28); that Impax has directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by selling and offering for sale Impax's FDA-approved "Omeprazole Delayed Release Capsules, 10 and 20 mg" (Second Am. Compl. Against Impax para.para. 19c, 31c); and that Impax has induced and contributed to infringement by others who administer or use Impax's products under 35 U.S.C. s. 271(b)-(c) (*Id*. para.para. 18, 19, 30, 31). Plaintiffs further assert that Impax had knowledge of the '505 and '230 Patents before the infringement referred to above, and therefore such infringement has been willful and deliberate. (Id. para. para. 19d, 31d.) Additionally, Plaintiffs claim this case is exceptional under 35 U.S.C. s. 285 (2000) based on Impax's litigation misconduct and lack of a meritorious defense. (*Id*. para.para. 20, 32.)

Impax's answers to the Amended Complaint and Second Amended Complaint deny infringement and assert additional affirmative defenses of patent invalidity for failure to comply with the U.S. patent laws, including

35 U.S.C. s.s. 102, 103, and/or 112, and unenforceability for patent misuse and inequitable conduct. Impax also sues for attorneys' fees and asserts counterclaims for treble damages under the antitrust laws and declarations of patent invalidity and unenforceability. (Impax's Answer & Countercls. to Am. Compl.; Impax's Answer & Countercls. to Second Am. Compl.) Impax's antitrust counterclaims have been severed and stayed pending resolution of the allegations of the complaints.FN8

FN8. Impax demanded a jury trial of the infringement claims in its February 15, 2005 Answer and Counterclaims. On December 1, 2005, at a hearing before this Court, Plaintiffs informed the Court that it would be willing to voluntarily dismiss its damages claims in order to allow for a consolidated bench trial. (Dec. 1, 2005 Hearing Tr. 25:5-26:2.) The Court requested both parties brief this issue, which were filed on December 12, 2005. Impax also submitted a reply brief on January 5, 2006. The Court directed Plaintiffs to submit its voluntary dismissal with prejudice of its damages claims and ordered that, upon entry of this dismissal, Impax's jury demand would be struck. (Jan. 13, 2006 Order at 9.) On February 26, 2006, this Court denied Impax's motion for reconsideration, and the Federal Circuit denied Impax's petition for a writ of mandamus on March 2, 2006. Impax has filed a petition for certiorari in the Supreme Court of the United States.

DISCUSSION

I. *Daubert Motions*

All parties made timely motions, pursuant to Federal Rules of Evidence 104, 402, 702, and 703, to exclude certain challenged testimony under Daubert v. Merrell Dow Pharmaceuticals Inc., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). Plaintiffs initially moved to exclude Mylan and Esteve's expert witness Dr. Richard Durst, Apotex's expert witness Dr. Michael Cima, Lek's expert witnesses Dr. John Coates, Dr. John White, Dr. Brian Herman, and Dr. Yuval Garini, and Impax's expert witnesses Mr. Andrew Hirt and Dr. David Piston, but withdrew all of their *Daubert* motions during trial. (Tr. 5226:23-25; 5227:1-6.)

All Defendants moved to exclude various portions of the testimony of Dr. Martyn Davies, one of Plaintiffs' expert witnesses who testified at the trial. In addition, Impax moved to exclude the testimony of Plaintiffs' expert witness Dr. Robert Langer, and Mylan and Esteve moved to preclude Plaintiffs' expert witness Dr. Alexander Klibanov. Although the Court had initially scheduled *Daubert* hearings to be held in advance of trial, upon consideration of Plaintiffs' motion for reconsideration of that scheduling decision, the Court elected to hear the *Daubert* proof during the trial itself. *See* Colon v. BIC USA, Inc., 199 F.Supp.2d 53, 71 (S.D.N.Y.2001). ("[N]othing in *Daubert,* or any other Supreme Court or Second Circuit case, mandates that the district court hold a *Daubert* hearing before ruling on the admissibility of expert testimony."); *see also* Astra v. Andrx, 222 F.Supp.2d at 486. The Court has now thoroughly considered all submissions and arguments relating to the motions of all Defendants. The Court has considered all of the testimony of the experts, as well as the other evidence offered at trial. For the following reasons, Defendants' motions to exclude or strike portions of the testimony of Dr. Davies, Dr. Langer, and Dr. Klibanov, as well as the exhibits offered through those three witnesses, are denied in their entirety.

A. *Choice of Law*

[1][2][3]When deciding issues in a patent case, a district court applies the law of the circuit in which it sits to nonpatent issues and the law of the Federal Circuit to issues of substantive patent law. Invitrogen Corp. v. Biocrest Mfg., L.P., 424 F.3d 1374, 1378-79 (Fed.Cir.2005). An "issue that is not itself a substantive patent law issue is nonetheless governed by Federal Circuit law if the issue pertains to patent law, if it bears an essential relationship to matters committed to [the] exclusive control [of the Federal Circuit] by statute, or if it clearly implicates the jurisprudential responsibilities of [the Federal Circuit] in a field within its exclusive

jurisdiction." Midwest Indus., Inc. v. Karavan Trailers, Inc., 175 F.3d 1356, 1359 (Fed.Cir.1999) (en banc in relevant part) (internal citations and quotations omitted). Under these rules, evidentiary rulings concerning the admissibility of expert testimony are generally governed by regional circuit law. Odetics, Inc. v. Storage Tech. Corp., 185 F.3d 1259, 1276 (Fed.Cir.1999) ("Because these evidentiary rulings raise procedural issues not unique to patent law, this court applies the law of the regional circuit where appeals from the district court would normally lie."). However, the determination of whether material is relevant in a patent case is governed by Federal Circuit law when the material relates to an issue of substantive patent law. *See* Midwest Indus., Inc., 175 F.3d at 1359 (citing Truswal Sys. Corp. v. Hydro-Air Eng'g, Inc., 813 F.2d 1207, 1212 (Fed.Cir.1987)). Thus, this Court is governed by the law of the Federal Circuit as to relevance and the law of the Second Circuit as to the other issues raised by Defendants' challenges to the testimony of Dr. Davies and Dr. Langer.

B. *Legal Requirements Under Daubert and* Rule 702

The admissibility of expert testimony is governed by Federal Rule of Evidence 702, which has been amended to codify the holdings of *Daubert* and its progeny. *See* Micro Chem., Inc. v. Lextron, Inc., 317 F.3d 1387, 1391-92 (Fed.Cir.2003.) Rule 702 provides:

If, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R.E. 702.

The admissibility of all expert testimony under Rule 702 is a preliminary question of law for the district court to determine pursuant to Federal Rule of Evidence 104(a), *see* Daubert, 509 U.S. at 592, 113 S.Ct. 2786, and district courts have broad discretion when determining whether or not to admit expert testimony, United States v. Feliciano, 223 F.3d 102, 120 (2d Cir.2000). The proponent of the evidence, in this case Astra, must establish admissibility under Rule 104(a) by a preponderance of the evidence. *See* Bourjaily v. United States, 483 U.S. 171, 175-76, 107 S.Ct. 2775, 97 L.Ed.2d 144 (1987); *see also* Colon, 199 F.Supp.2d at 69. However, when interpreting the requirements under *Daubert* and its progeny, the Second Circuit has noted that:

[a]lthough expert testimony should be excluded if it is speculative or conjectural, or if it is based on assumptions that are so unrealistic and contradictory as to suggest bad faith or to be in essence an apples and oranges comparison, other contentions that the assumptions are unfounded go to the weight, not the admissibility, of the testimony.

Boucher v. United States Suzuki Motor Corp., 73 F.3d 18, 21 (2d Cir.1996) (internal quotations and citations omitted).

In determining admissibility under *Daubert,* trial judges are charged with a gate-keeping function pursuant to Rule 702 whereby they must determine (1) whether the theory or methodology underlying the testimony is reliable and (2) whether the expert's theory or methodology is relevant in that it "fits" the facts of the case. *See* Daubert, 509 U.S. at 590-91, 113 S.Ct. 2786; Kumho Tire Co. v. Carmichael, 526 U.S. 137, 149-50, 119 S.Ct. 1167, 143 L.Ed.2d 238, (1999); Campbell v. Metro. Prop. & Cas. Ins. Co., 239 F.3d 179, 184-85 (2d Cir.2001). For consideration by district courts in determining the reliability of expert testimony, the Supreme Court set forth the following non-dispositive, non-exclusive factors as "flexible" guidelines in *Daubert:* (1) whether the theory or technique can be or has been tested; (2) whether the theory or technique

has been subjected to peer review and publication; (3) the known or potential rate of error associated with the technique along with the existence and maintenance of standards controlling the technique's operation; and (4) whether the technique or theory has been generally accepted in the scientific community. Daubert, 509 U.S. at 592-95, 113 S.Ct. 2786. In addition to the five factors explicitly discussed in *Daubert,* district courts in the Second Circuit have considered a variety of other factors when determining the admissibility of expert testimony. Some of the more commonly used factors include consideration of the foundation for the opinion, Nimely v. City of New York, 414 F.3d 381, 396-97 (2d Cir.2005) (stating that "when an expert opinion is based on data, methodology, or studies that are simply inadequate to support conclusions reached, *Daubert* and Rule 702 mandate the exclusion of that unreliable opinion testimony" (internal quotations and citations omitted)), its subjectivity, Highland Capital Mgmt., L.P. v. Schneider, 379 F.Supp.2d 461, 473 (S.D.N.Y.2005) ("Expert testimony that is speculative" or e. (internal quotations and citations omitted)), and any failure to test, Brooks v. Outboard Marine Corp., 234 F.3d 89, 91-92 (2d Cir.2000) ("[F]ailure to test theory can justify a trial court's exclusion of the expert's testimony.").

The "fit" or relevance requirement enunciated in *Daubert* has been interpreted to encompass several concepts. For scientific evidence to be admissible, it must be relevant, which means the evidence must have the "tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Fed.R.Evid. 401; Daubert, 509 U.S. at 587, 113 S.Ct. 2786. Thus, even if the methodology used by the expert is considered to be reliable, the expert's testimony will nevertheless fail to meet the "fit" requirement and should be excluded if the data relied upon by the expert is materially different from the data relevant to the facts of the case. *See* Raskin v. Wyatt Co., 125 F.3d 55, 67-68 (2d Cir.1997). If the expert has failed to consider the necessary factors, or if the analysis is premised upon a faulty assumption, his testimony may be excluded for lack of probative value. *See* Amorgianos v. Amtrak, 303 F.3d 256, 268-69 (2d Cir.2002). Likewise, where the proffered testimony is based on a methodology transposed from one area to a completely different context and there is no independent research supporting the transposition, the "fit" requirement may not be satisfied. Therefore, to the extent that any witness has based their opinions on studies, models, or experiments, it is their burden to connect those analyses to the facts of this case. *See* Gen. Elec. Co. v. Joiner, 522 U.S. 136, 144, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997).

[4]Even if an expert's methodologies satisfy the *Daubert* standard for admissibility, the court must still determine whether that evidence actually supports the expert's conclusions. Joiner, 522 U.S. at 146, 118 S.Ct. 512. The court must reject expert testimony where "there is simply too great an analytical gap between the data and the opinion proffered." *Id.;* Graham v. Playtex Prods., 993 F.Supp. 127, 132 (N.D.N.Y.1998) (noting that *Joiner* applies *Daubert* gate-keeping to conclusions as well as methodology). Failure to test for alternative causes or to use control experiments may provide a basis for exclusion. *See* In re Executive Telecard Ltd., Sec. Litig., 979 F.Supp. 1021, 1026 (S.D.N.Y.1997); Valentine v. Pioneer Chlor Alkali Co., 921 F.Supp. 666, 676-77 (D.Nev.1996). It is not required, however, that an expert categorically excludes each and every possible alternative cause in order to render the proffered testimony admissible. *See, e.g.,* Zuchowicz v. United States, 140 F.3d 381, 385-87 (2d Cir.1998).

C. *Expert Qualifications*

Before determining whether the testimony and evidence offered by the expert witnesses in this case meet the *Daubert* standards, the Court must first determine whether each expert is qualified to testify.FN9 *See* In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 741 (3d Cir.1994); Mancuso v. Consol. Edison, 56 F.Supp.2d 391 (S.D.N.Y.1999), *aff'd in relevant part, vacated in part,* 216 F.3d 1072, 2000 WL 730417 (2d Cir.2000). The ultimate issue for the court to determine is whether the witness has "specialized knowledge" through "experience, training or education" as to the contents of his proposed expert testimony. Fed.R.Evid. 702. The Court considered each expert's background and experience in order to determine whether each witness was qualified to render the opinion testimony he offered at trial. *See* McCullock v. H.B. Fuller Co., 61 F.3d

1038, 1043 (2d Cir.1995).

FN9. Of course, the issue of qualification as an expert in particular fields is also relevant to the Court's decision on Defendants' *Daubert* challenges. If a witness is not qualified as an expert in the scientific field that governs the topics covered in his testimony, that testimony cannot possibly meet the requirements mandated by *Daubert*.

Pursuant to those standards, the Court evaluated the background and experience of each expert witness offered, as described below.

1. Plaintiffs' Expert Witnesses

Plaintiffs presented three expert witnesses, Dr. Martyn Davies, Dr. Robert Langer, and Dr. Alexander Klibanov. Dr. Davies was accepted by the Court an expert in the testing, analysis, and characterization of drug formulations (Tr. 145:15-19), and Dr. Langer was accepted by the Court as an expert in drug delivery and pharmaceutical dosage forms (Tr. 1124:3-10). The Court accepted Dr. Klibanov as an expert in pharmaceutical chemistry and pharmaceutical formulation chemistry. (Tr. 5241:20-25.)

a. Martyn Davies

Dr. Martyn Davies is an expert in testing, analysis, and characterization of drug formulations. (PSWTX 804A; Davies Tr. 145:15-19.) Dr. Davies has over twenty years' experience in the area of characterization of pharmaceutical dosage forms, and conducts his research in that area. Dr. Davies has a pharmacy degree from University of Brighton, and attended the University College Hospital at the University of London, for six months. He then spent six months at Welsh Pharmaceuticals, where he focused on characterizing drugs, preparing dosage forms, and preparing samples for clinical trials. He also spent time in the production plant, operating production facilities, and in the marketing and development departments. Dr. Davies obtained a Ph.D. from the Universityof London. (Davies Tr. 123:22-125:11; PSWTX 804A.)

Dr. Davies has been a professor of biomedical surface chemistry in the school of pharmacy at the University of Nottingham since 1985. He has primarily taught in the areas of pharmaceutical technology, physical formulation, and advanced drug delivery. (Davies Tr. 123:9-13; 125:7-127:6; PSWTX 804A.) He was the Head of the School of Pharmaceutical Sciences and the Pharmacy School from 2000 until 2003. (PSWTX 804A.) Dr. Davies is the chair of the research committee at the school. Part of his responsibilities include teaching analytical techniques, including how to characterize drugs using vibrational spectroscopy, infrared, nuclear magnetic resonance ("NMR"), mass spectrometry, pH measurements, and fluorescence. He also performs independent research. (Davies Tr. 127:7-128:11; PSWTX 804A.)

Dr. Davies is the founder and chairman of Molecular Profiles Ltd., a company which assists pharmaceutical companies with developing better formulations and conducts research for the pharmaceutical industry in that same area. (Davies Tr. 128:20-130:2; PSWTX 804A.) Molecular Profiles has consulted for over seventy different pharmaceutical companies and over 250 different projects since its creation. (Davies Tr. 133:22-134:18; PSWTX 804A.) In his role as chairman, Dr. Davies also oversees the management of the company and research conducted by the company. He designs experiments, ensures experiments are performed properly, and reviews and collates the data. (Davies Tr. 128:20-130:2; PSWTX 804A.) Dr. Davies has been published in over 300 publications for his research on characterization of pharmaceutical dosage forms. He has published articles on the fluorescence techniques used in this litigation. (Davies Tr. 136:16-137:2; PSWTX 804A.)

Dr. Davies is involved in pharmaceutical scientific societies. He is a fellow of the Royal Pharmaceutical

Society of Great Britain. He was also the science chairman of the millennium meeting of the British Pharmaceutical Conference. Dr. Davies served on the Royal Pharmaceutical Society's science committee, helping the society develop their research activities. He is also a fellow of the Royal Society of Chemistry and has run several conferences for this society. Dr. Davies was also elected to serve as the scientific secretary of the Controlled Release Society, which has over 4,000 members and is the main international society for drug delivery. His responsibilities include serving on the board of the Controlled Release Society, coordinating the science activity, and overseeing all the science aspects of the society, including its publications. (Davies Tr. 142:6-143:24; PSWTX 804A.)

Dr. Davies has received awards for his work in characterizing pharmaceutical systems. He received the Pharmatech Award in recognition for his work on the characterization of pharmaceutical dosage forms. He received the Pfizer award, which is given annually in the United Kingdom across all sciences within the pharmaceutical sector. He was also awarded the young investigator award by the Controlled Release Society; this award is given once a year to an individual who has shown outstanding research activity in the field of drug delivery. Recently, Dr. Davies and the researchers at Molecular Profiles were given the GlaxoSmithKline international achievement award for their work in academic research and for implementing that research in the industrial sector. (Davies Tr. 144:2-18; PSWTX 804A.)

b. Dr. Robert Langer

Dr. Robert Langer is an expert in the fields of drug delivery and pharmaceutical dosage forms. (Langer Tr. 1124:3-10; PSWTX 964A.) Dr. Langer received a B.S. in Chemical Engineering from Cornell University and a Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology ("M.I.T."). Dr. Langer also did post-doctoral work at Harvard Medical School. He is currently an institute professor at M.I.T. (Langer Tr. 1120:7-12; PSWTX 964A.)

Dr. Langer teaches courses in biotechnology, chemical engineering, and drug delivery systems. In addition to teaching, Dr. Langer conducts research in the area of biomedical engineering, drug delivery systems, and pharmaceutical dosage forms. Dr. Langer holds appointments at Boston Children's Hospital and Harvard Medical School. (Langer Tr. 1119:12-1120:6; 1121:10-16; PSWTX 964A.) Dr. Langer also provides consulting in the area of drug delivery for over 150 companies. (Langer Tr. 1122:19-1123:5, 6967:9-18.)

Dr. Langer has published about 870 papers and 650 abstracts, and edited thirteen books. Dr. Langer has over 540 issued or pending patents worldwide in the area of drug delivery systems, pharmaceutical dosage forms, and biomedical engineering. (Langer Tr. 1120:13-24; PSWTX 964A.)

Dr. Langer has also received about 140 awards and honors, including the Charles Stark Draper prize, the General Motors prize, the Albany medical prize, and the Lemelson prize for invention. He was elected to the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine of the National Academy of Sciences, and has been inducted into the National Inventor's Hall of Fame. (Langer Tr. 1121:22-1122:18, 6966:20-6967:5; PSWTX 964A.)

c. Dr. Alexander Klibanov

Dr. Alexander Klibanov is an expert in chemistry, including pharmaceutical and pharmaceutical formulation chemistry. (Klibanov Tr. 5238:24-25, 5239:1-2; PSWTX 961.) He received both his master's and doctoral degrees in chemistry from Moscow University in Russia. He previously consulted for a state-owned pharmaceutical institute in the areas of medicinal chemistry, formulations, and drug delivery. (Klibanov Tr. 5239:3-16; PSWTX 961.)

Dr. Klibanov is currently a researcher and a professor of chemistry and bioengineering at M.I.T. Dr.

Klibanov has taught undergraduate and graduate courses in general chemistry, organic chemistry, biological chemistry, and analytical chemistry. (Klibanov Tr. 5238:13-5239:2; PSWTX 961.) He has also consulted for about two dozen pharmaceutical companies, started three biopharmaceutical companies, and served as a scientific advisor and member of the board of directors of several other biopharmaceutical companies. (Klibanov Tr. 5240:6-18; PSWTX 961.)

Dr. Klibanov has published over 250 articles dealing with various aspects of chemistry in peer-reviewed journals. He has fifteen United States patents and several foreign patents. (Klibanov Tr. 5239:17-5240:5; PSWTX 961.) Dr. Klibanov has served on the editorial board of more than a dozen scientific journals, including Proceedings of the National Academy of Sciences. (Klibanov Tr. 5240:19-25; PSWTX 961.)

Dr. Klibanov has also received several awards for his work and research, including election to the United States National Academy of Sciences and to the United States National Academy of Engineering. (Klibanov Tr. 5241:1-14; PSWTX 961.)

2. Mylan/Esteve's Expert Witnesses

Mylan's Dr. Richard Durst was accepted by the Court as an expert in electrochemistry and pH measurement (Durst Tr. 1758:4-9), and Dr. John Swenton was accepted by the Court as an expert in organic chemistry (Swenton Tr. 2263:12-15).

a. Dr. Richard Durst

Dr. Richard Durst is an expert in the field of electrochemistry and pH measurement. (Durst Tr. 1757:17-22, 1758:8-9.) Dr. Durst received his Bachelor's Degree in chemistry from the University of Rhode Island in 1960 and his Ph.D. in analytical chemistry from M.I.T. in 1963, specializing in electroanalytical chemistry. Electroanalytical chemistry includes the measurement of pH. After graduating from M.I.T., Dr. Durst was a post-doctoral fellow at the National Bureau of Standards. (Durst Tr. 1750:13-1751:5.)

Dr. Durst recently retired from the faculty of Cornell University, where he was hired to run the Cornell analytical laboratories and served as a full tenured professor for 15 years. (Durst Tr. 1756:14-20.) Before joining the Cornell University faculty, Dr. Durst spent about 25 years at the National Bureau of Standards. (Durst Tr. 1751:6-17.) During his 25 years at the National Bureau of Standards, Dr. Durst specialized in pH measurement and held the positions of research scientist in the analytical chemistry division, assistant director of the analytical division, and chief of the electrochemical analysis section. (Durst Tr. 1751:18-1752:8.) Dr. Durst's responsibilities included maintaining the national pH scale, certifying pH calibration standards, developing new techniques for obtaining precise and accurate pH measurements, and representing the United States in the field of pH measurements before various national and international standard setting bodies, including the National Committee for Clinical Laboratory Standards, the Association of Official Analytical Chemists, the International Federation of Clinical Chemistry, and the International Union of Pure and Applied Chemistry (IUPAC). (Durst Tr. 1752:9-1753:25.)

Dr. Durst has received numerous awards and honors for his work in the field of pH measurement, and has served in numerous professional associations and on scientific editorial boards. He has authored more than 200 peer-reviewed publications and presented scores of invited lectures at government and academic institutions, national and international symposia, and elsewhere on the subject of electroanalytical chemistry. (Durst Tr. 1754:1-1756:13; M/EX 155.)

b. Dr. John Swenton

Dr. John Swenton is an expert in organic chemistry. (Swenton Tr. 2258:10-13, 2259:24-25.) Dr. Swenton

graduated from the University of Kansas in 1962 with a degree in chemistry, and received his Ph.D. from the University of Wisconsin in 1965. He spent a year at Harvard University as a post-doctoral fellow. (Swenton Tr. 2254:19-2255:13.) He has been a chemistry professor at the Ohio State University since 1966, where his curriculum and research has been focused on organic chemistry and laboratory organic chemistry. (Swenton Tr. 2254:25-2255:2, 2255:14-2256:12.) Dr. Swenton has received numerous awards and honors for his work in the field of organic chemistry, has been involved in various professional associations and scientific editorial boards, and has authored well over 100 peer-reviewed articles on the subject of synthetic organic chemistry. (Swenton Tr. 2256:13-2258:9.)

3. Lek's Expert Witnesses

Lek presented the following expert witnesses: Dr. Gary Christian, Dr. Phillip E. Russell, Dr. John Coates, Dr. Brian Herman, Dr. Yuval Garini, Dr. Albert Padwa, and Dr. Calvin Quate. The Court acceptedDr. Christian as an expert in the field of analytical chemistry. (Christian Tr. 3752:16-20.) Dr. Russell was accepted by the Court as an expert in the fields of microscopy and microanalysis (Russell Tr. 4356:2-14), Dr. Coates was accepted as an expert in infrared spectroscopy, attenuated total reflectance Fourier spectroscopy ("ATR-FTIR"), analytical chemistry, and spectral data handling (Coates Tr. 3439:10-17), and Dr. Herman was accepted as an expert in fluorescence spectroscopy and optical microscopy (Herman Tr. 4606:16-21). Dr. Garini was accepted by the Court as an expert in optical microscopy and spectroscopy, including fluorescence microscopy and confocal laser scanning microscopy ("CLSM"). (Garini Tr. 2457:23-2458:4.) Dr. Padwa was accepted as an expert in organic and heterocyclic chemistry (Padwa Tr. 2925:21-2926:2), and Dr. Quate was accepted as an expert in atomic force microscopy ("AFM") (Quate Tr. 3103:2-7).

a. Dr. Gary Christian

Dr. Gary Christian is an expert in the field of analytical chemistry. (Christian Tr. 3746:1-25, 3748:2-3749:20, 3750:5-3752:2, 3752:16-20; LEKTX 227.) Dr. Christian received a bachelor's degree in chemistry from the University of Oregon in 1959, and a Ph.D. in analytical chemistry from the University of Maryland in 1964. (Christian Tr. 3744:11-20; LEKTX 227.) After receiving his Ph.D., Dr. Christian worked at the Walter Reed Army Institute of Research before joining the University of Kentucky faculty as an assistant professor of chemistry in 1967, where he was then promoted to associate professor. (Christian Tr. 3745:6-12.) In 1972, Dr. Christian moved to the University of Washington as a professor of chemistry, the position that he now holds. (Christian Tr. 3745:6-160.)

In 1990, Dr. Christian was the Acting Chair of the Department of Chemistry at the University of Washington. From 1991-1993, Dr. Christian was the Associate Chair of Undergraduate Education. Dr. Christian held the position of Divisional Dean of Sciences in the College of Arts & Sciences from 1993-2001, during which time he oversaw 15 science departments, including chemistry. (Christian Tr. 3745:17-25; LEKTX 227.)

Dr. Christian has published between 300 and 400 articles in peer-reviewed journals. (Christian Tr. 3748:23-3749:4; LEKTX 227.) He has authored approximately 14 textbooks in the field of analytical chemistry, including a textbook entitled *Analytical Chemistry* that is now in its sixth edition. (Christian Tr. 3749:5-20.) Dr. Christian is the editor of *Talanta,* an international journal of analytical chemistry. (Christian Tr. 3750:11-20.) Dr. Christian has received many awards, including the American Chemical Society Fischer Award in analytical chemistry. (Christian Tr. 3751:14-22; LEKTX 227.) Dr. Christian is a member of the American Chemical Society and was chairman of its Division of Analytical Chemistry, and is also a member of the Society for Electroanalytical Chemistry. (Christian Tr. 3750:21-3751:3.)

b. Dr. Phillip E. Russell

Dr. Phillip E. Russell is an expert in microscopy and mass spectrometry. (Russell Tr. 4356:13-14.) He is currently a professor of Materials Science and Engineering at North Carolina State University. (Russell Tr. 4343:1-2.) He obtained bachelor's and master's degrees in physics (Russell Tr. 4343:14-18), then obtained a Ph.D. in materials science and engineering. (Russell Tr. 4344:17-20; LEKTX 2132.) Dr. Russell has performed mass spectrometry for more than 20 years, since before he obtained his doctorate. (Russell Tr. 4354:4-5.) Dr. Russell also performed mass spectrometry extensively in his first career position in the Solar Energy Research Institute of the Department of Energy. (Russell Tr. 4354:5-8.) There, one of his responsibilities was to establish an ion mass spectrometry laboratory for the United States with state-of-the-art magnetic sector mass spectrometry equipment. (Russell Tr. 4354:8-12.)

Dr. Russell's current responsibilities as Director of the Analytical Instrumentation Facility at North Carolina State University include working with mass spectrometry systems. (Russell Tr. 4354:16-4355:2.)

c. Dr. John Coates

Dr. John Coates is an expert in the fields of infrared spectroscopy, attenuated total reflectance Fourier transform infrared spectroscopy ("ATR-FTIR"), analytical chemistry, and spectral data handling. (Coates Tr. 3439:6-9; LEKTX 626B.) He is qualified as both a chartered chemist and a chartered scientist by the Royal Society of Chemistry, and he is a fellow of the Royal Society of Chemistry. (Coates Tr. 3424:1-3425:2.) Dr. Coates has over 40 years of experience in analytical chemistry, including over 30 years of experience with infrared spectroscopy. (LEKTX 626B.) Dr. Coates was a consultant to the company that developed the instrument that he used for his ATR-FTIR analytical work on Lek's product. (Coates Tr. 3433:16-3434:11; LEKTX 626B.)

Dr. Coates has taught numerous courses on Fourier transform infrared spectroscopy ("FTIR"). He has taught for the American Chemical Society, on subject matters including sample handling. (Coates Tr. 3434:23-3435:9; LEKTX 626B.) He also routinely teaches a course to forensic scientists at the FBI Academy on infrared spectroscopy, including spectral interpretation, sample handling, and data handling. (Coates Tr. 3436:5-10; LEKTX 626B.) In addition, Dr. Coates has consulted with a wide range of companies, including pharmaceutical companies and instrumentation companies, regarding instrument design and sample handling. (Coates Tr. 3437:9-23; LEKTX 626B.)

Dr. Coates contributed a chapter to a treatise in the field of infrared spectroscopy, which was edited by Dr. Francis Mirabella. (Coates Tr. 3490:8-3491:7; LEKTX 593.)

d. Dr. Brian Herman

Brian Herman is an expert in the fields of fluorescence spectroscopy and optical microscopy. (Trial Tr. 4606:16-21.) After receiving his graduate degree in cell biology and biophysics from University of Connecticut, and completing his postgraduate training at Harvard Medical School, Dr. Herman became an assistant professor and then a full professor at the University of North Carolina at Chapel Hill, where he established the first research core facility for optical imaging at the university. (Herman Tr. 4595:2-4597:6; LEKTX 622A.)

Dr. Herman left Chapel Hill in 1998 to become chair of the Department of Cellular and Structural Biology at the University of Texas Health Science Center in San Antonio. He established the first optical imaging core facility there, and its first optical imaging course in partnership with a number of optical microscopic industrial partners.

In 2005, he became vice president for research. In that position, Dr. Herman is responsible for all research

activities at the institution, including human, animal and clinical. He also continues to run his own laboratory, supervising and conducting research. (Herman Tr. 4598:17-4599:4, 4605:1-4606:15; LEKTX 622A.) Over the past 20 years, Dr. Herman has also taught at Woods Hole and Cold Spring Harbor. (Herman Tr. 4597:7-4598:15, 24-25.) Dr. Herman also has a number of inventions, including optical imaging devices. (Herman Tr. 4604:18-25, LEKTX 622A.)

Dr. Herman is on the editorial board of a number of scientific journals and is a peer reviewer for grants issued by the National Institutes of Health and the National Science Foundation. He was selected as a chairperson for one of the major review groups at the National Institutes of Health, as well as reviewing grants for various state and European grant agencies. (Herman Tr. 4599:5-4501:7, LEKTX 622A.)

Dr. Herman's professional awards include two MERIT awards, received by about 2% of all NIH awardees. (Herman Tr. 4601:17-4602:12.) He has published extensively in the field of fluorescence spectroscopy and optical microscopy, as well as other areas. (Herman Tr. 4603:12-4604:17.)

e. Dr. Yuval Garini

Dr. Yuval Garini is an expert in the fields of optical microscopy and spectroscopy, including fluorescence microscopy and confocal laser scanning microscopes ("CLSM"). (Garini Tr. 2457:22-2458:3.)

Dr. Garini studied physics at Technion University in Israel, receiving his undergraduate and graduate degrees there. (Garini Tr. 2442:23, 2445:16-2446:25; LEKTX 854.) Dr. Garini is an assistant professor in the quantitative imaging group of the Department of Imaging Science and Technology at Delft University, where he established an optical microscopy, spectroscopy and imaging laboratory. (Garini Tr. 2443:23-2445:13; LEKTX 854.) Dr. Garini has published in fields that relate to physics, optical physics, genetics, cytometry, fluorescence microscopy, and CLSM. (Garini Tr. 2449:23-2452:25, 2457:10-21; LEKTX 854.)

f. Albert Padwa

Dr. Albert Padwa is an expert in synthetic organic chemistry and heterocyclic chemistry. (Padwa Tr. 2921:2-2926:2; LEKTX 855.) Dr. Padwa received a Bachelor of Arts and a Ph.D. from Columbia University. Since 1979, Dr. Padwa has been the W.P. Timmie Professor of Chemistry at Emory University. (Padwa Tr. 2921:4-12.) Dr. Padwa's research is focused on synthetic organic chemistry with a specific interest in heterocyclic molecules, usually those that have biological importance such as medicinal chemical compounds. (Padwa Tr. 2922:2-7.)

Dr. Padwa has published over 600 papers and has edited 10-12 books in this area of chemistry. He has also received numerous awards including the International Prize in Heterocyclic Chemistry from the International Society of Heterocyclic Chemistry as well as the Arthur C. Cope Award from the American Chemical Society. (Padwa Tr. 2922:16-2923:7.)

g. Calvin Quate

Dr. Calvin Quate is one of the inventors of the Atomic Force Microscope ("AFM"). (Quate Tr. 3095:19-3098:10; PSWTX 1143.) He co-authored the first article on the AFM, which was published in March of 1986. (Quate Tr. 3095:19-3098:19, 3099:18-20; PSWTX 1143.) Dr. Quate is the Leland T. Edwards Professor Emeritus of Electrical Engineering and Applied Physics at Stanford University, California. (Quate Tr. 3090:13-16; LEKTX 624A.) A full professor at Stanford from 1964 to 2004, he attained emeritus status in January 2004. (Quate Tr. 3090:17-19; LEKTX 624A.) He continues to be actively involved in AFM research and is on the Scientific Board on four AFM and nanotechnology companies. (Quate Tr. 3092:5-11; LEKTX 624A.) Dr. Quate also continues to publish papers in AFM. (Quate Tr. 3101:18-22.)

After receiving his Ph.D. in physics from Stanford, Dr. Quate worked at Bell Laboratories. (Quate Tr. 3092:12-3093:22.) In 1958, Dr. Quate joined Sandia Laboratories in New Mexico as the Director of Research. (Quate Tr. 3093:23-3094:17.) Dr. Quate returned to Stanford in 1961, where he developed acousto-optical devices. (Quate Tr. 3094:18-3095:1.) In the 1970's, Dr. Quate began working on microscopes and developed the acoustical microscope, for which he received the Rank Prize in 1982, given in London in the Queen's presence. (Quate Tr. 3095:2-25.) In the 1980's, Dr. Quate shifted the focus of his research to scanning probe microscope and developed the Atomic Force Microscope with Nobel laureates Gerd Binnig and Cristoph Berger. (Quate Tr. 3095:25-3097:8; PSWTX 1143.) Dr. Quate also has experience in interpreting a wide variety of AFM images and specimens, such as microchips in semiconductors, various polymers and cellular DNA in liquid. (Quate Tr. 3102:2-22.)

4. Apotex's Expert Witnesses

Apotex's expert witness Dr. Charles Signorino was accepted by the Court as an expert in the manufacture and production of enteric coated pharmaceutical dosage forms. (Signorino Tr. 3841:6-11.) Dr. Michael J. Cima was accepted by the Court as an expert in the testing and characterization of pharmaceutical dosage forms. (Cima Tr. 4037:6-11.)

a. Dr. Charles Signorino

Dr. Charles Signorino is an expert in the areas of the manufacture and production of enteric coated solid dosage forms. (Signorino Tr. 3841:5-9.) Dr. Signorino is currently the CEO of Emerson Resources, a laboratory which develops new pharmaceutical and nutriceutical products, and optimizes product and process. (Signorino Tr. 3826:5-12.) Emerson Resources is actively involved in the scaling up and scaling down of the processes for manufacturing pharmaceutical products. (Signorino Tr. 3829:15-3830-13.) Prior to his work at Emerson Resources, Dr. Signorino was a vice president and director of Colorcon, which provides coating materials including enteric resins. (Signorino Tr. 3830:19-3831:7, 3833:3-21.)

Dr. Signorino is on the scientific advisory boards for two trade publications, Pharmaceutical Technology (Signorino Tr. 3836:14-20), and American Pharmaceutical Review (Signorino Tr. 3838:11-14). Dr. Signorino has published articles regarding enteric coatings and/or the enteric coating process in both of these journals, as well as in a newsletter by Thomas Engineering. (Signorino Tr. 3835:19-3838:18.) He is the holder of eighteen patents, including fourteen patents related to coatings used in the pharmaceutical and/or food industries. (Signorino Tr. 3839:21:-3840:23.)

b. Dr. Michael J. Cima

Dr. Michael J. Cima is an expert in the area of the testing and characterization of pharmaceutical dosage forms. (Cima Tr. 4037:6-11.) Dr. Cima is a professor of material science and engineering at M.I.T. (Cima Tr. 4031:23-4032:1.) Dr. Cima was the scientific founder of Transform Pharmaceuticals, a company which develops proprietary new formulations for drug products. (Cima Tr. 4033:18-4034:1.) Throughout his career, Dr. Cima has used many analytical techniques, including ultra-violet ("UV") fluorescent imaging, UV fluorescence spectroscopy, Raman spectroscopy, FTIR spectroscopy, and ATR-FTIR spectroscopy. (Cima Tr. 4035:14-4036:7.) Dr. Cima has published between forty to fifty peer-reviewed articles dealing with the analysis and/or development of pharmaceuticals. (Cima Tr. 4036:22-4037:5.)

5. Impax's Expert Witnesses

Impax's Dr. David Piston was accepted as an expert in fluorescence generally, and specifically in the use of CLSM and fluorescence microscopy and UV. (Piston Tr. 4881:17-22.) Dr. Walter Chambliss was accepted

as an expert in pharmaceutics (Chambliss Tr. 5017:5-8), and Dr. Gerald Meyer was accepted as an expert witness in general chemistry, luminescence, carboxylic acid chemistry, and the use of FTIR (Meyer Tr. 5106:11-19). Dr. Griffiths was unable to testify at trial due to medical issues, and the Court instructed Impax to submit deposition designations for Dr. Griffiths. (Tr. 4799:6-23.) The Court now accepts Dr. Griffiths as an expert in vibrational spectrometry and FTIR.

a. Dr. David Piston

Dr. David Piston is an expert in the fields of fluorescence, CLSM and fluorescence microscopy, and UV and optical microscopy. (Piston Tr. 4881:17-22.) Dr. Piston works at Vanderbilt University in Nashville, Tennessee where he is a professor of physiology and biophysics and professor of physics. (Piston Tr. 4872:2-5; ITX 6445.) He holds joint appointments at the College of Arts and Science and the College of Medicine. (Piston Tr. 4872:7-8.) He also directs the Free Electron Laser Center, which is a Department of Defense and National Science Foundation funded research center at Vanderbilt. (Piston Tr. 4872:8-11.) Dr. Piston teaches the following subjects: quantitative fluorescence microscopy; biophysical approaches to biological systems; and protein design, structure and function. (Piston Tr. 4872:16-20.)

Dr. Piston's education includes a bachelor's degree in physics from Grinnell College in Iowa, and a master's and Ph.D. in physics from the University of Illinois. (Piston Tr. 4872:22-24.) He was awarded a postdoctoral research fellowship in applied physics at Cornell University. (Piston Tr. 4872:23-24.)

Dr. Piston has won several awards in his field, including being elected a Fellow of the American Physical Society (Piston Tr. 4873:15-19), the Young Fluorescence Investigator Award from the Biophysical Society (Piston Tr. 4873:19-25), and the Beckman Young Investigator Award (Piston Tr. 4873:25-4874:6).

Dr. Piston is on the editorial boards of *Biophysical Journal* and *Microscopy and Microanalysis* (Piston Tr. 4874:15-24), and was on the editorial board of the *Journal of Fluorescence* for more than four years (Piston Tr. 4874:25-4875:3). He has also been a peer reviewer for the following journals: *Science; Nature; National Academy of Science, Nature and Technology; Nature Methods;* and *Biochemistry*. (Piston Tr. 4875:6-14.) He is now the chair of the peer-review committee for microscopic imaging for the National Institute of Health. (Piston Tr. 4876:7-11.)

b. Dr. Walter Chambliss

Dr. Walter Chambliss is an expert in the field of pharmaceutics. (Chambliss Tr. 5017:5-10.) Dr. Chambliss is a professor of pharmaceutics at the University of Mississippi. (Chambliss Tr. 5008:25-5009:17; ITX 223.) He is also a research professor in the National Center for National Products Research, which is a drug discovery center at the University of Mississippi. (Chambliss Tr. 5011:14-16.) Dr. Chambliss's work for that group involves discovering potential pharmaceuticals, determining the appropriate drug development path, and identifying pharmaceutical companies to act as partners for toxicology and clinical trials. (Chambliss Tr. 5011:17-21.) Dr. Chambliss is also the Director of TechnologyManagement for the University of Mississippi, a position which involves responsibility for invention disclosure statements, and patent drafting (in conjunction with outside patent counsel) and licensing for potential inventors throughout the University of Mississippi. (Chambliss Tr. 5011:22-5012:6; ITX-223 at B-1.)

Dr. Chambliss received a bachelor's degree in pharmacy, a master's of science in pharmaceutics, and a Ph.D. in pharmaceutics, all from the University of Mississippi. (Chambliss Tr. 5012:7-19.) The subject of Dr. Chambliss's master's thesis was control release pellets and his dissertation research was on enteric coated dosage forms. (Chambliss Tr. 5012:12-19.)

From 1982 to 1984, Dr. Chambliss worked for G.D. Searle Pharmaceutical Company in formulation

development. (Chambliss Tr. 5012:23-5013:2.) Dr. Chambliss's work for Searle was concentrated in the area of oral control release pellet development with enteric and non-enteric polymers. (Chambliss Tr. 5013:1-4.) Dr. Chambliss also worked for the Bristol Laboratories Division of Bristol-Myers until 1986, where he was responsible for the process development of a large number of dosage forms and also formulation development of oral control release dosage forms. (Chambliss Tr. 5013:12-16.) A focus of Dr. Chambliss's work was acid-labile and/or acid sensitive compounds. (Chambliss Tr. 5013:11-17.) Dr. Chambliss then worked for Schering-Plough where he was Vice President of Research & Development for its Healthcare Division. (Chambliss Tr. 5014:5-9.) At Schering-Plough, Dr. Chambliss was in charge of the stability group. (Chambliss Tr. 5025:24-5026:3.)

Dr. Chambliss's publications include a book chapter on coating pellets, a book chapter on enteric coatings, a monograph he authored on shellac, an enteric polymer, and a journal article on enteric coating of penicillamine. (Chambliss Tr. 5014:23-5015:19.)

c. Dr. Gerald Meyer

Dr. Meyer is an expert in the fields of luminescence, carboxylic acid chemistry, and the use of Fourier transform infrared spectroscopy ("FTIR"). (Meyer Tr. 5106:11-19.) Dr. Meyer is a professor of chemistry and materials science at Johns Hopkins University. (Meyer Tr. 5100:23-5100:3; 5101:13-15; ITX-384.) He joined Johns Hopkins as an assistant professor in 1991. (Meyer Tr. 5101:11-12.) Dr. Meyer received a bachelor of science degree from the State University of New York at Albany in chemistry and mathematics. (Meyer Tr. 5101:4-8.) He then obtained a Ph.D. in chemistry from the University of Wisconsin at Madison, followed by postdoctoral work at the University of North Carolina at Chapel Hill. (Meyer Tr. 5101:9-11.)

Dr. Meyer has been engaged for twenty years in research concerning interfacial chemistry with an emphasis on molecular chemistry. (Meyer Tr. 5101:16-5104:2.) He teaches courses at Johns Hopkins in the analytical technique known as ATR-FTIR (Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy) (Meyer Tr. 5104:5-5106:1), and about half of Dr. Meyer's publications include some form of infrared spectroscopy (Meyer Tr. 5106:2-6; ITX-384 at C-1-8.) Dr. Meyer has continued his work in infrared techniques, usually FTIR, at the University of North Carolina. (Meyer Tr. 5104:17-24.)

Dr. Meyer is a member of the American Chemical Society, the Materials Research Society, the Society for Applied Spectroscopy, and the Electrochemical Society. (Meyer Tr. 5102:1-7.) He is also on the Board of the Inter-American Photo Chemical Society. (Meyer Tr. 5102:8-9.) Dr. Meyer received an award for his work in interfacial chemistry from the 3M Corporation. (Meyer Tr. 5102:10-14.)

d. Dr. Peter Griffiths

Dr. Peter Griffiths is an expert in vibrational spectrometry and FTIR. Dr. Griffiths has over 30 years of experience in the application of vibrational spectrometry to analytical, environmental and structural chemistry. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16, Jan. 1, 2005; ITX-362.) He was a Product Specialist for FTIR Spectrometers at Digilab, Inc. and served as the Manager of Analytical Services at Sadtler Research Labs. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.) He was a Professor at the University of California at Riverside and a Distinguished Professor at Ohio University. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.) He currently is a Professor of analytical and environmental chemistry at the University of Idaho and serves as the Chair of the Department of Chemistry. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.)

Dr. Griffiths holds a D. Phil. and a B.A. in Chemistry from Oxford University in England. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.) He has co-authored over 225 papers and 37 book chapters. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.) He has written two books and edited six others, including the *Handbook of Vibrational* Spectroscopy and *Fourier Transform Infrared* Spectroscopy. (Griffiths Dep. Tr. 24:21-25:15,

27:9-16.) Dr. Griffiths's work has focused on the development of better ways of measuring infrared spectra, including optics for diffuse reflection spectroscopy and the chromatographic/FTIR interface. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.)

Dr. Griffiths has received numerous honors and awards, including the Coblentz Award, the Spectroscopy Society of Pittsburgh Award, the Pregl Medal of the Austrian Society of Analytical Chemistry, the New York Society for Applied Spectroscopy Gold Medal Award in Spectroscopy, the University of Idaho Award for Research and Creative Activity, the Gerald S. Birth Award for Outstanding Work in Near-Infrared Spectroscopy and the Bomem Michelson Award in Vibrational Spectroscopy. (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.) Dr. Griffiths has also been awarded honorary membership in the Society for Applied Spectroscopy, where he served as President. (Griffiths Dep. 24:21-25:15, 27:9-16.) He is Associate Editor of *Applied* Spectroscopy and on the advisory boards of Spectroscopy *Letters, Spectrochimica Acta, Analytical and Bioanalytical Chemistry* (Germany), *Journal of Analytical Sciences* (Japan), and *Spectroscopy and Spectral Analysis* (China). (Griffiths Dep. Tr. 24:21-25:15, 27:9-16.)

D. *Daubert Analysis Applies to Weight and Credibility*

Many of the *Daubert* factors go not only to the admissibility of the evidence, but also to the weight that evidence is to be given and the credibility of the expert witness. *See* Libas, Ltd. v. United States, 193 F.3d 1361, 1366 (Fed.Cir.1999) ("[T] he proposition for which [*Daubert* and *Kumho*] stand, that expert testimony must be reliable, goes to the weight that [the] evidence is to be accorded as well as to its admissibility."); McCullock v. H.B. Fuller Co., 61 F.3d 1038, 1044 (2d Cir.1995) ("Disputes as to ... faults in his use of ... a methodology, or lack of textual authority for his opinion, go to the weight ... of his testimony."). A court must take a "hard look" at the expert scientific testimony offered to prove infringement, even the evidence admitted under the *Daubert* standard, and must reject an expert's conclusions where there is "too great an analytical gap between the data and the opinion proffered." Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997).

As previously noted, in the interest of efficiency, the Court decided to consolidate *Daubert* motions with the trial and considered the issues raised in Defendants' *Daubert* motions along with the evidence presented at trial. Therefore, the Court will address Defendants' motions in the context of its infringement analyses below.

II. *Infringement*

A. *General Principles*

[5][6]The infringement actions in this case were brought under 35 U.S.C. s. 271(a),(b),(c), and (e). Section 271(e)(2) provides, in relevant part, that "[i]t shall be an act of infringement to submit ... an application under [21 U.S.C. s. 355(j)] for a drug claimed in a patent or the use of which is claimed in a patent." As described above, this is an artificial act of infringement based on the filing of an ANDA and challenging existing patents through a Paragraph IV certification. 21 U.S.C. s. 355(j)(2)(A)(vii)(IV); Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676, 110 S.Ct. 2683, 110 L.Ed.2d 605 (1990). A claim of infringement brought under section 271(e)(2) focuses on the hypothetical product described in the ANDA. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1248 (Fed.Cir.2000). "The inquiry is grounded in the ANDA application ... therefore it is proper for the court to consider the ANDA itself, materials submitted by the ANDA applicant in support of the ANDA, and any other relevant evidence submitted by the applicant or patent holder." Bayer AG, 212 F.3d at 1248-49. "When a patentee seeks to block FDA approval of an [A]NDA under 35 U.S.C. s. 271(e) (2)(A), the infringement inquiry focuses on the hypothetical infringement that would occur if the defendant's [A]NDA were approved and the defendant began to make and sell the drug." Novartis Corp. v. Ben Venue Labs., Inc., 271 F.3d 1043, 1047 (Fed.Cir.2001) (citation

omitted).

All products-at-issue in this case are currently being sold in the United States. The Court must therefore also consider Plaintiffs' claims of direct, induced, and contributory infringement under 35 U.S.C. s. 271(a)-(c).

[7][8] A defendant is liable under 35 U.S.C. s. 271(a) if it "makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent." Intent is not an element of direct infringement, and neither ignorance nor good faith belief in non-infringement is a defense to a charge of direct infringement. Metal Film Co. v. Metlon Corp., 316 F.Supp. 96, 111 n. 15 (S.D.N.Y.1970). Making, using, selling, or offering to sell matter covered by a patent without authority of the owner constitutes infringement regardless of knowledge or intent. Soitec, S.A. v. Silicon Genesis Corp., 81 Fed.Appx. 734, 737 (Fed.Cir.2001) (approving jury instruction stating "that the same test for infringement should apply to any accused activity, regardless of whether the accused activity took place at the research and development stage or whether it took place at the manufacturing stage ... [b]ecause infringement during the early stages of process development is nonetheless a violation of patent law"); Hilton Davis Chemical Co. v. Warner-Jenkinson Co., Inc., 62 F.3d 1512, 1527 (Fed.Cir.1995) (en banc) ("Infringement is, and should remain, a strict liability offense."); Blair v. Westinghouse Elec. Corp., 291 F.Supp. 664, 670 (D.D.C.1968) ("[A]an infringement may be entirely inadvertent and unintentional and without knowledge of the patent.").

[9] [10] [11] [12] Liability under 35 U.S.C. s. 271(b) arises if a defendant "actively induces infringement of a patent." Inducedinfringement is found where a person actively and knowingly aids and abets another's direct infringement. Water Techs. Corp. v. Calco, Ltd., 850 F.2d 660, 668 (Fed.Cir.1988) ("Although section 271(b) does not use the word 'knowing,' the case law and legislative history uniformly assert such a requirement."). Defendants induce infringement if they cause, urge, encourage, aid, or otherwise make it possible for others to infringe the patents at issue here. Fromberg, Inc. v. Thornhill, 315 F.2d 407, 410 (5th Cir.1963). An alleged infringer is liable for induced infringement if: (1) the alleged infringer knew of the patent; (2) the alleged infringer's action induced the infringing acts, and (3) the alleged infringer intended to encourage another's infringement, or the alleged infringer "knew or should have known that his actions would induce actual infringement." Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 553 (Fed.Cir.1990). A party may be found liable for induced infringement when it sells a product and provides instructions on how to use it in an infringing manner. Golden Blount, Inc. v. Robert H. Peterson Co., 438 F.3d 1354, 1360 (Fed.Cir.2006); *see also* Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd., 545 U.S. 913, 936, 125 S.Ct. 2764, 162 L.Ed.2d 781 (2005) ("[I]nstructing how to engage in an infringing use, show[s] an affirmative intent that the product be used to infringe, and a showing that infringement was encouraged overcomes the law's reluctance to find liability when a defendant merely sells a commercial product suitable for some lawful use." (citations omitted)); Haworth Inc. v. Herman Miller Inc., No. 92 Civ. 877, 1994 WL 875931, at (W.D.Mich. Oct. 24, 1994) (evidence that defendant "demonstrate[d] and recommend[ed] infringing configurations" of its product could support inducement liability). Direct and induced infringement may both be proven through circumstantial evidence. Liquid Dynamics Corp. v. Vaughan Co., 449 F.3d 1209, 1219 (Fed.Cir.2006).

Under contributory infringement, a party is liable if it:

offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use.

35 U.S.C. s. 271(c). A party who sells an excipient which can be used for only one purpose is liable for contributory infringement. *See* Metro-Goldwyn-Mayer Studios, 545 U.S. at 932, 125 S.Ct. 2764 ("[W]here an article is 'good for nothing else' but infringement, there is no legitimate public interest in its unlicensed availability, and there is no injustice in presuming or imputing an intent to infringe." (citations omitted)).

B. *Infringement Analysis*

Infringement is a question of fact. Frank's Casing Crew & Rental Tools, Inc. v. Weatherford Int'l, Inc., 389 F.3d 1370, 1376 (Fed.Cir.2004); Glaxo Group Ltd. v. Ranbaxy Pharms., Inc., 262 F.3d 1333, 1335 (Fed.Cir.2001). Plaintiffs bear the burden to prove their claims of infringement by a preponderance of the evidence. Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 758 (Fed.Cir.1984). A preponderance of the evidence means such evidence which, when considered and compared with that opposed to it, produces a belief that what is sought to be proved is more likely true than not. *See* Warner-Lambert Co. v. Teva Pharms. USA, Inc., 418 F.3d 1326, 1341 n. 15 (Fed.Cir.2005). The fact that section 271(e)(2) creates an artificial act of infringement does not lessen that burden. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1567 (Fed.Cir.1997).

A patent infringement analysis consists of two steps: first the patent claims are construed, second the properly-construed claims are compared to the product accused of infringement. Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed.Cir.1995), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996).

In this Second Wave Litigation, Plaintiffs assert claims 1 and 10 of the ' 505 Patent against all Defendants. Claim 1 is a product claim and claim 10 is a method of treatment claim. Claims 2 through 9 and claims 11 through 13 of the '505 Patent are product claims that depend on claim 1, but add other features. Plaintiffs assert dependent claims 3, 4, 5, 6, 7 and 11 of the ' 505 Patent against Mylan and Esteve; dependent claims 5 and 6 against Apotex; dependent claims 5, 7, 8, and 9 against Lek; and dependent claims 5, 6, and 8 against Impax. In addition, Plaintiffs assert claim 14 of the '505 Patent, a process claim, against Mylan and Esteve.

Plaintiffs assert claims 1 and 13 of the '230 Patent against all Defendants. Claim 1 of the '230 Patent is a product claim and claim 13 is a method of treatment claim. Plaintiffs also assert dependent claims 6, 7, 8, 9, and 15 of the '230 Patent against Mylan and Esteve; dependent claims 6 and 7 against Apotex; dependent claims 6, 8, 10, and 11 against Lek; and dependent claims 6, 7, and 10 against Impax. As with the '505 Patent, dependent product claims add features to claim 1 of the '230 Patent. In addition, Plaintiffs assert claim 12 of the '230 Patent, an independent process claim, against Mylan and Esteve.

1. Claim Construction

a. Statement of the Law

In the first of the two steps necessary to the infringement analysis, the court construes the allegedly infringed patent claims to establish their meaning and scope. *See* Markman, 52 F.3d at 976; Netword, LLC v. Centraal Corp., 242 F.3d 1347, 1350 (Fed.Cir.2001). The interpretation of patent claims through claim construction is a determination made as a matter of law. Markman, 517 U.S. at 384, 116 S.Ct. 1384. The court construes the claims of each patent according to the hierarchy of evidence articulated in *Markman,* looking first to the claims, the specification, and the prosecution history. Markman, 52 F.3d at 979. "Expert testimony, including evidence of how those skilled in the art would interpret the claims, may also be used." *Id.*

[13][14][15] "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.' " Phillips v. AWH Corp., 415 F.3d 1303, 1312

(Fed.Cir.2005), *cert. denied,* 546 U.S. 1170, 126 S.Ct. 1332, 164 L.Ed.2d 49 (2006), (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed.Cir.2004)); *see also* Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996); Markman, 52 F.3d at 980. The claims are the measure against which validity and infringement are gauged. *See* SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed.Cir.1985). In order to understand their meaning, the Court must first look to the language of the claims themselves. *See* Phillips, 415 F.3d at 1312 ("[T]he Supreme Court made clear that the claims are 'of primary importance, in the effort to ascertain precisely what it is that is patented.' " (quoting Merrill v. Yeomans, 94 U.S. 568, 570, 4 Otto 568, 24 L.Ed. 235 (1876))). The Court may consider not only the language of the disputed claims themselves, but also the language of the unasserted claims. The claim terms of the patent are given the plain and ordinary meaning as understood by one skilled in the art at the time of the patent application. *See* id. at 1312-13. Thus, the focus in construing disputed claim terms is not the subjective intent of the inventor or examiner; rather, it is "the objective test of what one of ordinary skill in the art at the time of the invention would have understood a claim term to mean." *See* Markman, 52 F.3d at 986.

[16] [17] [18] The court must also take into consideration the language of the claims within the entirety of the patent, including the language and examples provided in the specification and prosecution history. *See* Phillips, 415 F.3d at 1313. Each and every word in a claim must be construed to have meaning. Exxon Chem. Patents, Inc. v. Lubrizol Corp., 64 F.3d 1553, 1557 (Fed.Cir.1995). The claims must also be "read in accordance with the precepts of English grammar." In re Hyatt, 708 F.2d 712, 714 (Fed.Cir.1983). This strong presumption "in favor of the ordinary meaning of claim language as understood by one of ordinary skill in the art" may be overcome: "(1) where the patentee has chosen to become his own lexicographer" by clearly and explicitly defining the claim term; or "(2) where a claim term deprives the claim of clarity such that there is 'no means by which the scope of the claim may be ascertained from the language used.' " Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc., 262 F.3d 1258, 1268 (Fed.Cir.2001) (quoting Johnson Worldwide Assoc. v. Zebco Corp., 175 F.3d 985, 989 (Fed.Cir.1999)). When a patentee chooses to be his own lexicographer and uses terms in a manner other than their ordinary meaning, the intended definition of the term must be clearly stated in the patent specification or file history. Vitronics Corp., 90 F.3d at 1582; *see also* Novo Nordisk of N. Am. v. Genentech, Inc., 77 F.3d 1364, 1368 (Fed.Cir.1996); Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1388 (Fed.Cir.1996).

[19] [20] The meaning of the claims must also be determined in the context of the specifications. *See* Phillips, 415 F.3d at 1315 ("The claims, of course, do not stand alone. Rather, they are part of 'a fully integrated written instrument' consisting principally of a specification that concludes with the claims. For that reason, claims 'must be read in view of the specification, of which they are a part.' " (quoting Markman, 52 F.3d at 978-79)). A court must look to the specification and the file history to see if the inventor varied the ordinary meaning of particular claim terms or if a claim term is unclear. Phillips, 415 F.3d at 1316 ("[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs."). Specifications can be the "single best guide to the meaning of a disputed term" and are usually dispositive. Phillips, 415 F.3d at 1315 (quoting Vitronics 90 F.3d at 1582); Novo Nordisk A/S v. Becton Dickinson & Co., No. 96 Civ. 9506, 2000 WL 294852, at (S.D.N.Y. Mar. 21, 2000); Amhil Enters. Ltd. v. Wawa, Inc., 81 F.3d 1554, 1559 (Fed.Cir.1996) (recognizing that the "entire specification, including all of the claims" should be considered in interpreting claim language). A patentee need not deliberately or precisely define a term in a lexicographical manner, but may provide a definition by implication. Vitronics, 90 F.3d at 1582. Thus, the Court of Appeals for the Federal Circuit has "specifically held that the written description of the preferred embodiments 'can provide guidance as to the meaning of the claims, thereby dictating the manner in which they are to be construed, even if the guidance is not provided in explicit definitional format.' " Bell Atl. Network Servs., Inc., 262 F.3d at 1268-70 (citing SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1344 (Fed.Cir.2001)).

A court must be careful when turning to the specification for guidance during claim construction. Examples may aid in the proper construction of a claim term, but the scope of a claim is not necessarily limited by the examples. Ekchian v. Home Depot, Inc., 104 F.3d 1299, 1303 (Fed.Cir.1997). Similarly, preferred embodiments like those often present in a specification are not claim limitations. Laitram Corp. v. Cambridge Wire Cloth Co., 863 F.2d 855, 865 (Fed.Cir.1988). It is improper either to "limit[ ] the claim invention to preferred embodiments or examples in the specification," Texas Instruments, Inc. v. U.S. Internat'l Trade Comm'n, 805 F.2d 1558, 1563 (Fed.Cir.1986), or to broaden the scope of a claim to include embodiments not covered by the claim language, Novo Nordisk of N. Am., 77 F.3d at 1369. *See also* Transmatic, Inc. v. Gulton Indus., Inc., 53 F.3d 1270, 1278 (Fed.Cir.1995); E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430 (Fed.Cir.1988) ("It is entirely proper to use the specification to interpret what the patentee meant by a word or phrase in the claim. But this is not to be confused with ... [reading] a limitation ... from the specification into the claims." (internal citation omitted)); *compare* Ekchian, 104 F.3d at 1303, *with* Philip v. Mayer, Rothkopf Indus., Inc., 635 F.2d 1056, 1061-62 (2d Cir.1980).

This is not to say that resort to the specification should be avoided. The court can and should use the specification to define claim terms. *See* Tap Pharm. Prods., Inc. v. Owl Pharms., L.L.C., 419 F.3d 1346, 1354 (Fed.Cir.2005) ("In light of the two different possible meanings for the term 'containing' it was entirely reasonable for the district court to look to the specification ... to determine the manner in which the term was used in the three patents at issue.") (citing Intel Corp. v. VIA Techs., Inc., 319 F.3d 1357, 1367 (Fed.Cir.2003)); Phonometrics, Inc. v. N. Telecom, Inc., 133 F.3d 1459, 1466 (Fed.Cir.1998) ("[Patentee] of course argues that additional limitations cannot be imported into a claim from the written description. We may, however, construe a specifically claimed limitation in light of the specification, which is all we do here."). For example, where the intrinsic evidence, and in particular "the specification makes [it] clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent." SciMed Life Sys., Inc., 242 F.3d at 1341; Phillips, 415 F.3d at 1315-16.

[21] In addition to claim language and the specification, a proper claim construction analysis requires consideration of the patent prosecution history. Markman, 52 F.3d at 980 ("The court has broad power to look as a matter of law to the prosecution history of the patent in order to ascertain the true meaning of language used in the patent claims ...."). The specification and prosecution history are both important evidence of "the problem the inventor was attempting to solve," which is critical to properly construing the scope and meaning of the claims of the patent. CVI/Beta Ventures, Inc. v. Tura LP, 112 F.3d 1146, 1160 (Fed.Cir.1997) (citing Applied Materials v. Advanced Semiconductor Materials, 98 F.3d 1563, 1573 (Fed.Cir.1996)). Like the specification, the prosecution history is intrinsic evidence and is "often of critical significance in determining the meaning of the claims." Vitronics, 90 F.3d at 1582; *see also* Alpex Computer Corp. v. Nintendo Co., 102 F.3d 1214, 1220 (Fed.Cir.1996). In addition, prior art consideredby the United States Patent and Trademark Office ("USPTO") during prosecution of a patent comprises intrinsic evidence for claim construction. Phillips, 415 F.3d at 1317.

[22] [23] These three items-the claim language, the specification, and the prosecution history-are the intrinsic evidence and the primary evidentiary sources for claim construction. In most situations, a thorough consideration of the intrinsic evidence will resolve any ambiguity in a disputed claim term. Vitronics, 90 F.3d at 1583. When the meaning cannot be determined by intrinsic evidence, a court may turn to extrinsic evidence to construe the claims in a patent. *See* Phillips, 415 F.3d at 1317; *see also* Pickholtz v. Rainbow Techs., Inc., 284 F.3d 1365, 1372-73 (Fed.Cir.2002) ("Only if a disputed claim term remains ambiguous after analysis of the intrinsic evidence should the court rely on extrinsic evidence." (citing Vitronics, 90 F.3d at 1583)). Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises," and may be useful to show the state of the art at the time of the invention. Markman, 52 F.3d at 980 ("The court may, in its discretion, receive extrinsic evidence in order 'to aid the court in coming to a correct conclusion' as to the 'true meaning

of the language employed' in the patent." (quoting Seymour v. Osborne, 78 U.S. (11 Wall.) 516, 546, 20 L.Ed. 33 (1871))). When consideration of extrinsic evidence is necessary to understand the meaning of claim terms, the court may consider testimony on how people skilled in the art would understand technical terms in the claims. Home Diagnostics, Inc. v. LifeScan, Inc., 381 F.3d 1352, 1355 (Fed.Cir.2004) ("The touchstone for discerning the usage of claim language is the understanding of those terms among artisans of ordinary skill in the relevant art at the time of invention.").

[24] Where the intrinsic evidence unambiguously describes the scope of the patent, however, it is improper to rely on extrinsic evidence to alter the meaning of the claims. *See* Vitronics, 90 F.3d at 1583-84. Further, a court should discount any extrinsic evidence that is clearly at odds with the claims themselves, the written description or the prosecution history. *See* Phillips, 415 F.3d at 1318. Thus, in most instances, a thorough consideration of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term, and the court may not rely on extrinsic evidence to construe the scope of a claim term unless the court first finds that the term is ambiguous even in light of the intrinsic evidence. *See* Vitronics, 90 F.3d at 1583-85.

b. Construed Claims of the '505 and '230 Patents

The Court has previous and extensive experience with the '505 and '230 Patents. In 2002, the Court rendered a 175-page opinion that addressed most of the claim construction issues in these cases. *See* Astra v. Andrx, 222 F.Supp.2d at 441-85. When rendering its claim construction in the First Wave litigation, the Court reviewed the claims, the specification, the file histories, and extrinsic evidence. Id. at 441-85. The Court also reviewed submissions relating to claim construction submitted by First Wave parties and Second Wave parties. Id. at 444 n. 9. In rendering its opinion in this Second Wave litigation, the Court also considered the decisions of the Court of Appeals for the Federal Circuit and additional submissions by Second Wave Parties relating to claim construction, including but not limited to the Second Wave Summary Judgment Submissions. (Jan. 12, 2006 Order Denying Defendants' Summary Judgment Motions (hereinafter "Jan. 12, 2006 Order"), affirming Order articulated at Nov. 25, 2005 Hearing.)

Because the '505 and '230 Patents have the same inventors and their inventive and claimed subject matters overlap, it is not surprising that the claims share much of the same language, a common background (as provided by their specifications), and similar prosecution histories. As a result, the intrinsic evidence for both patents overlaps.

In the First Wave Litigation, the Court acknowledged that the claims in each of these patents must be construed independently. *See* id. at 445. However, the Court also recognized that "the claims of the '505 and '230 Patents that have been asserted against Defendants often are directly paired together with no material differences between the corresponding claims in the two patents" and that "the parties' claim construction arguments are, for the most part, identical for the paired claims of the '505 and '230 Patents." Id. Therefore, the Court "analyzed the disputed terms within the '505 and '230 Patents by first addressing the terms occurring within corresponding claims in both patents," and then "address[ing] the few remaining claim construction issues pertinent to the '230 Patent alone." Id.

The Court may consider and rely on prior claim construction in subsequent actions. *See* Burke, Inc. v. Bruno Indep. Living Aids, Inc., 183 F.3d 1334, 1338 (Fed.Cir.1999). As the *Burke* court reasoned, "the interest of consistency in the construction of patent claims would be ill served" if the Court were precluded from considering "a prior claim construction rendered as a matter of law." *Id.* at 1337. As discussed at the conference on November 22, 2005 and reiterated in the Court's January 12, 2006 Order, the Court concluded that it will apply its claim construction determinations from the First Wave Litigation, including its previous constructions of the following terms: "effective amount," Astra v. Andrx, 222 F.Supp.2d at 462-64; "alkaline reacting compound," id. at 451-62; "core or core region," id. at 447-51; "enhanced stability," id. at 475; "inert subcoating," id. at 464, 468-75; "disposed on," id. at 469-71; "acid labile pharmaceutically active

substance," (also referred to as "acid labile compound") id. at 483-85; "except the compound omeprazole," *id*. at 484; and "alkaline core," *id*. at 447-61. The Court again considered its prior claim construction in light of the trial and post-trial submissions by the Second Wave parties and, as a result of that analysis, maintains its prior claim construction, as affirmed by the Federal Circuit, for the terms addressed therein. *Id*. at 441-85, *aff'd,* In re Omeprazole Patent Litig., 84 Fed.Appx. 76, 79-81 (2003). The Court's construction of claim terms is reiterated below only to the extent that the terms have been raised as issues in this Second Wave litigation.

To begin, the Court reiterates its previous finding that: "[i]n the context of the preamble of claims 1 of the '505 and '230 Patents, ... 'comprising' means that parts (a), (b), and (c) of claims 1 must be present, but that other elements may also be present." Astra v. Andrx, 222 F.Supp.2d at 446-47.

Claim 1(a) of the '505 Patent identifies: "a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone." (PSWTX 1A 16:44-47.) Similarly, '230 Patent claim 1(a) identifies: "an alkaline reacting core comprising an acid-labile pharmaceutically active substance and an alkaline reacting compound different from said active substance, an alkaline salt of an acid labile pharmaceutically active substance,or an alkaline salt of an acid labile pharmaceutically active substance and an alkaline reacting compound different from said active substance." (PSWTX 2A 13:1-9.)

The terms "core or core region" are defined as "the portion of the patented preparation that lies beneath the subcoating and contains the active ingredient and, in the case of omeprazole as the active ingredient, an ARC." Astra v. Andrx, 222 F.Supp.2d at 447. "[T]he terms 'core' and 'core region' are synonymous in the context of the '505 and '230 Patents." Id.

An "alkaline reacting compound" ("ARC") is defined as "(1) a pharmaceutically acceptable alkaline, or basic, substance having a pH greater than 7 that (2) stabilizes the omeprazole or other acid labile compound by (3) reacting to create a micro-pH of not less than 7 around the particles of omeprazole or other acid labile compound." *Id*. at 453.

An "effective amount" is expressly required in claim 1(a) of the '505 Patent and is implicit in the '230 Patent. Id. at 462. The term "effective amount" "applies to both omeprazole and the ARC and requires an amount of each substance such that the combination of omeprazole plus the ARC meets the stated goal of the invention of stabilizing the omeprazole." *Id*. at 463. "[A]n 'alkaline omeprazole salt alone' inherently satisfies the 'effective amount' requirement because the salt is alkaline (with a micro-pH of not less than pH 7) and self-stabilizing." (Jan. 12, 2006 Order at 10.) As the Court previously determined, an ARC may be absent when the formulation contains an "alkaline omeprazole salt." Astra v. Andrx, 222 F.Supp.2d at 453 ("[T]he claims of the '505 and '230 Patents both allow for the absence of [an alkaline reacting] substance only when omeprazole is formulated as an 'alkaline omeprazole salt.' ").

This Court previously construed "acid labile pharmaceutically active substance," found in claim 1 of the '230 Patent, as "those that are transformed into biologically active compounds by a rapid degradation or transformation in acid media." Id. at 483. The Court also determined that the claim language, specification, and '230 Patent file history all support a reading which includes omeprazole. Id. at 483-85. The Court confirmed its construction again in its order denying Eon and Mylan/Esteve's summary judgment motion arguing for its exclusion (Jan. 12, 2006 Order at 15-17) and now incorporates that construction here. However, Apotex's invalidity challenge raises the new issue of whether the term "acid labile pharmaceutically active substance" includes all acid sensitive materials, regardless of whether they are labile (degrade) in alkaline media. Accordingly, the Court now expands upon its prior claim construction of "acid labile pharmaceutically active substance."

[25] When previously construing "acid labile pharmaceutically active substance," the Court read claim 1 of the '230 Patent in light of the background specifications, specifically column 1, lines 14-27. Astra v. Andrx, 222 F.Supp.2d at 484; *see* Markman, 52 F.3d at 978-79 (A court must construe the terms of the claims in light of the language in the specification, because the claims are part of "a fully integrated written instrument" and "must be read in view of the specification, of which they are a part."). That part of the specifications specifically states that the '230 Patent is directed to "substances that are labile in acid media, but have better stability in neutral to alkaline media." (PSWTX 2A 1:23-25.) Therefore, the Court finds that the phrase "acid labile pharmaceutically active substance" (or "acid labile compound") refers to a compound that is sensitiveto acid but has better stability in alkaline conditions.FN10

FN10. This claim construction is consistent with the extrinsic evidence considered by the Court. For example, Plaintiffs' expert Dr. Langer, focusing on the same portion of the '230 patent specification (PSWTX 2A 1:23-27), testified that the '230 patent requires that the claimed acid labile compounds be stable in a base. (Langer Tr. 7143:8-11, 7144:5-10.)

[26] Along these lines, the Court also finds that, contrary to Apotex's belated argument, an "alkaline salt" refers to a salt with a pH not less than 7. (*See* June 30, 2006 Order at 9-10 (striking Dr. Block's new testimony that pH testing is not required to determine whether a substance is an alkaline salt because this opinion was not previously disclosed in his expert reports or deposition testimony).) When read in the context of the specifications, it is clear that the term "alkaline salt" refers to a salt with a basic pH, not necessarily, as Apotex argued for the first time at trial, a salt comprised of alkali metals or alkaline earth metals FN11 (*i.e.*, compounds of the elements that are part of Group I or II of the periodic table). To find otherwise would require ignoring the specifications of the ' 230 Patent, which state that a purpose of the invention is to "increase the stability of the active compound." FN12 (PSWTX 2A 1:24-25.)

FN11. The Court notes that the "alkaline earth" elements are so named because of their intermediate nature between the "alkalis" (oxides of the alkali metals) and the "rare earths" (oxides of rare earth metals). *See* Alkaline Earth Metal, *Wikipedia,* http:// en. wikipedia. org/ wiki/ Alkaline_ earth_ metal (last visited Feb. 12, 2007).

FN12. The '230 Patent also mentions that "the stabilizing, high pH value of the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound," which further suggests that the salts at issue must exhibit basic pHs. (PSWTX 2A 8:55-61.)

Claims 1(b) and (c) of the '505 Patent describe:

(b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds; and

(c) an outer layer disposed on said subcoating comprising an enteric coating.

(PSWTX 1A 16:48-54.) Similarly, claims 1(b) and (c) of the '230 Patent describe:

(b) an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds; and

(c) an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced.

(PSWTX 2A 13:10-21.)

The Court previously defined a "subcoating" as "a layer that is physically on and conforms to the contours of a core and is underneath another layer-the enteric coating." Astra v. Andrx, 222 F.Supp.2d at 464. The term "inert," "when modifying 'subcoating,' [ ] require[s] that the subcoating be chemically, pharmaceutically, and pharmacologically inactive such that the subcoating does not adversely affect the properties of the active ingredient or the enteric coating material in the formulation." Id. at 472-75. "[T]he subcoating layer isolates or separates the core from the enteric coating sufficiently to enhance the formulation's stability," which is achieved "by protecting against the 'degradation/discoloration of the acid labile compound during the coating process o[r] during storage.' " Id. at 475 (quoting PSWTX 2A 9:2-4).

"Stability," according to the Court's previous construction, "has two points of reference: the subcoating layer cannot decrease the gastric acid resistance or accelerate omeprazole degradation. Both properties must be better-enhanced-compared to the formulation without the subcoating." *Id*. at 570.

The Patent's instruction that the subcoating be "disposed on" the core region "does not require that the subcoating be applied using any particular process and that the subcoating need not necessarily be 'physically applied to' the core in a separate processing step." *Id*. at 470. Moreover, "the claims do not require a perfectly continuous, exactly uniform subcoating." *Id*. at 471. Rather, "the patent contemplates, and the court construes the claims to cover, subcoatings that are less than perfect, including subcoatings that contain inconsequential amounts of omeprazole or permit inconsequential contact between portions of the core and the enteric coat." *Id*.

The requirement that the subcoating be "soluble or rapidly disintegrating in water" is construed, as in the First Wave, to require that "the subcoating dissolves or breaks up quickly in water." *Id*. at 475.

Claim 5 of the '505 Patent describes "[a] preparation according to claim 1 wherein the alkaline core comprises omeprazole and pH-buffering alkaline compound rendering to the micro-environment of omeprazole a pH of 7-12." (PSWTX 1A 16:65-68.) "Alkaline core," as used in claim 5 of the '505 Patent, "refers to any core containing an ARC or an alkaline salt of omeprazole." Astra v. Andrx, 222 F.Supp.2d at 476. The Court also adheres to its previous construction of "microenvironment," which "is construed to refer to the regions immediately around or in close proximity to the omeprazole particles." Id. at 479.

2. Applying The Claims To The Allegedly Infringing Product

In the second step of the infringement analysis the properly construed claims are compared to the infringing product, process, or method. Karlin Tech., Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 971 (Fed.Cir.1999); Cybor Corp. v. FAS Techs., 138 F.3d 1448, 1454 (Fed.Cir.1998); Markman, 52 F.3d at 976. This is a question of fact. Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc., 261 F.3d 1329, 1336 (Fed.Cir.2001). "Infringement requires that *every limitation* of a claim be met literally or by a substantial equivalent." Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1389 (Fed.Cir.1992) (emphasis in original). "Demonstration that every limitation of the claim is ... met by the accused device [or product] must be shown by a preponderance of the evidence." Enercon GmbH v. Int'l Trade Comm'n, 151 F.3d 1376, 1384 (Fed.Cir.1998). The burden rests at all times on Plaintiffs to prove through an accurate, scientific method that the claimed invention is actually present in the allegedly infringing product. *See* Novartis Corp., 271 F.3d at 1046, 1050.

a. Literal Infringement

[27] A claim is literally infringed if each properly construed claim limitation reads on the accused product or process. In other words, literal infringement is present where every limitation recited in the claim is present in the allegedly infringing product, process, or method of use. Enercon, 151 F.3d at 1385. Where the accused products literally embody every limitation of the patent claim, the claim is infringed and that ends the inquiry. Karlin Tech., 177 F.3d at 971.

b. Infringement Under The Doctrine Of Equivalents

[28] An accused product that does not literally infringe may still be found to infringe under the doctrine of equivalents. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 25-30, 39-41, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997). "If an asserted claim does not literally read on an accused product, infringement may still occur under the doctrine of equivalents if there is not a substantial difference between the limitations of the claim and the accused product." Bayer AG, 212 F.3d at 1250-51; *see also* Warner-Jenkinson, 520 U.S. at 21, 117 S.Ct. 1040.

[29] The doctrine of equivalents was created to prevent what is in essence a "pirating of the patentee's invention" in situations where literal infringement does not exist. Miles Labs., Inc. v. Shandon, Inc., 997 F.2d 870, 876 (Fed.Cir.1993). "The doctrine of equivalents prevents an accused infringer from avoiding liability for infringement by changing only minor or insubstantial details of a claimed invention while retaining the invention's essential identity." Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 234 F.3d 558, 564 (Fed.Cir.2000) (en banc).

Equivalence is also a question of fact. Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 610, 70 S.Ct. 854, 94 L.Ed. 1097 (1950); *see also* Insta-Foam Prods., Inc. v. Universal Foam Sys., Inc., 906 F.2d 698, 702 (Fed.Cir.1990). "Proof can be made in any form: through testimony of experts or others versed in the technology; by documents, including texts and treatises; and, of course, by the disclosures of the prior art." Graver Tank, 339 U.S. at 609, 70 S.Ct. 854. "However, equivalents must be assessed on a claim-by-claim, limitation-by-limitation basis, not on any blanket comparison of the patent document generally to the accused device." Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1346 (Fed.Cir.2002) (citation omitted) (vacating judgment of infringement under doctrine of equivalents); *see also* Warner-Jenkinson Co., 520 U.S. at 18, 39 n. 8, 40, 117 S.Ct. 1040 (emphasizing that "[t]he determination of equivalence should be applied as an objective inquiry on an element-by-element basis" and summary judgment is appropriate only when "the evidence is such that no reasonable jury could determine two elements to be equivalent"). To determine whether the accused device includes equivalents for a claimed limitation, the court applies an "insubstantial differences" test. Toro Co. v. White Consol. Indus., Inc., 266 F.3d 1367, 1370 (Fed.Cir.2001).

As the Supreme Court has explained, there are several ways to determine equivalence under an objective standard. Warner-Jenkinson Co., 520 U.S. at 40-41, 117 S.Ct. 1040. One method is to determine whether the "differences between the two are 'insubstantial' to one of ordinary skill in the art." KCJ Corp. v. Kinetic Concepts, Inc., 223 F.3d 1351, 1359 (Fed.Cir.2000). The use of a substitute with "known interchangeability" with a literally claimed element is an objective factor to be considered in determining whether the substitute meets the claim limitation under the doctrine of equivalents. Warner-Jenkinson, 520 U.S. at 36, 117 S.Ct. 1040. The "known interchangeability test looks to the knowledge of a skilled artisan to see whether that artisan would contemplate the interchange as a design choice." Interactive Pictures Corp. v. Infinite Pictures, Inc., 274 F.3d 1371, 1383 (Fed.Cir.2001). Where skilled artisans would contemplate an interchange as a design choice, this is "substantial evidence" of equivalence. *Id.*

Courts have also sometimes employed a tripartite "function-way-result test" in determining whether a change is insubstantial. Warner-Jenkinson, 520 U.S. at 39-40, 117 S.Ct. 1040. The function-way-result test

focuses on the "the *function* served by a particular claim element, the *way* that element serves that function, and the *result* thus obtained by that element." *Id*. (emphasis in original). However, bioequivalence of a product is not an indication that the doctrine of equivalents has been met. *See* Upjohn Co. v. Mova Pharm. Corp., 225 F.3d 1306, 1309-10 (Fed.Cir.2000) (concluding that there was substantial evidence upon which the jury could find non-infringement under the doctrine of equivalents despite the fact that the product was bioequivalent to the patented product). Again, the doctrine is not applied to the invention as a whole, but to individual elements of the claimed invention. Warner-Jenkinson, 520 U.S. at 29, 117 S.Ct. 1040.

C. *Mylan/Esteve's Product*

[30] Mylan Pharmaceuticals Inc. is a manufacturer of generic pharmaceutical products in the United States. (Mylan's Answer & Countercls. to Second Am. Compl. para. 9.) Laboratorios Dr. Esteve, S.A. ("LDE") is a generic pharmaceutical manufacturer in Spain. (Esteve's Answer & Countercls. to Compl. para.para. 10, 11.) Esteve Quimica, S.A. ("EQ"), LDE's sister company, is a manufacturer of bulk active pharmaceutical ingredients in Spain. (*Id*. para.para. 8, 9.) LDE obtains omeprazole active ingredient raw material made by EQ and uses it to make omeprazole-containing pellets which are shipped to Mylan. (*Id*. para.para. 22, 23.) Mylan Pharmaceuticals places the pellets into capsules to make the finished Mylan product. (PSWTX 303 at OMP 004748.)

On May 17, 2000, Mylan filed Abbreviated New Drug Application (ANDA) No. 75-876 with the FDA, seeking the FDA's approval to sell Mylan's product called "omeprazole, capsule, delayed release pellets, oral, 10 mg"; "omeprazole, capsule, delayed release pellets, oral, 20 mg"; and "omeprazole, capsule, delayed release pellets, oral, 40 mg" (collectively referred to herein as "Mylan's product"), as a generic version of Plaintiffs' Prilosec(R) product. (Mylan's Answer & Countercls. to Second Am. Compl. para. 16; PSWTX 433.)

On June 2, 2003, the FDA granted final approval of the 10-mg and 20-mg strengths of Mylan's product and tentative approval of the 40-mg strength. (Mylan's Answer & Countercls. to Second Am. Compl. para.para. 23, 24a.) Mylan Pharmaceuticals began marketing its FDA-approved 10-mg and 20-mg product in August 2003. (*Id*. para. 24b.) On August 4, 2003, Mylan reported that it had begun the sale of 10-mg and 20-mg Mylan omeprazole products in the United States. (*Id*.)

As stated above, Plaintiffs assert that Mylan committed an act of infringement under 35 U.S.C. s. 271(e)(2) with respect to the '505 Patent and the ' 230 Patent by filing an ANDA seeking FDA approval to engage in the commercial manufacture, use or sale of Mylan's product prior to the expiration of the patents-in-suit (Second Am. Compl. Against Mylan para.para. 21, 32); that Mylan has directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by selling and offering for sale Mylan's FDA-approved 10-mg and 20-mg generic omeprazole product (*Id*. para.para. 24c, 35c); and that Mylan has induced and contributed to infringement by others who administer or use Mylan's product under 35 U.S.C. s. 271(b)-(c) (*Id*. para.para. 23, 24, 34, 35). Plaintiffs further assert that Mylan had knowledge of the '505 Patent before the infringement referred to above, and such infringement has been and will continue to be willful and deliberate. (Id. para. 24d.)

Plaintiffs assert that Laboratorios Dr. Esteve has directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by offering for sale and selling within the United States, and importing into the United States the pellets used in Mylan's product (Compl. Against Esteve para.para. 28, 53). In addition, Plaintiffs assert that both Laboratorios Dr. Esteve and Esteve Quimica have induced infringement of the '505 and '230 Patents under 35 U.S.C. s. 271(b) by inducing infringing sales of the Mylan omeprazole products (*Id*. para.para. 35, 60), and inducing infringement by others who administer or use Mylan's product (*Id*. para.para. 36, 61). Plaintiffs assert that Esteve Quimica has further induced infringement under 35 U.S.C. s. 271(b) by Laboratorios Dr. Esteve by inducing the import, sale, and offer for sale in the U.S. of the pellets used in Mylan's product (*Id*. para.para. 38, 63); and Laboratorios Dr. Esteve has contributorily infringed the

patents-in-suit under 35 U.S.C. s. 271(c) by supplying to Mylan the pellets used in Mylan's product (*Id.* para.para. 46, 71). Plaintiffs assert that Laboratorios Dr. Esteve had knowledge of the ' 505 Patent before the infringement referred to above, and such infringement has been and will continue to be willful and deliberate. (Id. para. 29.)

Plaintiffs allege that Mylan/Esteve's FN13 10-mg, 20-mg, and 40-mg ANDA omeprazole products infringe claims 1, 3, 4, 5, 6, 7, 10, 11, and 14 of the ' 505 Patent and claims 1, 6, 7, 8, 9, 12, 13, and 15 of the ' 230 Patent literally, and if not literally, under the doctrine of equivalents. (Langer Tr. 1126:8-13; PSWTX 1255-4.)

FN13. For brevity, Mylan and Esteve are collectively referred to as "Mylan/Esteve."

The infringement issues before the Court regarding Mylan/Esteve include determining whether Mylan/Esteve's omeprazole products have: (1) an alkaline reacting compound ("ARC") or its equivalent in their core regions; (2) the equivalent of an alkaline omeprazole salt in the cores; and (3) an inert subcoating which is water soluble or rapidly disintegrating in water.

1. Mylan/Esteve's Formulation and Manufacturing Process

Mylan/Esteve's products are oral pharmaceutical preparations in the form of capsules filled with omeprazole-containing pellets. Although Mylan/Esteve manufactures two types of pellets-Delayed Release Pellets and Super Delayed Release Pellets-both are comprised of a sugar seed, a drug layer, two sublayers, and an enteric coating. (Davies Tr. 165:15-21; PSWTX 1205 at OMP 005129, 005131; PSWTX 433.) More specifically, Mylan/Esteve's formulation contains: (1) an inert sugar/starch sphere; (2) an active coating of omeprazole, talc, and hydroxypropyl methylcellulose ("HPMC") ("Film Coating No. 1" or "active drug layer"); (3) a subcoating of HPMC, talc, and titanium dioxide ("Film Coating No. 2"); (4) a second subcoating of HPMC and ethylcellulose ("Film Coating No. 3"); and (5) an enteric coating of methacrylic acid copolymer, triethylcitrate, and talc (the "enteric coating"). (Lopez Tr.2076:4-2077:8; Langer Tr. 1127:3-1128:9, 1128:19-24; PSWTX 433; PSWTX 1205 at OMP 005129-33; M/EX 8335.)

Mylan/Esteve prepares its pellet cores by spraying a suspension of omeprazole, HPMC, and Microace(R) talc onto sugar spheres, resulting in a homogenous active drug layer. (Davies Tr. 146:15-147:8, 184:15-22, 185:15-187:6; Langer Tr. 1127:3-15; PSWTX 1205 at OMP 005129-005134; PSWTX 456 at OMP 510018, 510024-26; PSWTX 1255-6; PSWTX 677 at OMP 095843-44; PSWTX 677T at OMP 095843-44; Mancinelli Dep. Tr. 107:9-109:4, May 22, 2003.)

According to Mylan/Esteve's ANDA, Mylan/Esteve first makes an HPMC and micronized Microace(R) talc suspension in purified water and mixes and homogenizes the suspension. Mylan/Esteve then adds micronized omeprazole to the suspension and again mixes and homogenizes it. This suspension is referred to as Film Coating No. 1. Mylan/Esteve loads and preheats sugar seeds in the fluid bed, then sprays Film Coating No. 1 onto the sugar seeds. The spraying of the active drug layer is done at elevated temperatures, 40 to 80 (deg.)C, for about 10 hours. This results in the drug layered pellet. (Langer Tr. 1127:3-15; PSWTX 1205 at OMP 005129, 005132; PSWTX 456 at OMP 510018, 510023-26; PSWTX 1255-6; Davies Tr. 184:15-22, 690:22-691:6; PSWTX 677 at OMP 095843-44; PSWTX 677T at OMP 095843-44.)

Drug layered pellets are then coated with a suspension of 79% HPMC, 10.5% Microace(R) talc, and 10.5% titanium dioxide in purified water, referred to as Film Coating No. 2. Film Coating No. 2 forms the first sublayer in Mylan/Esteve's pellets. The drug layered pellets are sprayed with Film Coating No. 2 and dried in a Huttlin Kugelcoater to produce the seal coated, drug layered pellets. (Langer Tr. 1127:16-21; PSWTX 1205 at OMP 005130, 005132; PSWTX 456 at OMP 510018, 510026-28; PSWTX 1255-7; Davies Tr.

184:23-185:3, 185:15-186:8, 267:9-18, 285:15-17; 292:12-15; PSWTX 1250-34; PSWTX 1250-1; PSWTX 677 at OMP 095843; PSWTX 677T at OMP 095843.)

Mylan/Esteve loads and preheats the pellets, which at this point contain an active drug layer and a first sublayer, in a Huttlin fluid bed. A suspension of HPMC and Surelease(R) (ethylcellulose) in water, referred to as Film Coating No. 3, is then sprayed onto the pellets. Film Coating No. 3 forms the second sublayer.FN14 (Langer Tr. 1127:22-1128:1; Davies Tr. 690:22-691:6; PSWTX 1205 at OMP 005130, 005132-33; PSWTX 456 at OMP 510018, 510032-35, 510037; PSWTX 1255-8.)

FN14. This second sublayer (Film Coating No. 3) is added to Mylan/Esteve's U.S. Product to make it bioequivalent to Prilosec(R). (Langer Tr. at 1128:10-18; Lopez Tr. 2181:12-24.)

After drying, Mylan/Esteve loads and preheats the pellets in the fluid bed and sprays the pellets with a suspension composed of Eudragit L 30D 55(R) (methacrylic acid copolymer enteric coating), triethyl citrate (plasticizer) and talc, referred to as Film Coating No. 4. Film Coating No. 4 forms the outer layer, or enteric coating. The enteric coated pellets are then dried in a Huttlin Kugelcoater to produce the Omeprazole Delayed Release Pellets and Super Delayed Release Pellets. (Langer Tr. 1128:19-22; PSWTX 1205 at OMP 005130-31, 005133; PSWTX 456 at OMP 510018, OMP 510036-42, 510040-42; PSWTX 1255-9.)

Mylan/Esteve's final product is a capsule containing 80% Delayed Release pellets and 20% Super Delayed Release pellets. The Delayed Release pellets contain 45% HPMC and 55% ethylcellulose in the second sublayer, and the Super Delayed Release pellets contain 30% HPMC and 70% ethylcellulose in the second sublayer. (Langer Tr. 1128:2-9; PSWTX 1255-8.)

Mylan/Esteve's 10-mg, 20-mg, and 40-mg products are made in the same way but "differ only as to the number of delayed-release and super delayed-release pellets contained in the capsule and the size of the capsule." (Mylan's Resp. to Pls.' First Set of Req. for Admis. at No. 188.) The number of pellets is adjusted to account for the amount of omeprazole in the final product. (Langer Tr. 1128:19-24; PSWTX 1225-9.)

a. Bulk Omeprazole From Esteve

Mylan/Esteve's product is made using bulk omeprazole manufactured by Esteve. Esteve's omeprazole manufacturing process is described in Esteve's omeprazole Drug Master File ("DMF"). (Swenton Tr. 2275:13-16, 2389:14-2390:12 (explaining that the process used by Esteve is the same as process described in the DMF).) Esteve uses tryethylamine ("TEA") as a co-solvent with acetone to recrystallize its omeprazole. (Swenton Tr. 2345:18-24.) TEA is an organic base and is commonly considered a weak base; it is partially water soluble and has a boiling point of about 90 degrees. (Swenton Tr. 2267:7-18.)

Esteve maintains that it uses TEA as one of its co-solvents during purification to obtain a more pure omeprazole compound. (Swenton Tr. 2268:24-2269:8, 2269:17-2271:25; M/EX 549 at 54; M/EX 550 at 80; M/EX 832 at 11; M/EX 8361; Coppi Dep. Tr. 58:2-22, Mar. 12, 2004, 4:40PM.) The use of an organic base during recrystallization can prevent decomposition during the purification process.FN15 (Swenton Tr. 2268:14-2269:8.)

FN15. Plaintiffs use the organic base ammonia during their recrystallization of omeprazole. (Langer Tr. 1448:1-4; Davies Tr. 766:24-767:9; Swenton Tr. 2281:11-22; M/EX 828; M/EX 8052.)

Esteve's crystallization process for purifying crude omeprazole involves dissolving the omeprazole and soluble impurities, filtering off any insoluble material, crystallizing the omeprazole from solution, washing

the crystals, and then drying the crystals to obtain a pure compound. Specifically, crude omeprazole (with impurities) is placed in water and stirred with TEA and acetone. That mixture is then heated to dissolve the omeprazole, leaving behind any insoluble foreign matter. This foreign matter is removed by filtration. The remaining solution is reduced in volume and cooled, causing omeprazole to precipitate out of the solution. The mixture is then centrifuged to remove the acetone and TEA along with dissolved impurities. The omeprazole crystals are washed again with a mixture of acetone and TEA to dissolve any impurities that remained on the surface of the crude omeprazole after the first centrifugation. The resulting crystals are then dried under a vacuum to remove remaining volatiles including acetone and TEA. (Swenton Tr. 2269:17-2271:25, 2278:2-2279:10, 2279:16-2280:1, 2281:23-2282:8; M/EX 549 at 54-55.) To meet United States Pharmacopeia ("USP") standards and to be legally sold, Esteve's omeprazole must be tested for purity against USP Reference Standard omeprazole. *See* 21 U.S.C. s. 351(b); Langer Tr. 1429:5-25; M/EX 203. Esteve's omeprazole complies with the USP standard for purity. (Langer Tr. 1429:13-1430:3.)

2. Claim 1(a): An Effective Amount of an Alkaline Reacting Compound (ARC)

a. Presence of an ARC

As stated above, claim 1(a) of the '505 Patent requires:

1. An oral pharmaceutical preparation comprising

(a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;

(PSWTX 1A 16:42-47.) An "alkaline reacting compound" ("ARC") is "(1) a pharmaceutically acceptable alkaline, or basic, substance having a pH greater than 7 that (2) stabilizes the omeprazole or other acid labile compound by (3) reacting to create a micro-pH of not less than 7 around the particles of omeprazole or other acid labile compound." Astra v. Andrx, 222 F.Supp.2d at 453. The term "effective amount" "applies to both omeprazole and the ARC and requires an amount of each substance such that the combination of omeprazole plus the ARC meets the stated goal of the invention of stabilizing the omeprazole." *id*. at 463.

Plaintiffs allege that the carbonates in Mylan/Esteve's Microace(R) talc and HPMC, and the TEA in its omeprazole are all individually, and collectively, ARCs-each having a pH greater than 7, and present in an effective amount to stabilize the omeprazole by creating a micro-pH of not less than 7. (Davies Tr. 146:15-149:19, 165:22-166:23, 189:17-190:16, 262:15-263:7, 292:4-18; Langer Tr. 11523:2-1153:17; PSWTX 1250-2; PSWTX 1250-10; PSWTX 1250-13; PSWTX 1255-33.)

i. Talc

With respect to Mylan/Esteve's product, Plaintiffs' experts claim that (1) Mylan/Esteve's Microace(R) talc is alkaline (Davies Tr. 191:10-194:3; 195:3-198:8; PSWTX 1250-16; PSWTX 935; PSWTX 936; PSWTX 993A; Durst Tr.1953:21-1955:17; M/EX 97; M/EX 110A; M/EX 103); (2) the substance that imparts alkalinity to the talc in Mylan/Esteve's product is carbonate (Davies Tr. 200:13-203:4; 204:22-205:2; PSWTX 937; PSWTX 1030 at 78-79; Langer Tr. 1132:19-1133:5; PSWTX 1255-17); and (3) one of ordinary skill in the art would understand that carbonates in talc are ARCs (Langer Tr. 5475:14-17; *see also* 1133:16-1135:20; PSWTX 966). As the Court stated in the First Wave Litigation, "[r]egardless of whether the posited alkaline reacting compound is [a core ingredient] itself or an impurity contained within [a core ingredient], the infringement analysis remains the same." Astra v. Andrx, 222 F.Supp.2d at 551 n. 80.

Talc is a naturally occurring material, which is comprised of purified, hydrated, magnesium silicate. (Langer

Tr. 1131:23-1132:2; PSWTX 940 at 1999.) Different grades or types of talc can have different properties and different pHs. The Handbook of Pharmaceutical Excipients lists a range of pH values for talc, from an acidic pH of 6.5 to a highly alkaline pH of 10. (Davies Tr. 1063:15-1065:14; PSWTX 2016 at 555; PSWTX 2016A at 519; PSWTX 1664 at 555.) Mylan/Esteve's active drug layer and enteric coating include the same brand and grade of talc, called Microace(R) talc.FN16 (Lopez Tr. 2105:6-11; Langer Tr. 1352:21-25; Davies Tr. 803:16-22; PSWTX 1205 at OMP 005129, OMP 005131.) The active layer in Mylan/Esteve's product is roughly 12 percent talc and the enteric coat contains about 11 percent talc. (Langer Tr. 1352:14-20; *see also* M/EX 321 at OMP 057376.)

FN16. Mylan/Esteve also uses Alphafil(R) talc to dust the outside of its completed pellets. (Davies Tr. 207:15-25.)

Mylan/Esteve's specifications for Microace(R) talc require that it have a pH of not less than 7.0. (Langer Tr. 1132:3-10; Davies Tr. 210:22-211:9; PSWTX 1199; PSWTX 1200; PSWTX 1255-15; Lopez Dep. Tr. 308:23-310:21.) Mylan/Esteve's certificate of analysis for two batches of talc used to make Mylan/Esteve's ANDA batches report that 2% suspensions raised the pH of water to 7.6 and 7.8. (Langer Tr. 1132:3-10; PSWTX 1199; PSWTX 1200; PSWTX 1255-15.) Dr. Davies also obtained alkaline pH results for samples of both Microace(R) talc (Davies Tr. 190:23-199:21; PSWTX 935; PSWTX 936; PSWTX 993A; PSWTX 1250-16), and Alphafil(R) talc (Davies Tr. 207:15-19, 208:1-209:5, 209:15-210:6; PSWTX 993C).

Plaintiffs assert that Mylan/Esteve relies on the alkalinity of its talc to stabilize the omeprazole in its product. (Davies Tr. 224:15-22; Langer Tr. 1139:13-1143:14; PSWTX 1255-21.) Plaintiffs further assert that carbonates are the source of the alkalinity in Mylan/Esteve's talc. (Davies Tr. 200:13-203:4, 204:22-205:2; Langer Tr. 1132:19-1133:5; PSWTX 937; PSWTX 1030 at 78-79; PSWTX 1250-18; PSWTX 1255-17.) The '505 Patent lists carbonates as potential ARCs, discussing "salts of ... carbonic acid" and disclosing sodium carbonate as an ARC in Example 9. (Langer Tr. 1133:6-15; PSWTX 1A 3:38-51, 11:54 (Ex. 9); PSWTX 1255-18.)

Talc is known to contain materials such as calcium carbonate and magnesium carbonate. (Langer Tr. at 1132:19-1133:5; PSWTX 940 at 1999; PSWTX 1255-17.) According to the European Pharmacopoeia 4, talc "may contain variable amounts of associated minerals among which chlorites (hydrated aluminum and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate) and dolomite (calcium and magnesium carbonate) are predominant." (PSWTX 940 at 1999; Langer Tr. 1132:23-1133:1; Davies Tr. at 206:18-207:14.)

To determine the cause of the alkalinity in Mylan's Micorace(R) talk, Dr. Davies performed attenuated total reflectance Fourier spectroscopy, or ATR-FTIR, tests on Mylan's talc.FN17 (Davis Tr. 200:13-23.) Dr. Davies made a 20% suspension of the talc, centrifuged the solution, and dried it down; this produced a white deposit, which Dr. Davies measured with ATR-FTIR. (*Id*.) The infrared spectrum showed that the deposit contained peaks at 1422, 1070, and 865. Using the *Infrared Spectra of Inorganic Compounds,* Dr. Davies confirmed that the peaks at 1422 and 865 are diagnostic of carbonates present within talc. (201:3-203:4; PSWTX 937; PSWTX 1030A at 78-79; PSWTX 1250-18; PSWTX 1250-19.)

FN17. Attenuated total reflectance Fourier spectroscopy, or ATR-FTIR, is a form of infrared spectroscopy that is widely used within the pharmaceutical industry to determine the chemical characterization of pharmaceuticals. (Davies Tr. 370:8-16.) In ATR-FTIR, infrared light is projected through a crystal onto the sample to a depth ranging from one to three microns or more, depending on the crystal being used and the wavelength of light being examined. (Davies Tr. 370:17-227, 386:17-387:13; PSWTX 1251-23.) Some of the infrared light is absorbed by the molecules in the layer. The difference between the absorbed and reflected light is analyzed by the ATR equipment and represented as a graph, or spectrum, providing a

fingerprint of the chemical content of the material being analyzed. The peaks within the spectrum reflect molecular vibrations within the molecule which can be identified by comparison to standard reference materials. (Davies Tr. at 370:17-371:5; PSWTX 1251-17.)

Dr. Davies also conducted energy dispersive x-ray analysis (EDX analysis) FN18 of the white deposit obtained from the centrifugation described above, to determine the type of carbonate present in Mylan's talc. Dr. Davies's tests of the supernatant show peaks that indicate that calcium and magnesium are present. (Davies Tr. at 200:24-201:2, 205:14-206:11; PSWTX 939.)

FN18. EDX is a technique whereby a sample is irradiated with primary electrons, which produces an emission of x-ray photons. These x-ray photon emissions are characteristic for each particular element being analyzed, allowing detection of the elemental composition of the sample. (Davies Tr. 205:19-24.)

In contrast to Dr. Davies's results, both Esteve and the supplier of Microace(R) talc, Nippon, tested batches of Microace(R) talc for the presence of carbonates and found no detectable amount of carbonate. (Lopez Tr. 2111:21-2114:1; M/EX 841; M/EX 842.) This result does not conclusively establish that carbonate is not present, as carbonate could be present in an amount below the level of detection; however, it does suggest that if there is any carbonate present, it is only in very small amounts. (PSWTX 694 at EQ-FD 38098.)

Thus, the Court finds that the empirical evidence of the presence of carbonates in the talc used in Myan/Esteve's product is inconclusive.

Further weighing against Plaintiffs' assertion that the talc is an ARC is the fact that talc is not included in the patents' list of potential ARCs. (Langer Tr. 1351:5-10.) Although, the Court recognizes that "the appropriate inquiry is whether a particular compound has the required properties to perform the functions required of an ARC, not whether the compound is included in a non-exhaustive list of examples in the specification," Astra v. Andrx, 222 F.Supp.2d at 461, the '505 and '230 Patents explicitly mention talc as an "ordinary additive" to be used in the separating layer, *in addition to an ARC* (PSWTX 1A 4:14-56; PSWTX 2A 9:9-50), and as a dispersant to be added into the enteric coating (PSWTX 1A 5:16-18; PSWTX 2A 10:10-12; Davies Tr. 696:9-697:6). The patent teaches by implication that talc is not an ARC. *See* Vitronics, 90 F.3d at 1582 ("The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." (citing Markman, 52 F.3d at 979)).

Example 1 of the '505 Patent further demonstrates that the patents disclose talc as a conventional pharmaceutical excipient. (PSWTX 1A 6:27-7:54.) Example 1 describes an experiment comparing the stability of seven different enteric-coated tablet formulations having various core components. (PSWTX 1A 6:28.) All of the cores in Example 1 contained the same amounts of omeprazole, lactose, hydroxypropylcellulose ("HPC"), and talc. (*Id*.) Core formulation 1 in the Example contained only the above four ingredients, while the remainder of the formulations also included one or more of the compounds that the patents specifically identify as ARCs. Formulation 1, which contained talc but none of the ARCs, showed greater discoloration and was reported as unstable in comparison to the others. (PSWTX 1A 6:67-7:37.)

In a submission to the European Patent Office ("EPO") in connection with the prosecution of the application for Plaintiffs' European counterpart to the ' 505 Patent, EP No. 0 247 983, Plaintiffs' patent attorney, Margarita Linderoth, confirmed that talc was not an ARC within the meaning of the patents:

We have also shown in the specification that the claimed preparation really has the properties defined above and that it is important that the preparation contains

a) alkaline core containing omeprazole

b) subcoting (sic)

c) enteric coating

If one of these characteristics is lacking the preparation is not suitable for practical use. Cf Table 3, page 12 in our specification from which it can be seen that the core material 1 and 7 [*i.e.*, core formulations 1 and 7 in Example 1], *without alkaline compound in the core* are unstable....

(M/EX 824 at 4-5.) Although the Court recognizes that that "the varying legal and procedural requirements for obtaining patent protection in foreign countries might render consideration of certain types of representations inappropriate for consideration in a claim construction analysis of a United States counterpart," TI Group Auto. Sys. (N. Am.), Inc. v. VDO N. Am., L.L.C., 375 F.3d 1126, 1136 (Fed.Cir.2004), in this case, Plaintiffs' representations are relevant to a determination of how one skilled in the art would understand whether talc is considered an ARC. *See* Tanabe Seiyaku Co. v. U.S. Int'l Trade Comm'n, 109 F.3d 726, 733 (Fed.Cir.1997) (finding that representations made to foreign patent office are relevant to the determination of how one of skill in the art would understand interchangeability of chemical solvents). Accordingly, this Court finds that Example 1 of the '505 Patent actually teaches away from relying on talc to stabilize omeprazole. *See* Merck & Co. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1371 (Fed.Cir.2003) ("[T]he claims must be construed so as to be consistent with the specification, of which they are a part.").

While the Court agrees that a constituent present in another substance can serve as an ARC (Langer Tr. 1133:16-1136:23; PSWTX 1255-19), the patents-in-suit do not list a particular brand, grade, or purity level for talc (Davies Tr. 698:18-699:9, 774:8-775:1). General references to ingredients for use in a pharmaceutical formulation, including those in the '505 and '230 Patents, are understood by persons of ordinary skill in that art as references to ingredients that meet acceptability criteria for pharmaceutical use, including any impurities. (Langer Tr. 1363:12-24.) Plaintiffs do not contest that the talc used by Mylan/Esteve complies with applicable Pharmacopeia standards. (Langer Tr. 1366:16-1367:10.) Plaintiffs' experts also failed to identify any source of talc that would be devoid of all trace amounts of carbonate. (Langer Tr. 1380:20-1381:3; *see also* Davies Tr. 701:13-702:2.) Thus, nothing in the patents suggests, much less discloses, that pharmaceutical grade talc with naturally occurring impurities is or should be distinguished from the talc referred to in Example 1 or elsewhere in the patent as an ordinary additive.

ii. HPMC

As with talc, Plaintiffs' experts claim that (1) Mylan/Esteve's HPMC is alkaline (Davies Tr. 147:1-3; 224:23-231:22, 1070:23-1078:8; PSWTX 994; PSWTX 992C; PSWTX 942; PSWTX 943; PSWTX 996; PSWTX 1250-29; PSWTX 1667A); (2) the substances that imparts the alkalinity to the HPMC in Mylan/Esteve's product are carbonates (i.e., bicarbonates and carbonates) (Davies Tr. 233:2-240:15; Langer Tr. 1146:22-1147:17; PSWTX 943; PSWTX 992B; PSWTX 115; PSWTX 115TA; PSWTX 1250-28; PSWTX 1250-29 PSWTX 1250-31); and (3) the carbonates in HPMC stabilize the omeprazole and are ARCs under the '505 and '230 Patents (Davies Tr. 240:16-246:21; Langer Tr. 1147:15-17; 1153:7-25; PSWTX 1250-30; PSWTX 1250-31; PSWTX 1255-26; PSWTX 1255-27; PSWTX 115; PSWTX 115TA; PSWTX 1045).

HPMC is classified in the *Handbook of Pharmaceutical Excipients Third Edition* in the functional categories of coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent,FN19 suspending agent, tablet binder, and viscosity increasing agent. (M/EX 8376 at 252.) Similarly, HPMC has

been classified in the USP/NF list of excipients by functional category (both before and after the filing dates of the patents-in-suit) as a coating agent, a suspending and/or viscosity-increasing agent, and a tablet binder. (M/EX 200; M/EX 201.)

FN19. In this context "stabilizing agent" refers to its use in topical gels and ointments to "prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments." (M/EX 8376 at 252.)

HPMC has a range of possible pH values-from 5.5 to 8.0. (M/EX 8376 at 253.) The HPMC used in Mylan/Esteve's ANDA product is Pharmacoat 603, sold by Shin Etsu Chemical Co. (Davies Tr. 233:2-10, 269:22-25; *see* PSWTX 1205 at OMP 005129, 005131.) As explained by Esteve's Dr. Lopez, Mylan/Esteve's original specification for the HPMC used in its drug layer indicated a possible pH range of about 5.5 to 8.0. (Lopez Tr. 2116:2-4; PSWTX 1953.) In November 2002, Mylan/Esteve restricted its HPMC specification to pHs ranging from 5.5 to 6.3. (Lopez Tr. 2114:9-2115:1; M/EX 69; PSWTX 1667A.) Nevertheless, Dr. Davies testified that his pH testing of the HPMC used in Mylan/Esteve's product showed mean pH values in the range of 7.34-8.22 for 10-60% sample concentrations. (Davies Tr. 224:23-229:9, 780:4-8; 782:8-20; Langer Tr. 1146:22-1147:7; PSWTX 992B; PSWTX 942; PSWTX 1250-29.)

Based on titration and gas chromatography-mass spectrometry ("GC-MS") FN20 testing of Pharmacoat 603 HPMC by Astra scientist Dr. Jorgen Lindquist, Plaintiffs' experts assert that carbonates are the source of the alkalinity in Mylan/Esteve's HPMC. (Davies Tr. 233:2-240:15; Langer Tr. 1147:9-19; PSWTX 115TA; PSWTX 1250-31.) Dr. Lindquist conducted titration testing of a 20% solution of HPMC. According to Dr. Davies, Dr. Lindquist's data showed a pKa value and titration curve that could be bicarbonate. (Davies Tr. 233:2-240:15; PSWTX 115TA at SWD000101, SWD000104.)

FN20. Gas chromatography-mass spectrometry combines the features of gas chromatography with mass spectrometry. Gas chromatography allows you to separate multiple volatile species evolving from a single sample. (Russell Tr. 4461:24-4462:2; 4462:23-4463:3.) The gas chromatogram is made up of a long capillary tube through which the gas or liquid species travel through. (Russell Tr. 4461:18-4462:17.) The gaseous species diffuse through the column at different rates and arrive at the mass spectrum at different times. (Id.; *Russell Tr. 4462:23-4463:3*.) This allows the mass spectrometer to analyze each species separately and will produce mass spectra for each individual species. (*See Russell Tr*. 4461:18-4462:17; *4462:23-4463:3*.) For a detailed discussion of mass spectrometry, *see infra* note 46.

Dr. Lindquist also used gas chromatography-mass spectrometry to analyze the HPMC, and detect and measure the presence of CO2. (Davies Tr. 237:4-239:5; PSWTX 115TA at SWD000105-106). Dr. Lindquist added 0.1 molar HCL to a small sample of HPMC Solution in a sealed bottle to acidify it and convert the bicarbonates to carbonic acid. The solution was incubated overnight so the carbonic acid would convert to CO2, and escape into the air above the solution. The gas phase was then analyzed with a gas chromatograph-isotope ratio mass spectrometer to detect the presence of CO2. (Davies Tr. 237:4-239:5; Lindquist Dep. Tr. 442:20-450:25, May 16, 2003.) Dr. Lindquist detected an average of about 1.5 CO2 in the test tubes, which coverts to about .13 percentage CO2 in HPMC. This amount corresponds to 0.25 percent of sodium bicarbonate in that HPMC sample. (Davies Tr. 237:4-239:5; Lindquist Dep. Tr. 442:20-450:25, May 16, 2003; PSWTX 115TA at SWD000105-106.)

However, the presence of carbonates in the HPMC used by Mylan/Esteve does not automatically make the HPMC and its constituent carbonates ARCs within the meaning of the '505 and '230 Patents. As this Court stated in the First Wave opinion, "HPMC is specifically disclosed in the '505 and '230 Patents, not as an ARC, but rather as an inert, nonreactive substance that may be used as a subcoat or separating layer, which

has nothing to do with the ARC in the core." Astra v. Andrx, 222 F.Supp.2d at 553 (citing PSWTX 1A 4:31-42, PSWTX 2A 9:26-36). When addressing Plaintiffs' allegations that HPMC in Kremers Urban Development Co./Schwarz Pharma, Inc.'s ("KUDCo") core was an ARC, this Court recognized that the same compound cannot be both "alkaline reacting" and "inert":

Astra has made a clear distinction in these patents between substances that are 'alkaline reacting' and substances that are 'inert.' The same compound cannot be both. Thus, those compounds that the applicant explicitly defined as 'inert,' including HPMC, cannot be 'alkaline reacting' within the meaning of the patents.

Id. at 554. The same reasoning applies here. HPMC which is identified as "inert" by the patents cannot simultaneously be claimed to be "alkaline reacting" within the meaning of the patents.

Moreover, as with talc, nothing in the patents supports Plaintiffs assertion that HPMC with any impurities is an ARC within the meaning of the patents. Plaintiffs do not contest that the HPMC used by Mylan/Esteve complies with applicable Pharmacopeia standards (Langer Tr. 1417:18-1418:8), and the patents-in-suit do not list a particular brand, grade, or purity level for the HPMC referred to therein. First Wave Defendant KUDCo, who was found not to infringe, used the same source of HPMC in its core. Astra v. Andrx, 222 F.Supp.2d at 551. Here, as with KUDCo, the Court is not convinced that Mylan/Esteve selected Pharmacoat 603 HPMC for anything other than its film-forming and binding properties. (Lopez Tr. 2109:24-2110:20; M/EX 75 at OMP 004313; Mancinelli Dep. Tr. 20:15-24, 21:7-23, 22:9-13, 23:18-24:21.)

iii. TEA

Plaintiffs assert that during the final crystallization step of Esteve's omeprazole manufacturing process, triethylamine or TEA becomes entrained, or embedded, in the omeprazole crystals, and stabilizes the omeprazole. (Davies Tr. 297:5-13, 352:25-353:24; Langer Tr. 1148:9-1150:2, 11-1180:20 (citing Hafner-Milac Dep. Tr. 82:23-83:10, July 21, 2003); Langer Tr. 1545:9-16; Hafner-Milac Tr. 2887:3-2890:6; LEKTX 611T; PSWTX 1874A; PSWTX 1029A at 22:26-29; PSWTX 2113.) Plaintiffs claim that Esteve ensured it would entrain as much TEA as possible in the omeprazole by concentrating its solution with TEA just prior to crystallization.FN21 Dr. Klibanov testified that, because the boiling point of acetone will remain lower than that of TEA, the solvent will become even more enriched in TEA during the vacuum distillation just prior to crystallization of omeprazole.FN22 (Klibanov Tr. 5258:19-5260:6.) TEA has a boiling point of 89 (deg.) to 90 (deg.)C while acetone has a boiling point of 56.5 (deg.)C. (Swenton Tr. 2354:19-2355:5; PSWTX 2074; PSWTX 1259-17; *see also* Klibanov Tr. 5259:1-6.) Dr. Klibanov stated that acetone will be evaporated to a greater extent due to its lower boiling point, the solvent will become enriched in TEA, and more TEA will become entrained in omeprazole crystals that are formed. (Klibanov Tr. 5258:19-5260:6.) Moreover, Dr. Klibanov testified that the "fast crystallization" used by Mylan/Esteve (and Lek, as discussed below) will result in even more inclusions. (Klibanov Tr. 5263:14-5265:14.)

FN21. Plaintiffs' assertion that statements made by Mylan/Esteve's Dr. Swenton (Swenton Tr. 2399:1-22; *see also* PSWTX 1029A at DAVIES2W3011950, DAVIES2W3011971, DAVIES2W301990) and Dr. Coppi (Coppi Dep. Tr. 142:15-144:25, Mar. 12, 2004, 9:30AM; PSWTX 2142 at 41:4-16), as well as Lek's Dr. Sirca (Sirca Dep. Tr. 403:14-405:23, Sept. 11, 2003; PSWTX 216), Dr. Padwa (Padwa Tr. 2983:18-25, 2984:7-17, 2984:22-2985:3, 2985:15-2986:25; PSWTX 701 at p. 11), and Dr. Kanalec (Kanalec Dep. Tr. 93:22-94:6, 95:22-96:17, Sept. 9, 2003), indicate that Esteve intentionally uses TEA to stabilize its bulk omeprazole is inapposite. As discussed in more detail later, even if Plaintiffs are correct that Mylan/Esteve uses TEA for stabilization purposes in its *bulk omeprazole,* to meet their burden of proof Plaintiffs must demonstrate (1) that TEA survives into Mylan/Esteve's *final formulation* and (2) that TEA has a stabilizing effect in Mylan/Esteve's *final ANDA product*.

FN22. Mylan/Esteve moves to exclude the testimony of Dr. Klibanov on the grounds that under *Daubert* his opinions are untested hypotheses, have not been subjected to peer-review or publication, are litigation-motivated, and are internally inconsistent. The Court has admitted Dr. Klibanov's testimony. However, recognizing that it is not supported by empirical evidence or experiment, has given it little weight.

Esteve maintains, however, that it uses TEA solely as a solvent in the purification of the omeprazole active ingredient and that it seeks to remove all TEA from the omeprazole during the purification process. (Swenton Tr. 2282:13-18.) Esteve asserts that its purification process leads to an almost complete removal of impurities. The certificates of analysis for Esteve's omeprazole compound show that it consistently has total impurities of about 0.1% or less. (M/EX 19; M/EX 16A; M/EX 17A; M/EX 18A.) Esteve's Dr. Coppi also testified that Esteve works to remove TEA from their omeprazole:

Q. Would Esteve deliberately rely upon the presence of any amount of triethylamine to perform a function in the bulk drug substance?

. . . . .

A. No.

Q. Why not?

A. The residual TEA in the final drug substance are we talking about?

Q. Yes.

A. No. Because this is not absolutely-well, first of all, the presence of TEA in the final drug substance is, I would say, accidental. Just because it is used in some previous stage. So the purpose of using TEA is limited to the step where it is used and it doesn't have anything to do with the subsequent stages of the process.

Our objective is to remove, as best as we can, all the impurities. And residual solvent and everything. We are limited in that only by intrinsic limitation of the reality, the material reality. But our purpose is to remove as much as possible of any impurity that is present in the final drug substance.

In the case of triethylamine I think we have done quite a good job as so many batches of residual amount that is below the detection limit.

(Coppi Dep. Tr. 71:16-72:20, Mar. 12, 2004 4:40PM.)

Plaintiffs argue that pH tests conducted by Dr. Davies in which Esteve's bulk omeprazole exhibited pHs of 7.0 or greater (as compared to the pH of 6.4 for pure omeprazole) demonstrate the presence of TEA in Esteve's bulk omeprazole.FN23 (Davies Tr. 251:4-258:2, 303:11-305:3, 746:21-748:19; PSWTX 938; PSWTX 984; PSWTX 991A; PSWTX 1251-4; PSWTX 1251-5; PSWTX 1251-6; PSWTX 1858.) FN24 However, according to the testimony of Mylan/Esteve's Dr. Durst, pH testing is a quantitative measurement but it cannot identify what is causing the rise in pH. (Durst Tr. 1798:23-1799:15.)

FN23. Dr. Davies obtained an alkaline pH of 6.7 for one batch of Esteve omeprazole (98-504). Dr. Davies attributes this reading to the age of the sample, which, he testified, was expired at the time of testing. (Davies Tr. 251:10-258:2; PSWTX 984; PSWTX 991A.)

FN24. However, as described in greater detail below with respect to Lek's product, other scientists, including Astra's Dr. Lindquist, Mylan/Esteve's Dr. Durst, and Lek's Dr. Christian, obtained acidic pH values for Esteve's bulk omeprazole. (*See, e.g.,* Durst Tr. 1786:1-1788:14, 1806:18-1807:12; Swenton Tr. 2318:2-11, 2318:19-2320:1; M/EX 424; M/EX 8046A; M/EX 8345; M/EX 8362; M/EX 8300; M/EX L4; PSWTX 115TA at SWD 97.)

In addition, Dr. Davies's assertion that TEA causes the elevated pH results he obtained is called into question by the absence of any correlation between his pH measurements and the amount of TEA measured in Esteve's omeprazole compound as reported in Esteve's certificates of analysis. (Durst Tr. 1796:11-1798:22; Swenton Tr. 2316:2-2318:1.) For example, Dr. Davies reported virtually the same pH (about 7.4) for three different lots for which the reported TEA amounts were 36 parts per million ("ppm"), 26 ppm, and "none detected." In addition, one lot of omeprazole with a reported TEA content of 10 ppm was found to have a lower pH than four lots of omeprazole that had no detectable TEA. (Durst Tr. 1796:11-1798:22; Swenton Tr. 2316:2-2318:1; M/EX 8049A; PSWTX 938; PSWTX 1046; PSWTX 1047A; PSWTX 1049A; PSWTX 1050; PSWTX 1051; PSWTX 1052; PSWTX 1053; PSWTX 1099.)

Plaintiffs further point to the certificates of analysis for Esteve manufactured omeprazole as evidence of the presence of TEA. The analytical certificates for the Esteve omeprazole batches on which Dr. Davies conducted his pH tests permit up to 300 ppm TEA, however none actually contained more than 36 ppm and four out of eight batches did not contain a detectable amount of TEA. (Davies Tr. 311:24-314:9; PSWTX 1046; PSWTX 1047A; PSWTX 1049A; PSWTX 1050; PSWTX 1051; PSWTX 1052; PSWTX 1053, PSWTX 1099.) In fact, approximately 30% of batches of Esteve's bulk omeprazole contain no detectable amount of TEA. (Swenton Tr. 2291:5-2292:5; M/EX 8379; *see also* M/EX 16; M/EX 16A; M/EX 17A; M/EX 18A.) The detection limit for TEA is 7 ppm. Therefore, those batches in which TEA was not detected may contain 0 to 7 ppm TEA. (Davies Tr. 311:24-314:9; Swenton Tr. 2285:6-2286:25, 2288:2-21; *see also* M/EX 552 at 208; PSWTX 1046; PSWTX 1047A; PSWTX 1049A; PSWTX 1053.) However, Plaintiffs presented no empirical or experimental evidence that bulk omeprazole in which no TEA was detected by Esteve necessarily contains TEA in some amount below Esteve's 7 ppm detection limit. (Swenton Tr. 2266:9-22; M/EX 8118.)

iv. Combination of Carbonates/Bicarbonates in Talc and HPMC and TEA in Omeprazole

Plaintiffs also assert that a claimed formulation may have more than one ARC and, in the case of Mylan/Esteve's product, the HPMC (with carbonates), talc (with carbonates), and TEA in omeprazole collectively meet the ARC limitation. Again, there is no support in the intrinsic record for a conclusion that the use of these ingredients in combination constitutes an ARC. The mere presence of alkaline substances in Mylan/Esteve's active drug layer-even if, as Plaintiffs assert, every substance is alkaline (Langer Tr. 270:11-271:2, PSWTX 1250-36)-does not establish the presence of a collective ARC. Plaintiffs make no arguments that the use of these ingredients in combination is anything other than the sum of the parts. Plaintiffs cannot establish infringement by attempting to capture a combination of materials, at least two of which are disclosed in the intrinsic record as substances distinct from ARCs.

b. Effective Amount of an ARC in Mylan/Esteve's Final Product

Even if the Court were to find that talc (with any impurities), HPMC (with any impurities), and TEA in omeprazole could function as ARCs within the meaning of the patents, Plaintiffs have failed to show that Mylan/Esteve's product contains an effective amount of talc, HPMC, or TEA, alone or in combination, to stabilize the omeprazole by creating a micro-pH of not less than seven. Claim 1(a) of the '505 Patent requires an "effective amount of a material selected from the group consisting of omeprazole plus an

alkaline reacting compound." (PSWTX 1A 16:43-45.) The Court previously determined that

[e]ven though the claim limitation of an 'effective amount' is not present in [the] '230 Patent, [the Court's] construction of the term 'alkaline reacting compound' requires the stabilization of the acid labile compound. Even though no explicit ratio or quantity relationship is present in the claims of the '230 Patent, that requirement is implicit in the characteristics of the ARC as defined by the patentees.... [and] 'effective amount' is found implicitly in the ARC claim limitation.

Astra v. Andrx, 222 F.Supp.2d at 462 n. 24. An "effective amount" of an ARC "is an amount sufficient to stabilize the omeprazole in the formulation's core. As the specification discloses, that stabilization is achieved by using an ARC in the core to create a micro-pH around the omeprazole particles of not less than pH 7." *Id*. at 463-64. The amount of alkaline reacting compound sufficient to be "effective" in relation to the omeprazole depends on the nature of the formulation and how it was made. *Id*.

Thus, to meet their burden of proof Plaintiffs must demonstrate (1) that the carbonates or bicarbonates in talc and HPMC and/or the TEA in omeprazole survive into Mylan/Esteve's *final formulation* and (2) that the carbonates and/or TEA, alone or in combination, have a stabilizing effect in Mylan/Esteve's *final ANDA product*.

i. Carbonates in Talc and HPMC

Plaintiffs have pointed to no evidence of how much carbonate, if any, is present in Mylan/Esteve's *fully formulated product*. Dr. Davies detection of the presence of carbonates in Mylan/Esteve's talc (*see, e.g.,* Davies Tr. 200:13-203:4, 204:22-205:2; PSWTX 937; PSWTX 1250-18) simply confirms what the literature and Pharmacopeia guidelines already disclosed-that pharmaceutical grade talc contains a small amount of impurities, including carbonates. Plaintiffs present no evidence that such impurities are present in Mylan/Esteve's fully formulated product.

Plaintiffs argue that Esteve developers knowingly use talc in their formulation to stabilize the omeprazole, largely based on statements made by Esteve's Dr. Lopez (Lopez Tr. at 2165:15-2167:5, 2168:4-7; PSWTX 697T at EQ-FD 139996; Lopez Dep. Tr. 218:l0-219:17, 222:4-10, 223:17-224:13, 226:16-228:24, 230:3-233:4, Apr. 1, 2004), Dr. Parera (Parera Dep. Tr. 122:6-19, Mar. 26, 2004), Dr. Augsburger (Augsburger Dep. Tr. 157:3-159:25, Oct. 20, 2004), and Ms. Ballester (Ballester Tr. 1743:5-1744:6; PSWTX 602). However, even if Esteve's developers believed the presence of talc would improve the stability of their bulk omeprazole during the formulation process, Plaintiffs must demonstrate that the Microace(R) talc used in Mylan/Esteve's fully formulated product is, in fact, an ARC under the patents-in-suit. Plaintiffs' mere assertion that Esteve's developers used talc for stability purposes is not sufficient to overcome the inconclusive (or absent) empirical evidence regarding the presence of carbonates in Mylan/Esteve's active layer (Lopez Tr. 2111:21-2114:1; M/EX 841; M/EX 842; Davies Tr. 200:13-203:4, 204:22-205:2; PSWTX 937; PSWTX 1250-18; PSWTX 1250-19; PSWTX 1030 at 78-79) and the teaching of the '505 and '230 Patents that talc is a conventional pharmaceutical excipient and not an ARC (*see* PSWTX 1A 6:27-7:54; *see also* M/EX 8033).

Plaintiffs' experts rely on Dr. Davies's acid titrations (or "acid challenge tests") to demonstrate the "buffering ability" of the talc and HPMC used in Mylan/Esteve's product (*see, e.g.,* Davies Tr. at 197:2-198:21, 707:11-710:7; PSWTX 993A; PSWTX 936) and rebut the assertions of Mylan/Esteve's expert, Dr. Durst, based on his own titrations, that these substances cannot maintain an alkaline pH upon exposure to acid (*see, e.g.,* Durst Tr. 1812:10-1841:19; M/EX 8351; M/EX 103; M/EX 110A). However, because there is no buffer capacity test requirement for an ingredient to be considered an ARC, *see* Astra v. Andrx, 222 F.Supp.2d at 477-78, the Court considers the acid titration data largely irrelevant to the question of whether talc, HPMC, and/or TEA are ARCs in Mylan/Esteve's product.FN25

FN25. In support of his assertion that the bicarbonates in HPMC stabilize omeprazole, Dr. Davies also relied on tests where "cakes" made of (a) omeprazole and purified HPMC and (b) omeprazole and Pharmacoat 603 HPMC were subjected to accelerated stress conditions and then visually compared for signs of degradation. (Davies Tr. 240:16-246:2; PSWTX 115TA at SWD00098-99; PSWTX 1045; PSWTX 1250-30.) The Court finds this evidence equally unpersuasive, as it fails to address whether HPMC stabilizes the omeprazole in the active layer of Mylan/Esteve's fully formulated ANDA product by creating a micro-pH of at least 7.

Rather, Plaintiffs must demonstrate that the carbonates in Mylan/Esteve's talc and HPMC are actually present in an amount sufficient to stabilize the omeprazole in the active layer of Mylan/Esteve's product. As the Court explained in rejecting Plaintiffs' reliance on analogous evidence in KUDCo's case:

Astra failed to prove that the HPMC in the KUDCo product stabilizes omeprazole, as all ARCs must do. Astra did present some evidence that HPMC, as a compound *in a solution in water* with omeprazole, may stabilize omeprazole. Omeprazole is quickly degraded in pure water, and the patent teaches that the half-life of omeprazole at neutral pH values is about 14 hours. (P1, col.1:24-29.) In tests to determine how long its omeprazole would remain stable in the 10% HPMC solution used in its process to coat the lactose particles, KUDCo found that it could be held overnight without degradation. KUDCo's own expert, Dr. Auslander, admitted that he could not think of any way that stability could be achieved other than by having an ARC in the composition. Thus, KUDCo's own data provide some evidence, though by no means definitive evidence, that the 10% solution of HPMC used in KUDCo's process to suspend the micronized omeprazole stabilizes the micronized omeprazole *while in that solution*. However, that data does not demonstrate that the HPMC forms a protective film around that micronized omeprazole that continues to protect the omeprazole *throughout the remainder of the formulation process and during its shelf-life;* therefore, it is irrelevant because it fails to test the *core* of KUDCo's products.

Id. at 560 (emphasis in original).

In concluding that talc stabilizes the omeprazole in Mylan/Esteve's fully formulated product, Plaintiffs' experts rely in large part on a comparative stability tests conducted by Mylan/Esteve. (M/EX 8415; PSWTX 681; PSWTX 681T; PSWTX 682; PSWTX 682T.) In response to Plaintiffs' lawsuits in Europe alleging that talc was an ARC, Esteve conducted a number of studies concerning the stability of variations of its formulations made without talc in the active layer. (Lopez Tr. 2128:8-20.) These included (1) formulations of Esteve's European pellet without any talc in the entire pellet manufactured in a pilot plant setting ("pilot plant study"), (2) Esteve's European formulation without any talc in the entire pellet made at an industrial scale ("industrial scale study"), and (3) Esteve'sFrench formulation (delayed release pellet) with all the talc ordinarily in the active and seal coat layers placed in the enteric coating ("French formulation study"). (Lopez Tr. 2129:4-19; M/EX 8415.)

Plaintiffs' experts rely in large part on the pilot plant study in particular, which compares stability data relating to Esteve's three-layered European pellet formulated with and without talc,FN26 to conclude that talc stabilizes Mylan/Esteve's product. (David Tr. 212:5-221:13; Lopez Tr. 2129:22-2130:20, 2131:2-10, 2131:20-2133:14; PSWTX 681; PSWTX 681T; PSWTX 682; PSWTX 682T.) The Court finds this conclusion unpersuasive.

FN26. The "without talc" formulation has no talc in the entire pellet. (Lopez Tr. 2129:22-2130:5; M/EX 305.)

First, the data from this study relates to formulations that are significantly different than Mylan/Esteve's

formulation because, as Drs. Davies and Langer both admitted, they lack the additional outer subcoating layer. (Davies Tr. 213:10-19; Langer Tr. 1397:22-1398:19; *see also* M/EX 8087.) Indeed, Dr. Davies agreed that "the pellets supplied to France and the United States are different from the Esteve pellets all over the rest of the world." (Davies Tr. 723:3-7, 13-20; M/EX 8087.)

Second, the long-term data for the pilot plant study Plaintiffs' experts relied on shows that after two years (23.5 months) under normal storage conditions, both formulations with and without talc remained stable, within specifications. (*See* Davies Tr. 722:3-12; Langer Tr. 1397:6-14; M/EX 8085; *compare* 681T and 682T, *with* M/EX 540 at EQ-FD 059399 and M/EX 537 at EQ-FD 059419.) Both formulations with and without talc had total impurities at the same low level of only 0.4% after 2 years. (Lopez Tr. 2129:22-2130:20, 2131:2-10, 2131:20-2133:14; M/EX 537; M/EX 540; M/EX 8085.) Furthermore, in the industrial scale study a batch of the same talc-free three-layered European formulation, manufactured at Esteve's industrial plant (DF00116), was found to have impurities within specifications, not only for at least 18 months under ordinary storage conditions, but also after three months under the accelerated conditions. (Lopez Tr. 2133:15-2136:12; M/EX 171; M/EX 171T; M/EX 172T.)

Third, Esteve's comparative stability testing of its French formulation study containing the same four-layered delayed release pellets used in Mylan/Esteve's product, but having all the talc usually in the active and seal coat layers placed in the enteric coating (Lopez Tr. 2136:24-2138:23, 2141:1-2142:18), contradicts Plaintiffs' conclusion that talc stabilizes the omeprazole in Mylan/Esteve's product. During this study Esteve manufactured three separate batches of modified delayed release pellets according to its commercial practices with the exception that all the talc in the pellet was placed in the enteric coating. (Lopez Tr. 2141:1-2142:18; M/EX 187TA; M/EX 188TA; M/EX 189TA.) Rather than having 13.28 mg/g talc in the enteric coating and the balance of the 41.44 mg/g of talc in the active and subcoating layers, the modified delayed release pellets contained all 41.44 mg/g of talc in the enteric coating. (Lopez Tr. 2141:14-2142:8.) Esteve's stability testing of the three lots of modified delayed release pellets showed that after six months, both the commercial formulation and the modified formulation had very low levels of impurities. (Lopez Tr. 2155:11-2156:20; M/EX 1111; M/EX 1112; M/EX 8400C.) Even after storage under harsh accelerated conditions for three months, the formulation with no talc in the active layer had total impurities within specifications, and the stability of the modified formulation was equivalent to that of the commercial delayed release pellet formulation. (Lopez Tr. 2157:25-2158:22; M/EX 1111; M/EX 1112; M/EX 8414C.) This study, unlike the study on which Plaintiffs rely, involves the identical formulation as Mylan/Esteve's four-layered delayed release pellet rather than Esteve's three-layered European formulation.FN27

FN27. To the extent Plaintiffs argue that Esteve's French formulation study was not a "side by side" study or that the results are not reliable, the evidence does not support such a claim. This Court denied Plaintiffs' request that all the data relating to the French formulation study be excluded or given no weight, finding that Plaintiffs were not denied discovery and that Dr. Lopez was qualified to testify about the tests and results. (*See* June 11, 2006 Order on Mylan/Esteve's Motion Regarding Stability Studies of French (Delayed-Release Pellet) Formulations). Moreover, Dr. Lopez's testimony and Esteve's manufacturing records confirm that the commercial and modified pellets both were manufactured using the same ingredients and process, with the exception of the location of the talc within the pellets (Lopez Tr. 2141:1-2142:18; M/EX 187TA; M/EX 188TA; M/EX 189TA), and that the stability studies for the commercial and modified pellets were both done according to the same regulatory guidelines (Lopez Tr. 2154:21-2155:10).

The comparative stability data, considered as a whole, do not support Plaintiffs' assertion that talc (with its impurities) stabilizes the omeprazole Mylan/Esteve's product.

ii. TEA in Omeprazole

Plaintiffs also present no empirical or experimental evidence showing that any amount of TEA is present in Mylan/Esteve's fully formulated pellet. (Swenton Tr. 2267:2-2269:8, 2304:2-7, 2321:5-11; M/EX 8385.) Plaintiffs' claim that trace amounts of TEA stabilize Esteve's omeprazole is based on assumptions that, taken together, are insufficient to support such a finding. (Swenton Tr. 2334:2-2335:16.) First, Plaintiffs assume that ppm amounts of TEA detected in some batches of Esteve's omeprazole make the omeprazole self-stabilizing. (Swenton Tr. 2334:16-24). Second, they assume that an unknown amount of TEA is present in Esteve's omeprazole compound, even when none is detected. (Swenton Tr. 2334:25-2335:4.) Third, they assume that an unknown portion of some unknown amount of TEA in the omeprazole compound survives the formulation process to make Mylan/Esteve's pellet. (Swenton Tr. 2335:5-11.) Fourth, they assume that this unknown amount of TEA that they claim survives the formulation process stabilizes the formulated pellet. (Swenton Tr. 2335:12-16.)

Plaintiffs cannot reasonably rely on Dr. Davies's tests for the presence of TEA in Lek's fully formulated product to infer the presence of TEA in Mylan/Esteve's fully formulated product because their pellet formulation process differs in ways that Mylan/Esteve claims are material. (Davies Tr. 758:16-24, 759:8-10; Langer Tr. 1443:14-1444:7; Klibanov Tr. 5349:17-20; *Compare* M/EX 262, M/EX 8336 *with* LEKTX 7234.) Mylan/Esteve asserts that to the extent any TEA is able to reach the surface of the omeprazole particle to be available to combat protons, it would be lost during Esteve's pellet formulation process, which is distinct from Lek's process. (Counsel for Mylan/Esteve Trial Tr. 5281:2-5282:1 (discussing Swenton testimony).)

Here, as with KUDCo, something is stabilizing the omeprazole in Mylan/Esteve's core, but Plaintiffs have failed to show that the talc (allegedly containing an unknown quantity of carbonates), the HPMC (allegedly containing an unknown quantity of carbonates), the omeprazole (allegedly containing an unknown quantity of TEA) or some combination thereof act as an ARC in Mylan/Esteve's product. *See* Astra v. Andrx, 222 F.Supp.2d at 560 ("Something is stabilizing the omeprazole in KUDCo's core, but Plaintiffs have failed to prove that it is the HPMC acting as an ARC.").

c. Micro-pH of the Omeprazole in Mylan/Esteve's Product

As described in the '505 and '230 Patents, an ARC functions to create "a 'micro-pH' around each omeprazole particle of not less than pH = 7, preferably not less than pH = 8, when water is adsorbed to particles of the mixture or when water is added in small amounts to the mixture." FN28 (PSWTX 1 at 3:43-47; *see also* PSWTX 2 at 8:38-42.) Accordingly, an alkaline micro-pH is a necessary but not a sufficient condition for finding the presence of an ARC.

FN28. Mylan contends that there is no evidence of sufficient water in the microenvironment around omeprazole in Mylan's ANDA product to enable the alkaline constituents present in Mylan's drug layer to react, and that there is not sufficient water in Mylan's product to measure the micro-pH of the formulation. (*See, e.g.,* Durst Tr. 1853:8-1855:12.) The Court finds no merit to this argument, as the '505 Patent itself expressly refers to the creation and measurement of micro-pH in a solid formulation and teaches the benefits of reducing the water content of omeprazole formulations, preferably to 1.5% or less (Langer Tr. 1183:8-24; PSWTX 1A 5:63-67, 14:43-61, 15:32-33, 17:20-22; PSWTX 1256-18).

The Court previously determined that "different testing procedures are appropriate to determine the micro-pH of the omeprazole present in different types of cores," Astra v. Andrx, 222 F.Supp.2d at 517, and "the specific steps taken to measure micro-pH must depend on how the formulation is made," id. at 566. Therefore, which test or tests best approximate the micro-pH of a given formulation is a question of fact.

The parties dispute the appropriate test for determining the micro-pH of the omeprazole in Mylan/Esteve's

product. Plaintiffs' Dr. Davies tested the active drug layer alone by removing a piece of the drug layer from the sugar seed (Davies Tr. 166:24-167:18), while Mylan/Esteve's Dr. Durst tested both the entire pellet with the sugar seed as well as a suspension of the active drug layer before it had been applied to the sugar sphere (Durst Tr. 1897:20-1898:1). Mylan/Esteve asserts that because a proper test of micro-pH in Mylan/Esteve's product should include the acidic sugar sphere, Dr. Davies's pH tests of the active layer without the sugar sphere are not good indicators of the micro-pH. Mylan/Esteve further contends that the correct procedure for measuring the micro-pH was used by Dr. Durst, who tested the pH of the entire pellet, including the sugar sphere, and obtained acidic results. (Durst Tr. 1870:22-1878:8; M/EX 8372; M/EX L1; M/EX 624.)

The Court disagrees. In the First Wave, the Court found that it was appropriate to remove the drug layer from the sugar sphere to test the micro-pH of the omeprazole in Genpharm's product, *see* Astra v. Andrx, 222 F.Supp.2d at 507, and the Court sees no reason to distinguish Mylan/Esteve's product. While some of the sugar sphere is in contact with some of the active drug layer, that does not make it part of the microenvironment of the active drug layer as a whole. Accordingly, the Court finds that the pH of the active drug layer alone represents the microenvironment of the omeprazole in Mylan/Esteve's product.FN29

FN29. Mylan/Esteve refers to an internal method for determining "micro-pH" of an active coated sugar sphere used by Plaintiffs in 1993, consisting of placing a single active coated pellet in water and measuring the pH. (Durst Tr. 1870:22-1872:10; M/EX 179; M/EX 8105.) This evidence, without more, does not warrant a finding that the appropriate micro-pH test for a formulation with a sugar sphere necessarily includes the sugar sphere.

In conducting his pH tests of the active drug layer, Dr. Davies took the uncoated, active-layered pellets (i.e., the sugar seeds coated with just the Film Coat 1) provided by Mylan/Esteve, and, using a scalpel, "cracked off" the active layer. He then used ATR-FTIR to confirm that the test samples contained only the active drug layer and not part of the sugar seed. (Davies Tr. 166:24-167:18; PSWTX 1250-11.) Dr. Davies then added boiled, cooled water with a pH within the USP specification to the active layer material of numerous pellets. (Davies Tr. 168:13-23; PSWTX 994.) Dr. Davies found that the omeprazole-containing region for the Delayed Release pellets (Batch D03157) exhibits a pH range of 7.82-8.19 and the Super Delayed Release pellets (Batch T026) exhibits a pH range 8.41-8.57. (Davies Tr. 176:13-182:6; Langer Tr. 1152:23-1153:6; PSWTX 934; PSWTX 1250-12; PSWTX 1255-32.) Dr. Davies also found that "the more active [layer] you place in the solution, the higher the pH. Whatever is causing the pH ... the more of it you put in the sample, the higher the pH. That shows that you've got alkaline materials, the more of which are in solution, the higher the pH." (Davies Tr. 178:25-179:4.) Dr. Davies did not test the pH of the amount of material harvested from the active layer of a single pellet. (Davies Tr. 798:12-23.)

In addition to disagreeing with Dr. Davies's exclusion of the sugar sphere from the pH tests, Mylan/Esteve asserts that by combining the materials from many pellets Dr. Davies creates an artificial environment that exaggerates the effect of any impurities present in the active layer components. (Durst Tr. 1865:17-1866:23.) Dr. Durst testified that increasing the amount of insoluble or inert material in a sample artificially concentrates the impurities in the solution and amplifies their effect. (Durst Tr.2020:20-2021:2.)

In addition to testing single pellets, Dr. Durst tested the pH of suspensions of the active drug layer (Film Coating No. 1) before it had been placed on the sugar sphere. When testing the suspension alone, Dr. Durst consistently obtained pH results slightly less than 7. (Durst Tr. 1841:12-16; M/EX 8352; M/EX 89; M/EX 122A.)

Dr. Davies did not test the pH of a suspension of Film Coating No. 1 (Davies Tr. 1100:22-1101:5), but rather relied, in part, on early development reports showing pH values for Mylan/Esteve's film coating suspensions (Davies Tr. 184:9-12; PSWTX 677T). Those development reports, however, predated the 2002

change in specification for the pH of the HPMC used in Mylan/Esteve's omeprazole products. (Lopez Tr. 2114:9-2115:1; M/Ex 69.) Therefore, the film coating suspensions that are the subject of those development reports may not have contained ingredients complying with Mylan/Esteve's newer specifications. (Davies Tr. 1102:5-20.) Accordingly, the Court finds the development tests relied upon by Plaintiffs to be of little value.

The difference in the pH of Mylan/Esteve's active drug layer as tested by Dr. Durst and Dr. Davies and the concern that "high concentration" tests may not be representative of the active layer in Mylan/Esteve's product create more than a modicum of doubt as to whether the micro-pH of Mylan/Esteve's omeprazole is alkaline. Even if the Court were persuaded that the pH of the active drug layer is alkaline, this showing, without more, is insufficient to find the presence of a stabilizing amount of ARC in Mylan/Esteve's core.FN30 Although Plaintiffs point to dicta from the First Wave opinion stating that "there is no requirement that Astra identify the particular alkaline compound that creates the microenvironmental pH," Astra v. Andrx, 222 F.Supp.2d at 516 n. 53, in affirming the Court's decision the Federal Circuit clearly stated that it does not suffice to infer an ARC in the core based on a micro-pH of 7 or higher, Astra v. Andrx, 84 Fed.Appx. 76, 83 ("Astra contends that it suffices to show pH > 7 in regions 'immediately around or in close proximity to the omeprazole particles.' From this showing, Astra would infer an ARC in the core. This court disagrees, because the claims plainly require an ARC.").

FN30. Mylan/Esteve moves to exclude Dr. Davies's test evidence and opinions based on *Daubert* on the grounds that (1) his reliance on stability tests that used HPMC that is different from that used in Mylan/Esteve's product renders the results irrelevant, (2) his microenvironment pH tests are unsupported by scientific principles, (3) his simulated film coating suspension stability test and conclusions related thereto are scientifically invalid, and (4) his conclusion that TEA stabilizes the omeprazole in Mylan/Esteve's formulated product is speculative and without support. The Court finds that, while Dr. Davies's opinions and test results do not warrant exclusion under *Daubert,* his opinions and test results also have failed to persuade the Court by a preponderance of the evidence.

Accordingly, Plaintiffs have failed to show by a preponderance of the evidence that Mylan/Esteve's product literally contains an ARC.

d. Doctrine of Equivalents

Plaintiffs argue that if Mylan/Esteve's product does not infringe literally, it infringes under the doctrine of equivalents. Plaintiffs assert that the carbonates in the talc and HPMC, and the TEA in the omeprazole are the equivalent of an ARC because they are alkaline, act as buffers, increase the pH of the omeprazole microenvironment to at least 7.0, and stabilize omeprazole used in the Mylan/Esteve formulation.

In order to assert a case of infringement under the doctrine of equivalents, the patentee "must present *evidence* and *argument* concerning the doctrine and *each* of its *elements*." Lear Siegler, Inc. v. Sealy Mattress Co., 873 F.2d 1422, 1425 (Fed.Cir.1989) (emphasis in original) (citation omitted). "The evidence and argument on the doctrine of equivalents cannot merely be subsumed in plaintiffs' case of literal infringement." Lear Siegler, 873 F.2d at 1425 (citation omitted). Here, Plaintiffs simply present the same evidence for infringement under the doctrine of equivalents as they rely upon for literal infringement.

Moreover, having expressly described talc, HPMC, and omeprazole as something other than an ARC in the '505 and '230 Patents, and therefore outside the scope of the ARC limitation, Plaintiffs cannot now assert that those commodity pharmaceutical ingredients are equivalent to an ARC. Subject matter not included in the literal scope of the claim is necessarily excluded from coverage under the doctrine of equivalents where, as here, its inclusion would be "inconsistent with the language of the claim." Ethicon Endo-Surgery, Inc. v.

U.S. Surgical Corp., 149 F.3d 1309, 1317 (Fed.Cir.1998); *see also* Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1582 (Fed.Cir.1996) ("As a corollary to the 'all limitations' rule, ... we have held that 'the concept of equivalency cannot embrace a structure that is specifically excluded from the scope of the claims.' " (quoting Dolly, Inc. v. Spalding & Evenflo Cos., 16 F.3d 394, 400 (Fed.Cir.1994))); *see also* SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1345 (Fed.Cir.2001) ("A particular structure can be deemed to be outside the reach of the doctrine of equivalents because that structure is clearly excluded from the claims whether the exclusion is express or implied."); Moore U.S.A., Inc. v. Standard Register Co., 229 F.3d 1091, 1106 (Fed.Cir.2000); *Johnson & Johnston Assocs.,* 285 F.3d at 1054 (Fed.Cir.2002) (holding matters disclosed but not claimed are not within the claims of the patent and may not be recaptured under the doctrine of equivalents).

Finally, Plaintiffs have failed to show by a preponderance of the evidence that talc, HPMC, and omeprazole perform the same function (stabilizing the omeprazole), in substantially the same way (by reacting to create a micro-pH of not less than 7 around the particles of omeprazole), to produce the same result as an ARC (long-term shelf-life stability of the formulated product). *See, e.g.,* Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608, 70 S.Ct. 854, 94 L.Ed. 1097 (1950); Upjohn Co. v. Mova Pharm. Corp., 225 F.3d 1306, 1309 (Fed.Cir.2000). Accordingly, Plaintiffs' claims under the doctrine of equivalents must fail.

e. Alkaline Omeprazole Salt Equivalent

Plaintiffs further assert that Mylan/Esteve's product infringes the ' 505 and '230 Patents because the Esteve omeprazole is the equivalent of an alkaline omeprazole salt.

A salt is formed through a combination of an acid and a base. (Langer Tr. 1149:20-21; PSWTX 1255-29; Klibanov Tr. 5322:5-10; PSWTX 1259-41.) According to the patents-in-suit, and as this Court has previously stated, an alkaline omeprazole salt has a micro-pH of not less than 7 and is self-stabilizing. (Jan. 12, 2006 Order at 10.)

Plaintiffs' support for its assertion that Mylan/Esteve's product contains the equivalent of an alkaline omeprazole salt is limited to theoretical, conclusory statements from Drs. Langer and Klibanov. (Langer Tr. 1149:15-1150:3, 1542:7-17, 1180:21-1181:5; 1166:20-1167:7 ("TEA-stabilized omeprazole is like an alkaline omeprazole salt;" "TEA is a base, and it combines with omeprazole, which is an acid;" "alkaline salts of omeprazole are self-stabilizing;" and "Mylan's core contains the equivalent of an ammonium salt."); Klibanov Tr. 5326:24-5327:15, 5322:5-10.) Plaintiffs present no evidence that Esteve's omeprazole is self-stabilizing or that it has stability even remotely similar to that of any omeprazole salt. (Swenton Tr. 2332:3-6.)

Accordingly, the Court finds that Plaintiffs have not proven by a preponderance of the evidence that Mylan/Esteve's products contain an ARC as required by subpart (a) of claims 1 of the '505 and '230 Patents, either literally or under the doctrine of equivalents.

3. Claim 1(b): An Inert Subcoating That is Soluble or Rapidly Disintegrating in Water

Claim 1(b) of the '505 Patent requires "an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film forming compounds." (PSWTX 1A 16:48-52.) Similarly, claim 1(b) of the '230 Patent requires "an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds." (PSWTX 2A 13:10-15.)

a. Presence of A Subcoating

As discussed above, Mylan/Esteve's subcoating includes two sublayers: a first sublayer (Film Coating No. 2) containing hydroxypropyl methylcellulose ("HPMC"), talc and titanium dioxide, and a second sublayer (Film Coating No. 3), which Mylan/Esteve refers to as a "controlled release" sublayer, containing HPMC and Surelease (ethylcellulose).FN31 (Lopez Tr.2076:4-2077:8; M/EX 321; M/EX 8335; Langer Tr. 1154:1-11; PSWTX 1205 at OMP 005129, 31; PSWTX 1255-35.) Mylan/Esteve's product is a capsule containing a combination of two different pellets having this composition; the only difference between the two pellets is the amount of ethylcellulose in the second sublayer. (Lopez Tr. 2104:6-23.)

FN31. The Court finds that the intrinsic evidence indicates that the claims of the '505 and '230 Patents include subcoatings comprised of multiple layers: both patents state in their "Detailed Description of the Invention" that the "separating *layer(s)* can be applied to the cores ...." (PSWTX 1A 4:31-35; *see also* PSWTX 1A 16:60-61 (Claim 3 of the '505 Patent covering "a preparation according to claim 1 wherein the subcoating comprises two or more sublayers"); PSWTX 2A 13:52-53 (Claim 4 of the ' 230 Patent stating "wherein the subcoating comprises two or more sublayers").)

b. Inert

In the First Wave, the Court construed the term "inert" to "require that the subcoating be chemically, pharmaceutically, and pharmacologically inactive such that the subcoating does not adversely affect the properties of the active ingredient or the enteric coating material in the formulation." Astra v. Andrx, 222 F.Supp.2d at 474-75. The patents do not require the "absolute absence of any pharmaceutically active or chemically reactive substances" for a subcoating to be inert. Id. at 472.

The Court has found that HPMC and talc are inert ingredients, and not ARCs, within the meaning of the patent and as they are used in Mylan/Esteve's product.FN32 (*Supra* Parts II.C.2.a.1, II.C.2.a.ii.) Furthermore, the ' 505 Patent itself identifies the ingredients used in Mylan/Esteve's subcoating as inert: The patent describes HPMC as a pharmaceutically acceptable, water soluble, inert, and polymeric film forming compound used for the separating layer, and titanium dioxide and talc as subcoating additives and tablet excipients. (PSWTX 1A 4:35-41, 4:54-56; PSWTX 1255-36.) Mylan/Esteve's Senior Scientific Officer, John O'Donnell, also testified in his deposition that both of Mylan/Esteve's sublayers are inert. (O'Donnell Dep. Tr. 90:9-20, 91:9-92:5, June 5, 2003.)

FN32. Even if the Court erred in finding that HPMC and talc are not ARCs, Mylan/Esteve's subcoating would still be considered inert. In the First Wave, the Court held that word "inert" does not mean that ARCs cannot be present in the subcoating. Astra v. Andrx, 222 F.Supp.2d at 482. The subcoating may, in fact, contain ARCs as long as the ARCs do not compromise the enteric coat or cause degradation of the active layer. (*See* Langer Tr. 1154:19-1155:6; PSWTX 1255-37.) The Court has seen no evidence indicating that Mylan/Esteve's subcoating causes such degradation in the enteric coat or the core.

The only evidence Mylan/Esteve offers to rebut Plaintiffs' assertion that its subcoating is inert is the alkaline results of pH tests conducted by Dr. Davies on the film coating suspensions of Mylan/Esteve's first and second sublayers. (PSWTX 992E.) However, Dr. Davies's pH testing is of little relevance to determining whether Mylan/Esteve's subcoatings are inert, as the patent does not dictate any pH requirement for the materials in the subcoating and pH testing alone does not show the subcoating's effect on either the core or the enteric coating of Mylan/Esteve's product. *See* Astra v. Andrx, 222 F.Supp.2d at 520. Accordingly, the Court finds that the subcoating in Mylan/Esteve's product is inert within the meaning of the '505 and '230

Patents.

c. Water Soluble or Rapidly Disintegrating in Water

As the Court recognized in the First Wave, the terms "soluble" and "rapidly disintegrating" refer to what happens to the physical structure of the subcoating itself when exposed to water. Thus, the Court construed this limitation to mean "the subcoating dissolves or breaks up quickly in water." Astra v. Andrx, 222 F.Supp.2d at 475. In the case of Mylan/Esteve's product, the Court finds that it contains a sublayer that is "soluble or rapidly disintegrating" within the meaning of the '505 and '230 Patents.

Dr. Davies testified that when Mylan/Esteve's delayed release pellets (prior to enteric coating) are placed in water, the delayed release pellets start to disintegrate in less than two minutes, and are completely disintegrated in less than twenty minutes. (Davies Tr. 278:15-281:17; Langer Tr. 1155:7-21; PSWTX 947; PSWTX 948; PSWTX 949; PSWTX 950; PSWTX 951; PSWTX 1063A; PSWTX 1250-3; PSWTX 1255-38.) Likewise, Dr. Davies found that when the super delayed release pellets were placed in water (prior to application of the enteric coating), there was a complete "loss of the integrity of the coating" after about four minutes in water and the pellets completely disintegrated in less than twenty minutes. (Davies Tr. 149:12-24, 282:18-285:3; Langer Tr. 1155:7-21; PSWTX 952; PSWTX 953; PSWTX 954; PSWTX 955; PSWTX 956; PSWTX 1063B; PSWTX 1250-3; PSWTX 1255-38.) Using an ATR-FTIR microscope, Dr. Davies determined that only sugar and starch remained on the pellets after disintegration; the ATR-FTIR spectra did not exhibit the diagnostic ethylcellulose peaks from Surelease (at 2970 and 1370), which were present in the spectra of the pellets before disintegration (Davies Tr. 285:4-288:9; PSWTX 957).FN33

FN33. Mylan/Esteve argues that Dr. Davies's conclusions regarding the rapidly disintegrating nature of Mylan/Esteve's subcoating are unreliable because he did not personally conduct the disintegration and FTIR tests and because of the lack of protocol or written record. The Court is not persuaded by Mylan/Esteve's assertions. Even though other scientists conducted the disintegration and FTIR tests at issue, Dr. Davies testified that he personally attended the initial testing of each experiment to ensure it was done properly. (Davies Tr. 128:20-130:16; 133:3-21.) Also, Dr. Davies testified that Dr. Luk conducted the testing under his supervision and that Dr. Luk kept an electronic record of his tests, which is the standard manner in which such experiments are recorded. (Davies Tr. 829:9-24, 830:1-2.)

The central dispute concerning the subcoating involves the definition of "rapid" as used in the patents-in-suit. Astra maintains that "soluble or rapidly disintegrating" would be understood by a person of ordinary skill in the art to include a subcoating that releases omeprazole within thirty to sixty minutes, the length of time Plaintiffs assert allows for drug release in the proximal part of the small intestine. (Langer Tr. 1156:12-1160:12, 1467:12-1467:15; PSWTX 1255-39.) Mylan/Esteve, on the other hand, asserts that a "rapidly disintegrating" layer is understood to be one that does not delay the physical disintegration of the underlying formulation or impede the rate of drug release from the underlying formulation.

As support for their asserted "rapid" timeframe, Plaintiffs argue that Table 5 of the '505 Patent teaches that the inventors considered a dissolution timeframe of twenty to thirty minutes to be rapid. The Court, however, finds that Plaintiffs' reliance on Table 5 is misplaced. (*See* Langer Tr. 1156:12-1157:6; PSWTX 1A 14:19-40.) Table 5 relates to the rate of release of omeprazole from *fully formulated pellets containing an enteric coating*. Table 5 does not relate to the disintegration rate of the claimed *subcoating*. Furthermore, a comparison of the data for Examples 2 and 5 in Table 5 confirms that the rate of drug release from a fully formulated pellet provides no indication of how quickly the subcoatingwithin that formulation dissolves or disintegrates. Specifically, even though the pellets of Examples 2 and 5 as tested in Table 5 had exactly the same subcoatings (PSWTX 1A 10:9-10 ("[T]he uncoated pellets [of Example 5] were subcoated as described in Example 2.")), the Example 2 pellets released 100% of the omeprazole after ten minutes while

the pellets of example 5 released 70% in thirty minutes (PSWTX 1A 14:20-40; Langer Tr. 1475:1-6).

Both Plaintiffs and Mylan/Esteve cite to external evidence to support their respective definitions of "rapidly disintegrating" including: EP 1,145,711, EP 0,122,815, U.S. Patent No. 5,326,586, U.S. Patent No. 3,371,015, and "The Production of Pharmaceuticals, Basic Course of Drug Development" (the "Tsuda Publication"). (Langer Tr. 1158:5-1160:9, 1467:24-1471:23; PSWTX 79 at 22, 31; PSWTX 1776; Block Tr. 6925:15-1626:9; M/EX 9 at 8:6-8, 25-2; M/EX 83 at 6:18-73, 7:30-32; M/EX 170 at AFL-102103-4.) Because these publications present varied views of what timeframe is considered "rapid," (*Compare* the '815 Patent, Langer Tr. 1159:19-1160:9, PSWTX 79 at 31 (Indicating disintegration in sixty minutes is rapid), *with* the '586 Patent, M/EX 9 at 8:6-27 (Describing rapidly disintegrating as leaving disintegration time "virtually unaffected")), and because none of the publications specifically address the definition of "rapid" within the meaning of the '505 and '230 Patents, the Court is unable to give weight, individually or collectively, to the publications.

While the Court previously found that a subcoating that dissolved within fifteen seconds was rapidly disintegrating, Astra v. Andrx, 222 F.Supp.2d at 539, the Court also explained that the purpose of the "rapidly disintegrating subcoating" requirement is to "afford omeprazole release in the very upper portion of the small intestine," FN34 *id*. at 475. Here, the Court finds that disintegration beginning at two to four minutes, as observed for Mylan/Esteve's pellets by Dr. Davies, is sufficiently rapid to allow the release of omeprazole in the proximal part of the small intestine. Thus, Mylan/Esteve's subcoating is rapidly disintegrating within the meaning of the '505 and ' 230 Patents.

FN34. This does not mean that any product that is the bioequivalent of Prilosec(R) necessarily contains a "rapidly disintegrating" subcoating such that it infringes claim 1(b) of the '505 and '230 Patents.

Mylan/Esteve asserts that Dr. Davies's tests do not support a finding that its subcoating is rapidly disintegrating because the delayed release pellet only *starts* to disintegrate "within 2 minutes" and the super-delayed release pellet only *starts* to disintegrate several minutes later. (Davies Tr. 825:19-21; Langer Tr. 1155:16-21.) As support for this argument, Mylan/Esteve contends that the materials released from the pellet during testing were not released because the pellets' subcoating had disintegrated, but because the controlled release sublayer was functioning as intended to slowly release the active ingredient. (Lopez Tr.2093:18-2094:8; Mancinelli Dep. Tr. 61:8-62:10; M/EX 8111(DVD); M/EX 8111A.) Complete disintegration of the subcoating, however, in a timeframe considered "rapid" is not required under the '505 and '230 Patents. Therefore, the fact that Mylan/Esteve's pellets start to release materials two to four minutes after exposure to water, as seen in Dr. Davies's tests, is sufficient to render Mylan/Esteve's subcoating rapidly disintegrating. (Davies Tr. 149:12-24, 282:18-285:3; Langer Tr. 1155:7-21; PSWTX 952; PSWTX 953; PSWTX 954; PSWTX 955; PSWTX 965; PSWTX 1063B; PSWTX 1250-3; PSWTX 1255-38.) The fact that the rate of disintegrationof Mylan/Esteve's pellet may be regulated or slowed by a controlled release layer is not relevant-the fact remains that Mylan/Esteve's pellets start to dissolve in a timeframe considered rapid under the '505 and '230 Patents.

Mylan/Esteve's argument that its subcoating is not "soluble" within the meaning of the '505 Patent because its outer subcoating layer is composed of more than 50% water- *insoluble* film-forming polymer, ethylcellulose, is unpersuasive. (M/EFF 97.) Although pure ethylcellulose is insoluble in water by itself, the mixture used by Mylan/Esteve for its outer sublayer also contains HPMC, a soluble material. (Davies Tr. 802:20-803:15.) The presence of insoluble components does not prevent a determination that a subcoating is rapidly disintegrating in water. For example, talc is insoluble in water but is expressly listed as an appropriate ingredient in the separating layer in the '505 and '230 Patents (PSWTX 1A 4:54-56; PSWTX 2A 9:48-50), and the Court previously found that an HPMCP salt layer containing talc was water soluble and rapidly disintegrating within the meaning of the patents, Astra v. Andrx, 222 F.Supp.2d at 539.

4. Claim 1(c): Enteric Coating and Enhanced Stability

Part "(c)" of claim 1 of both the '505 and '230 Patents requires an enteric-coating layer on top of the subcoating layer. (PSWTX 1A 16:53-54; PSWTX 2A 13:16-20.) Claim 1(c) of the '230 Patent contains additional language further characterizing the subcoating. (PSWTX 2A 13:16-20.) Specifically, the '230 Patent claims a pharmaceutical preparation comprising "an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced" (Id.), which means that the subcoating layer must sufficiently isolate or separate the core from the enteric coating to enhance the formulation's stability. According to the specification of the '230 Patent, the subcoating of claim 1 isolates the core from the enteric coating through the creation of a "pH-buffering zone" between them. (*See* PSWTX 2A 9:4-8 ("The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles.").) As explained in the '230 Patent specification (PSWTX 2A 8:67-9:4), the subcoating, in combination with the other claimed elements, enhances stability by protecting against the "degradation/discolouration of the acid labile compound during the coating process o[r] during storage." (PSWTX 2A 9:2-4.)

Mylan/Esteve's final layer, which is disposed on the subcoating required by claim 1(b) of the '230 and '505 Patents, is composed of Eudragit L 30D-55 (an enteric coating polymer dispersion), triethyl citrate (a plasticizer), and talc (an inert ingredient). (Langer Tr. 1128:19-22; PSWTX 456 at OMP 510040-42; PSWTX 1205 at OMP 005129-32, 33; PSWTX 1255-9.) Clearly, the final layer of Mylan/Esteve's product is an enteric coating as described in claim 1(c). In addition, even Mylan/Esteve acknowledges that its sublayer enhances the stability of its preparation by separating the core from the enteric coating. (Solanas Dep. Tr. 202:18-203:2, Mar. 25, 2004.) Accordingly, Mylan/Esteve's product meets the limitations of claim 1(c).

5. Conclusion

Although Mylan/Esteve's product meets the limitations of claim 1(b) and 1(c), it does not meet the limitation of claim 1(a). Thus, the Court finds that Plaintiffs have failed to prove by a preponderance of the evidence that Mylan/Esteve infringes, either literally or under the doctrine of equivalents, any of the claim 1 of the '505 and '230 Patents. Because all of the independent claims of the '505 and '230 Patents asserted against Mylan/Esteve require an ARC, the Court holds that Mylan/Esteve's products do not infringe any of the independent claims of those patents. Furthermore, it is axiomatic that any claims that depend from those independent claims also will not be infringed. *See* Wilson Sporting Goods Co. v. David Geoffrey & Assocs., 904 F.2d 677, 685 (Fed.Cir.1990). Accordingly, the Court holds that Mylan/Esteve also does not infringe any of the dependent claims of the '505 and '230 Patents asserted against Mylan/Esteve. As for the process claims, claim 14 of the '505 Patent and claim 12 of the '230 Patents, these also require an ARC; thus, the Court finds that Mylan/Esteve do not infringe the process claims of the '505 and '230 Patents.

D. *Lek's Product*

[31] Lek filed ANDA No. 75-757 with the U.S. FDA, seeking approval to sell its 10-mg and 20-mg strength "Omeprazole Delayed Release Capsules" as generic versions of Astra's Prilosec(R) product (Lek's Amended Answer to Second Am. Compl. para. 16), and filed ANDA No. 76-515, seeking approval to sell its 40-mg strength "Omeprazole Delayed Release Capsules" as a generic version of Plaintiffs' Prilosec(R) product (Lek's Answer to Compl. para. 16).

On February 4, 2003, the FDA granted final approval for the 10-mg and 20-mg strengths of Lek's product.

On August 19, 2003, Lek began the sale of its FDA-approved 10-mg and 20-mg product. (Lek's Amended Answer to Second Am. Compl. para. para. 24a, 24b.) Lek's 40-mg product has not yet been approved by the FDA.

Plaintiffs assert that Lek committed acts of infringement under 35 U.S.C. s. 271(e)(2) with respect to the '505 Patent and the '230 Patent by filing ANDAs seeking FDA approval to engage in the commercial manufacture, use, or sale of Lek's products prior to the expiration of the patents-in-suit (Second Am. Compl. Against Lek para.para. 21-23, 32-35;Compl. Against Lek para.para. 19-21, 28-30); that Lek has directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by manufacturing, selling and offering for sale Lek's FDA-approved 10-mg and 20-mg generic omeprazole products (Second Am. Compl. Against Lek para.para. 24a, 24b, 24c, 35a, 35b, 35c); and that Lek has induced and contributed to infringement by others who administer or use Lek's products under 35 U.S.C. s. 271(b)-(c) (*Id*. para.para. 23, 24, 34, 35).

Plaintiffs allege that Lek's 10-mg, 20-mg, and 40-mg ANDA omeprazole products infringe '505 Patent claims 1, 5, 7, 8, 9, and 10, and '230 Patent claims 1, 6, 8, 10, 11 and 13 literally, and if not literally, under the doctrine of equivalents. (Tr. 1171:14-23; PSWTX 1256-1.)

In deciding whether Lek has infringed the '505 and '230 Patents, the Court must determine whether Lek's omeprazole products have: (1) an alkaline reacting compound ("ARC") or its equivalent; (2) the equivalent of an alkaline omeprazole salt; and (3) an inert, water soluble/rapidly disintegrating subcoating.

1. Lek's Formulation and Manufacturing Process

Lek's omeprazole products are orally administered capsules. Each capsule contains multiple pellets. The 10-mg and 20-mg dosage strengths contain the same pellets. The number of pellets is adjusted to account for the amount of omeprazole in the final capsule. The 40-mg dosage strength is made in the same way as the 10- and 20-mg products, but each pellet contains a higher percentage of omeprazole. (Langer Tr. 1173:25-1174:8; PSWTX 1074B; PSWTX 1225; PSWTX 1256-5.)

a. Bulk Omeprazole Used in Lek's Product

Lek received FDA approval to manufacture its 10- and 20-mg products with bulk omeprazole from two sources, Esteve and Lek itself. While Esteve uses triethylamine ("TEA") during its bulk omeprazole manufacturing process, Lek employs methylamine ("MA"). (Davies Tr. 296:8-14; Langer Tr. 1174:25-1175:11; Klibanov Tr. 5257:2-21; PSWTX 1251-2.)

Esteve's process for synthesizing and purifying bulk omeprazole is described above. (*See supra* Part II.C.1.a.)

Lek's process for synthesizing its bulk omeprazole, as described in Lek's Drug Master File ("DMF"),FN35 includes five steps: (1) condensation, (2) oxidation, (3) purification, (4) crystallization, and (5) digestion/redispensing.FN36 (LEKTX 645/645T; LEKTX 658A.) In the condensation step, omeprazole chloromethylpyridine is mixed with 2-mercapto-5-methoxybenzimidazole, sodium hydroxide, demineralized water, and acetone. (LEKTX 658A at L 209383.) After completion of the reaction, the mixture is cooled to temperature between 0 (deg.)C and 5 (deg.)C. (*Id*.) The condensation step results in the preparation of omeprazole sulfate, the intermediary form of omeprazole. (Hafner-Milac 2842:9-12.) This product is then mixed with chloroperoxybenzoic acid, ethyl acetate, sodium carbonate, and demineralized water, to result in the formation of crude omeprazole. (Hafner-Milac 2842:12-14; Padwa Tr. 2931:6-2935:17; LEKTX 7167-7176.) During the next steps, purification and crystallization, the omeprazole is dissolved in a solution containing MA. (Padwa Tr. 2946:9-2950:14; LEKTX 7194-7197.) Following crystallization, the omeprazole is combined with a four-fold excess of water and vigorously mixed. (Padwa Tr. 2955:17-2956:24; LEKTX

7198-7202.) After redispensing, the omeprazole is dried under a vacuum and the omeprazole particles are reduced in size through a milling step. (*See* Padwa Tr. 2962:10-2963:6; LEKTX 581 at LK 209382, LK 209388; LEKTX 7204-7206; LEKTX 7209-7211.)

FN35. Since filing its DMF, Lek has made several amendments. These amendments include changes to the drying parameters and the length of the redispensing phase. (PSWTX 1631; LEKTX 7212.)

FN36. The word "digestion," "redispersing," and "redispensing" are used interchangeably to refer to the purification procedure in which omeprazole particles are vigorously stirred in a large column of water to break the crystals of omeprazole into smaller crystals.

The bulk omeprazole produced by Lek or Esteve is then used as the active ingredient in the core of Lek's product.

b. Lek's Product Manufacturing Process

Lek's process for manufacturing its final product was described at trial through the testimony of Lek employees Petra Platner and Joze Kojc, in the Master Batch Record, and on the videotape of the process observed by Plaintiffs' representatives. (Platner Tr. 3270:17-3281:17; Kojc Tr. 3288:2-3321:7; LEKTX 163D; LEKTX 7237.)

Lek's final product is comprised of an extruded, omeprazole-containing core and an enteric coat. The granulate core of Lek's product is made by drying and mixing together low substituted hydroxypropyl cellulose ("HPC"), microcrystalline cellulose ("MCC"), anhydrous lactose, croscarmellose sodium, and povidone ("PVP"). Omeprazole, polysorbate 80, and dehydrated alcohol are then added to the mixture. (Platner Tr. 3270:17-3272:14; Langer Tr. 1172:14-1173:7; Sirca Dep. Tr. 161:18-163:4, Sept. 10, 2003; LEKTX 7234; PSWTX 1256-3; PSWTX 185A.) Next, the omeprazole-containing granulate is extruded and spheronized into "pellet cores." (Platner Tr. 3272:4-14; Langer Tr. 1172:14-1173:5; LEKTX 7234; PSWTX 1256-3; PSWTX 185A.) The spheronized cores are then transferred to a Huttlin fluid bed for drying and coating. (Kojc Tr. 3298:16-3299:5; Platner Tr. 3272:20-3273:16; LEKTX 7234.) Lek sprays onto the pellet cores an enteric coat made of hypromellose phthalate ("HP-50"), dibutyl sebacate, talc, anhydrous ethanol, and anhydrous acetone. FN37 (Langer Tr. 1173:8-24; LEKTX 7234; PSWTX 1256-4; PSWTX 185A.) After the pellets are coated, they remain in motion in the Huttlin for drying. (Kojc Tr. 3317:13-19.)

FN37. During a tour of Lek's manufacturing facilities, Dr. Davies observed that the pellets stuck to each other and to an observation window of the enteric coating vessel, which, he testified, suggests that the pellets are wet. (Davies Tr. 398:11-402:5; Kojc Tr. 3332:10-16, 3332:21-3334:1, 3334:9-18; Kojc Dep. Tr. 215:6-217:4, Jan. 16, 2004; PSWTX 284B-287B, 289B.) Lek's employees, however, assert that because of the dry air used in the Huttlin, the movement of the cores, the heating, and the rapidly-evaporating character of the ethanol/acetone solvent, the drying of the coating solution "occurs immediately" when it hits the cores. (Kojc Tr. 3307:13-25; Platner Tr. 3278:25-3279:8.)

2. Claim 1(a) of the '505 Patent: An Effective Amount of an Alkaline Reacting Compound (ARC)

a. Micro-pH of the Omeprazole in Lek's Product

The core of Lek's product is of specific importance for limitation 1(a). As stated above, Lek's core is made

by intimately mixing low-substituted hydroxypropyl cellulose, microcrystalline cellulose, lactose, sodium croscarmellose and PVP with omeprazole, granulating the mixture with dehydrated ethanol and a surfactant (polysorbate 80), and then extruding and spheronizing the resultant mixture to form omeprazole-containing pellets. (Langer Tr. 1172:18-1173:5; Sirca Dep. Tr. 161:18-162:5, 162:16-163:4; Platner Tr. 3270:22-25, 3271:20-3272:14.)

All of the excipients in Lek's core are acidic, each having a pH of less than 7. (Davies Tr. 327:2-328:4, 542:19-21; PSWTX 983A, PSWTX 992E; LEKTX 96.) Dr. Davies's pH testing of the excipients in Lek's core (provided by Lek), excluding omeprazole, is consistent with the testing of the two Lek experts who also tested the pH of these materials. (PSWTX 2156; Christian Tr. 3816:2-21.) For example, Dr. Davies recorded pHs of 3.69-3.87 for PVP while Lek recorded results of 3.56-3.94. (LEKTX at tbl. 2 & 3.)

While the '505 Patent teaches that an alkaline microenvironment is required for omeprazole stability, Lek scientists testified that they found that if the environment of the omeprazole pellet was kept very dry, an alkaline pH was not required to ensure the stability of the omeprazole in the formulation. (Venturini Tr. 3193:8-3194:10; LEKTX 29T at LK 008171-72.) Therefore, Lek's manufacturing process was designed to "avoid moisture as much as possible." (Platner Tr. 3253:24-3254:1.) For example, Lek uses drying techniques, including heat and vacuum, and monitors moisture in both the product itself and the air to which the product is exposed throughout the manufacturing process. (*See* Platner Tr. 3254:5-16, 3261:10-19, 3268:19-3271:1, 3298:16-3299:5; LEKTX 1 7:61-66; LEKTX 7233-7235; Kojc Tr. 3298:16-3299:5.) Although Plaintiffs note several instances during the Lek production process when the Lek product may be exposed to moisture (*See* Kojc Tr. 3321:17-3330:2, 3332:10-16, 3332:21-3334:1, 3334:9-18; Kojc Dep. Tr. 215:6-217:4; Davies Tr. 398:2-402:5; Sirca Dep. Tr. 239:4-25, 221:22-222:5; PSWTX 249A-254A; PSWTX 256A-PSWTX 257A; PSWTX 259A-262A; PSWTX 267A-PSWTX 269A; PSWTX 271; PSWTX 272A; PSWTX 279A; PSWTX 280A; PSWTX 281A; PSWTX 282A; PSWTX 284B; PSWTX 285A; PSWTX 286A; PSWTX 287B; PSWTX 289B), tests conducted by Dr. Davies revealed an average water content in Lek's product of approximately 1%, and tests conducted by Lek demonstrate that the water content is typically below 1% (Davies Tr. 353:25-356:8; Klibanov Tr. 5397:3-9, 5400:19-5401:14; PSWTX 925; PSWTX 1165; PSWTX 1166; LEKTX 2196; LEKTX 88.)

i. Microenvironment of Lek's Omeprazole

In determining the pH testing procedure to be used, the Court must take into account the "significant structural differences that can exist among different omeprazole formulations." Astra v. Andrx, 222 F.Supp.2d at 516-17. As the Court previously determined, "different testing procedures are appropriate to determine the micro-pH of the omeprazole present in different types of cores," *id*., and "the specific steps taken to measure micro-pH must depend on how the formulation is made," *id*. at 566. Therefore, which test or tests best approximate the micro-pH of a given formulation is a question of fact dependent on the particular product.

Plaintiffs assert that to determine the micro-pH of the omeprazole in Lek's product, a person of ordinary skill would measure the pH of Lek's omeprazole, as opposed to the pH of the entire core pellet, which includes the core and the excipients. (Langer Tr. 1183:1-7, 1527:23-1528:8.) Dr. Langer testified that because Lek's formulation has a low water content and is very dry, the acidic excipients are immobile and do not contribute to the microenvironment. (Langer Tr. 1535:10-14; 1538:2-20.) Lek, on the other hand, argues that the proper way to determine the micro-pH of its product is to measure the pH after adding a small amount of water to the mixture of omeprazole and excipients that compose the core of Lek's product, as described in the '505 Patent:

Omeprazole is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture and with an alkaline reacting,

otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each omeprazole particle of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture.

(PSWTX 1 at 3:37-47; *see also* PSWTX 2 at 8:32-42.)

The Court's analysis of First Wave Defendant Cheminor's product is pertinent to the determination of what is the correct way to test the micro-pH of Lek's product. Dr. Davies testified that, despite its low water content (approximately 0.83%), the excipients in First Wave Defendant Cheminor's product contributed to the microenvironment of the omeprazole in that product. (Davies Tr. 585:15-586:16.) Dr. Klibanov testified that even low amounts of moisture, like that found in Lek's product, will mobilize protons in the acidic excipients and carry them to the omeprazole and can degrade the omeprazole. (Klibanov Tr. 5244:10-5245:25.) As with Cheminor, the core excipients in Lek's product contribute to the microenvironment of the omeprazole even if the moisture content of the product is below 1%. (Davies Tr. 585:13-15, 585:12-589:3, 816:16-817:6.) Thus, the Court's finding in the First Wave is equally applicable to Lek's product:

The '505 and '230 patents specifically discuss the measurement of micro-pH in the context of the "mixture" of omeprazole, an ARC, and the "conventional pharmaceutical constituents" found in the core.... For Cheminor's products, Dr. Davies found that it was sufficient to conduct the pH test on the bulk contents of the omeprazole-containing core.... This is because Cheminor makes its cores by mixing all of its core excipients together ..., which means that the omeprazole resides throughout the core, the omeprazole comes into contact with all of the other excipients in the core, and the core itself is the omeprazole-containing region of the pellets.... Because the ingredients in Cheminor's core are mixed together, the microenvironment of the omeprazole contains all the excipients present in the core itself. *Just as the pH of the core is a result of the pH from the combination of all excipients present in the core region ..., the pH of the microenvironment around the omeprazole results from the combination of all the excipients present in the core*.... Therefore, the court finds that a pH value for the core as a whole, when tested in keeping with the method required by the patents, represents the pH value for the microenvironment of the omeprazole in the Cheminor formulation.

Astra v. Andrx, 222 F.Supp.2d at 517 (citations omitted) (emphasis added).

Nothing in the patent suggests that the micro-pH test described is not applicable to a product having a moisture content of 1%. (Davies Tr. 587:24-588:1.) There is no discussion in the patent of measuring the micro-pH of omeprazole alone. (PSWTX 1A, PSWTX 2A.) Accordingly, the Court finds that the proper way to determine the micro-pH of Lek's product is to measure the pH after adding a small amount of water to the mixture of omeprazole and excipients that compose the core of Lek's product, as the '505 Patent expressly provides. (*See* PSWTX 1A at 3:38-47.)

When a small amount of water is added to all of Lek's core excipients, the measured pH is acidic, with a pH of less than 7. (Davies Tr. 327:2-328:4, 542:14-18, 589:1-5; Ornik Tr. 3364:18-3367:4, 3370:3-3371:25, 3372:5-3374:1; LEKTX 96, LEKTX 7238, LEKTX 7239, LEKTX 7240, LEKTX 7241, PSWTX 990.) Lek tested the pH of solutions containing different concentrations of its core excipients, including omeprazole, at different time intervals, and obtained pH values between 6.04 and 6.76. (Ornik Tr. 3364:18-3367:4, 3370:3-3371:25; LEKTX 96 (Tbl. 4 and accompanying text).) Lek also conducted a second set of experiments to measure the pH of its pellet cores. In the first experiment, pellet cores were cut into two halves and a microliter of water was added, the pH of this solution was then tested. In the second experiment, water was added to the pellet and the PH measurements were performed at two different locations. Both experiments gave pH values between 6.26 and 6.69. (Ornik Tr. 3371:25-3374:1; LEKTX 96 (Tbls. 6 & 7 and accompanying text).) Dr. Davies's testing of Lek's cores exhibited pH values from 5.17-5.41. (Davies Tr. 327:2-328:4; PSWTX 990.)

Therefore, because the micro-pH of Lek's product is acidic, there is no alkaline reacting compound in Lek's product.FN38 *See* Astra v. Andrx, 222 F.Supp.2d at 462.

FN38. Plaintiffs are correct in their assertion that this Court previously found that the core as a whole need not always be alkaline to meet the '505 and '230 Patent claims. Astra v. Andrx, 222 F.Supp.2d at 458-59. However, even in an acidic core, an ARC, or alkaline omeprazole salt must create a micro-pH of at least 7 around the particles of the active ingredient. As the Court stated:
The '505 patent does not teach that the core must not contain any acidic components or that the pH of the entire core as a whole must exceed 7. It only states that if an acid is in the core, it must not be in contact with the omeprazole. The '505 patent also allows that the pH of the entire core may be less than 7, yet still contain an ARC.

Id. at 459. However, even in an acidic core, an ARC or alkaline omeprazole salt must create a micro-pH of at least 7 around the particles of the active ingredient. In Lek's core, the proper test for micro-pH includes all of the core materials because, as with Cheminor in the First Wave litigation, id. at 517, the homogenous mixture of excipients and omeprazole in the core means that acidic components are in direct contact with the omeprazole particles. Accordingly, in Lek's product, the micro-pH of the omeprazole and the pH of the core mixture are the same.

ii. pH of the Omeprazole Used in Lek's Formulation

Even if the Plaintiffs were correct to test the pH of the omeprazole alone, the results, taken as a whole, are inconclusive.FN39 The theoretical pH of omeprazole is 6.4. (Davies Tr. 251:4-9, 300:4-8.) Using the same pH testing methods from the First Wave, Dr. Davies tested the pH of Lek's bulk omeprazole (manufactured by both Esteve and Lek). (Davies Tr. 421:3-14; Langer Tr. 1179:14-18, 1148:9-18, 1174:25-1175:11.) Dr. Davies's results generally show pH values of 7.0 or higher. (Davies Tr. 251:10-258:2, 302:13-306:17; PSWTX 893; PSWTX 938; PSWTX 984; PSWTX 989; PSWTX 991A; PSWTX 1251-4; PSWTX 1251-5; PSWTX 1251-6; PSWTX 1858.)

FN39. Prior to trial, Lek submitted a motion for summary judgment based on *Daubert*. Because the Court had decided to consolidate *Daubert* proceedings with trial, the Court "construe[d] [Lek's] motion as a *Daubert* motion to exclude evidence and defer[ed] judgment on the merits until that time." (*See* Jan. 12, 2006 Order at 34.)

Lek seeks to exclude certain testimony of Dr. Davies. Lek argues that under the standard for admissibility of scientific evidence stated in *Daubert:* (1) the results of Dr. Davies's pH testing and mass spectrometry testing are scientifically unreliable and must be excluded; (2) two steps in Dr. Davies's inert subcoating analysis, fluorescence microscopy and ATR-FTIR, are invalid and must be excluded; and (3) without Dr. Davies's tests, Plaintiffs have not and cannot show that Lek's ANDA product infringes the claims of Plaintiffs' patents. Apotex joins Lek's motion, and Mylan/Esteve have joined that portion of Lek's motion related to Dr. Davies's pH testing of omeprazole.

The Court has admitted and considered Dr. Davies's opinions and experiments but finds them unpersuasive as applied to Lek's product.
However, numerous experts reported acidic results in their pH tests of the omeprazole used in Lek's product, including Dr. Lindquist (an Astra scientist), Dr. Durst (Mylan/Esteve's expert in electrochemistry and pH measurements), and Dr. Christian (Lek's expert in analytical chemistry). (Durst Tr. 1558:4-7, 739:7-740:13, 1793:11-15, 1795:4-7; Christian Tr. 3753:5-10; PSWTX 893; PSWTX 938; M/EX L-4; LEKTX 235; LEKTX 236; LEKTX 7350; M/EX 8300; M/EX 8046A; M/EX 8345.) The sample Dr. Durst tested and

found to be acidic was from one of the lots that Dr. Davies found to be alkaline. FN40 (Durst Tr. 1790:7-10.) Likewise, Lek's 2001 internal testing of its own bulk omeprazole reported a pH value of 6.76 for a sample (A03343007C) that Dr. Davies reported to have a pH value of 7.15. (Ornik Tr. 3398:4-3402:18; PSWTX 2154; PSWTX 163; PSWTX 2210.) Dr. Davies offered no persuasive explanation for Lek's acidic pH result of 6.76 for a sample he found to be alkaline.

FN40. Dr. Durst also measured the pH of a control sample of omeprazole obtained from the United States Pharmacoepia ("USP"). (Durst Tr. 1786:22-1787:13.) Dr. Durst measured the pH of the USP sample of omeprazole at the same concentrations, on the same day, using the same equipment that he used to measure the pH of the Esteve-made omeprazole. (Durst Tr. 1786:22-1787:13.) Dr. Durst found that the pH of the control sample of omeprazole obtained from the USP was near the expected value and comparable to the pH of the Esteve-made omeprazole. (Durst Tr. 1787:10-13, 1791:4-12.)

Additionally, even Dr. Davies obtained acidic pH values of about 6.7 for one sample of Esteve-manufactured omeprazole. (PSWTX 984.) Dr. Davies attributes this reading to the age of the sample, which he testified was expired at the time of testing. (Davies Tr. 257:11-258:2, 304:3-11.)

Plaintiffs make much of the fact that Lek and Dr. Christian also obtained alkaline pH results in their pH testing of Lek's omeprazole.FN41 (See Christian 3807:1-3809:21; PSWTX 2152). However, for the *one* sample (out of five) of Lek-manufactured omeprazole for which Dr. Christian obtained alkaline readings (A03343107C), his results "varied from 6.74 to 7.53." (Christian Tr. 3807:25.) Dr. Christian concluded that the "results just don't make sense" and "[s]omething was wrong with that sample." (Christian Tr. 3807:6-3808:9.) When Dr. Christian tested a second and third sample from that same lot of omeprazole, Dr. Christian reported acidic results. (PSWTX 2152 (reporting pH values of 6.03-6.44 for A03343107C Sample 2 and 3).) Moreover, when Dr. Christian returned to the first sample five hours after its preparation, pH paper tests showed that the sample was acidic. (Christian Tr. 3809:6-20; PSWTX 2152.)

FN41. Lek's 2001 internal testing of three batches of its own bulk omeprazole, A03343007C, A03343107C, and A03343207C, produced pH values of 6.76, 7.02, and 7.56, respectively; while Dr. Davies's 2006 testing produced values of 7.15, 7.36, and 7.53, respectively. (PSWTX 2154; PSWTX 163; PSWTX 2210; Ornik Tr. 3398:4-3402:18.) Dr. Ornik, former director of research and development at Lek and leader of the Omeprazole Project (Ornik Tr. 3352:20-3353:9), testified that the alkaline results were unexpected and unusual and therefore required retesting (Ornik Tr. 3398:4-3402:18).

Plaintiffs also point to a laboratory notebook recording the results of an internal research study which shows that when sulfuric acid was used to calibrate the electrodes, pH values of 6.97 and 7.08 were obtained for Lek's omeprazole. (Ornik Tr. 3388:24-3391:8; PSWTX 161 at 108.) Dr. Ornik approved a report stating that these tests "are more accurate by comparison with the results where buffer solution was used for calibration of the electrode." (PSWTX 164 at p.3; Ornik Tr. 3393:22-3395:8.) However, Dr. Ornik testified that even at the time of the report she understood that the tests were not conducted under controlled conditions and therefore it is "not acceptable to consider these results as relevant." (Ornik Tr. 3395:6-3398:3.)

Dr. Davies's further asserts that the pH of Lek's omeprazole is dependent on concentration. Dr. Davies found the mean pH of 5% suspensions of the Esteve supplied omeprazole was 7.07, the mean pH of 33% suspensions was 7.27-7.58, and the mean pH of 50% solutions was 7.49-7.51. (Davies Tr. 304:12-305:8; PSWTX 1251-4.) According to Dr. Davies and Dr. Langer, when lower concentrations of omeprazole are tested (such as the 0.2% suspension tested by Dr. Lindquist), the pH values obtained are artificially low and do not provide information about whether an alkaline material is present that impacts the microenvironment. (Davies Tr. 740:24-741:12; Langer Tr. 1558:4-16; PSWTX 115TA at SWD 000097.) However, Dr.

Christian's tests of Esteve-made and Lek-made omeprazole used the same concentrations that Dr. Davies tested. (Christian Tr. 3753:11-23-3754:8; LEKTX 235; PSWTX 893; PSWTX 990.) Furthermore, this argument is inconsistent with Dr. Klibanov's assertion that even parts per million quantities of TEA/MA significantly impact the micro-pH of omeprazole.FN42 (Klibanov Tr. 5304:6-5305:13; PSWTX 1259-33.)

FN42. Dr. Klibanov also theorized that the pH of pure water "jumps from 7 to 9 or above, even at one PPM concentration [of TEA or MA]." (Klibanov Tr. 5305:13.)

b. Presence of an ARC

As described above, Esteve uses triethylamine ("TEA") in the recrystallization step of the omeprazole synthesis. (Davies Tr. 296:15-24; Langer Tr. 1174:25-1175:11; PSWTX 1874A; PSWTX 1251-2; PSWTX 1256-8.) Plaintiffs assert that during the dissolution step before crystallization Esteve adds TEA in vast excess to the amount of omeprazole. (Davies Tr. 310:16-311:11; PSWTX 1259-16; Langer Tr. 1148:19-1149:7; Klibanov Tr. 5257:16-21; Swenton Tr. 2350:16-2351:13; Padwa Tr. 2982:11-16; PSWTX 1149A; PSWTX 1874A.) Lek uses methylamine ("MA") in the recrystallization step when manufacturing bulk omeprazole. (Langer Tr. 1177:18-1178:15; Davies Tr. 352:25-353:24; PSWTX 1038A; PSWTX 1256-11; PSWTX 1259-16; PSWTX 1706.) Plaintiffs assert that during the crystallization process Lek uses an excess of 40% methylamine solution relative to the amount of omeprazole (Davies Tr. 352:25-353:24; PSWTX 1706), and the MA becomes entrapped and entrained within the crystals "helping to stabilize the omeprazole" (Davies Tr. 353:7-24). Plaintiffs further allege that Esteve adds TEA, and Lek adds MA, to omeprazole solution to act as "proton [acid] scavengers" during the manufacturing processes and thereby prevent the acid from damaging the omeprazole. (Klibanov Tr. 5257:2-25.)

As support for this argument, Plaintiffs rely on statements made and reports written regarding the development of Lek's omeprazole manufacturing process by Lek scientists Judita Sirca, Natasa Hafner-Milac, Alenka Kanalec, and Esteve scientist Laura Coppi. (*See* Sirca Dep. Tr. 403:14-405:10; Hafner-Milac Tr. 2893:10-2894:19, 2896:13-20, 2897:19-2899:1, 2900:6-2901:4, 2902:11-16, 2904:19-23; Kanalec Dep. Tr. 93:22-94:6, 98:9-14, Sept. 3, 2003; Coppi Dep. Tr. 143:4-145:24, Mar. 12, 2004, 9:30AM; Padwa Tr. 2985:15-2986:25; Swenton Tr. 2399:1-22; Langer Tr. 1177:24-1178:3, 1178:15-25 (citing Hafner-Milac Dep. Tr. 68:17-24); PSWTX 216; LEKTX 635T at LK 038254; LEKTX 636; LEKTX 636T; LEKTX 638; LEKTX 638T; LEKTX 642; LEKTX 642T at LK 038037; PSWTX 701 at p. 11.) Plaintiffs also argue that it is possible to manufacture omeprazole without a base.FN43 (Langer Tr. 1653:7-1655:25; PSWTX 2030; PSWTX 2031.)

FN43. Dr. Swenton also confirmed on cross-examination that it is "possible to recrystallize omeprazole from a solvent without using a base" (Swenton Tr. 2347:6-10) and that one can obtain an omeprazole product without using a base (*id*. at 2347:22-2348:13).

Lek admits that TEA and MA are alkaline organic bases with pHs greater than 7. (Davies Tr. 296:15-20; Langer Tr. 1175:12-21, 1179:3-12; Swenton Tr. 2267:7-18; Hafner-Milac Tr. 2902:14-16; PSWTX 1655 at Admission Nos. 57, 58, 64, 65; PSWTX 1256-9; PSWTX 1256-12 (64, 65).) TEA is an organic base with a pH of 12.5.FN44 (Langer Tr. 1148:9-16.) However, Esteve asserts that it uses the base TEA as one of its co-solvents during purification to obtain a more pure omeprazole compound (Swenton Tr. 2268:12-2269:8; M/EX 549; M/EX550; M/EX 832; M/EX8361; Coppi Dep. Tr. 58:2-22, Mar. 12, 2004, 4:40PM), and Lek maintains that MA is merely used to purify omeprazole during its bulk manufacturing process (*See* Padwa Tr. 2939:4-2940:1, 2970:21-2971:4; LEKTX 7181; LEKTX 1312 at LK 208331.)

FN44. The pK_a value of MA is approximately 10.6 and the pK_a value of TEA is approximately 10.7.

(Klibanov Tr. 5255:12-16; PSWTX 1259-14 *citing* PSWTX 1065 (D.D. Perrin, *Buffers for pH and Metal Ion Control,* 163 (1974)).) The higher the pK_a value, the stronger the base. (Klibanov Tr. 5255:10-11.)

Even if Plaintiffs are correct that Lek and Esteve use MA and TEA to stabilize their *bulk omeprazole*, to meet their burden of proof Plaintiffs must demonstrate (1) that TEA/MA survives into Lek's *final formulation* and (2) that TEA/MA has a stabilizing effect in Lek's *final product*.

i. Presence of MA in Lek's Bulk Omeprazole

Plaintiffs claim that lowering the temperature during the final crystallization step in the presence of a vast excess of base (Swenton Tr. 2356:21-24, 2949:18-22), results in the MA being entrained in the alkaline form, which helps to stabilize and protect the omeprazole (Davies Tr. 353:7-24; Klibanov Tr. 5404:19-5406:1). Plaintiffs' experts testified that MA is entrained in the omeprazole crystals the same way as TEA, and will be retained in larger quantities than TEA. (Davies Tr. 1546:3-16, 1586:7-1587:23; 419:8-420:3; Klibanov Tr. 5268:16-5269:13; PSWTX 1259-22.) Dr. Klibanov put forward three rationales for this proposition. First, "MA has a greater propensity to act as a hydrogen donor in hydrogen bonding with omeprazole, since due to its chemical structure, TEA does not have any hydrogen to donate to a hydrogen bond." (Klibanov Tr. 5268:23-5269:1.) Second, MA has a higher dipole moment than TEA, and therefore "MA has a greater propensity to engage in dipole-dipole interactions with omeprazole." (Klibanov Tr. 5269:2-4.) Third, "MA is a much smaller molecule than TEA [and][t]he molecular weight is less than one third of TEA," allowing MA to penetrate more effectively into the imperfections in the omeprazole crystal. (Klibanov Tr. 5269:5-10.)

Lek's Dr. Padwa testified that MA, like acetone, is completely miscible in water and will be removed along with the acetone during redispensing. (Padwa Tr. 2957:18-2958:17; LEKTX 7203.) According to Dr. Padwa, a certain amount of omeprazole dissolves in the water used during the redispensing step, and any residual solvent (such as acetone or MA) occluded in the dissolved portion of omeprazole is released and removed.FN45 (Padwa Tr. 2956:13-15; Swenton Tr. 2313:11-2314:7.)

FN45. Plaintiffs allege that Lek's amendments to its DMF reduce the possibility of MA removal; however, this argument merely references the amendments to the process and is not supported by any additional evidence. Accordingly, the Court gives this argument little weight.

Unlike Esteve's certificates of analysis concerning permissible levels of TEA, Lek's certificates of analysis do not describe permissible amounts of MA in Lek-manufactured omeprazole. (Langer Tr. 1652:21-1653:6.) According to internal tests performed by Lek, however, two of three batches of Lek's bulk omeprazole each contained 14 ppm of residual methylamine, and the test of the third batch reported MA quantities below the limit of detection of 14 ppm. (LEKTX 2035 at LK 474992.) Lek's expert Dr. Padwa testified that "there may very well be on the order of 10 parts per million, 20 parts per million" of MA present in Lek's bulk omeprazole, which he regards as an "insignificant number." (Padwa Tr. 2991:7-10.)

ii. Presence of TEA and MA in Lek's Final Formulation

Plaintiffs allege that the MA present in parts per million in Lek's manufactured bulk omeprazole becomes entrained in the omeprazole crystals and survives into the final formulation of Lek's product, and acts to stabilize the omeprazole in the final product. (Langer Tr. 1179:19-1180:20 (citing Hafner-Milac Dep. Tr. 82:23-83:10, July 21, 2003); Langer Tr. 1544:8-21; Davies Tr. 352:25-353:24; Hafner-Milac Tr. 2889:3-2893:5; LEKTX 611T; PSWTX 2113; PSWTX 1256-14.) Dr. Davies testified that mass spectrometry testing on Lek's fully formulated product shows that the TEA in the bulk omeprazole survives the

manufacturing process, remains in the omeprazole crystals in Lek's fully formulated product, and helps stabilize Lek's omeprazole. (Davies Tr. 349:25-350:14, 351:6-352:7; PSWTX 1251-13.) In addition to Dr. Davies's mass spectrometry testing, Plaintiffs rely on the following evidence to show the presence of TEA and MA in the final formulation: (1) the absence of steps to remove the TEA or MA before placing the omeprazole in Lek's final formulation; (2) deposition testimony by Esteve's employee Dr. Coppi, allegedly stating that TEA in the bulk omeprazole will be carried into the final formulation; and (3) the testimony of Plaintiffs' experts Drs. Davies, Langer, and Klibanov explaining how the TEA and MA are locked into the omeprazole crystal structure and carried into the final formulation.

Plaintiffs' first point-the absence of steps taken to remove TEA or MA-neglects to address testimony that at least some of any TEA or MA entrained in the omeprazole during its synthesis will be removed during the process of formulating Lek's product. During the granulation step, anhydrous ethanol is used as the granulation fluid (Klibanov Tr. 5384:21-5385:23; LEKTX 2193 at KLIB 2001006), and there is a several fold molar excess of ethanol as compared to omeprazole (Klibanov Tr. 5388:5-25). Omeprazole is soluble in ethanol; therefore, according to Lek, all of the omeprazole that dissolves in the ethanol granulation fluid will release any TEA or MA entrained during the synthesis of the omeprazole. (Klibanov Tr. 5387:21-5388:1, 5389:10-13.)

Second, Plaintiffs' reliance on the deposition testimony of Esteve employee Dr. Coppi to support its theory that TEA is retained in the formulated product of Lek is improper because (1) Dr. Coppi never testified about Lek's product or formulation process (Klibanov Tr. 5349:17-5350:21 (recognizing differences between Lek and Esteve formulation process)), and (2) when questioned whether TEA in the bulk drug would be retained in the formulation, Dr. Coppi initially replied "I should think so" (Coppi Dep. Tr. 76:16-76:25, Mar. 12, 2004, 4:40PM), but later clarified that her statement applied "for the bulk drug, but not necessarily for the final product because additional processing takes place" (Errata Sheet for Mar. 12, 2004 Coppi Dep. Tr. at 76:25.)

Because the Court finds reliance on the above evidence insufficient or improper, the Court turns to Plaintiffs' mass spectrometry evidence and the testimony of Plaintiffs' experts to determine whether Plaintiffs have shown by a preponderance of the evidence that TEA and MA are present in Lek's final formulation.

(a) Mass Spectrometry Testing of Lek's Final Product.

Dr. Davies applied mass spectrometry testing to detect the presence of TEA in Lek's fully formulated 10-mg and 20-mg products.FN46 (Davies Tr. 339:25-341:12; PSWTX 1018, PSWTX 1275B, PSWTX 1275C.) Dr. Davies used an atmospheric pressure chemical ionization gas phase analyzer ("APCI-GPA") equipped with an MS Nose(R) sampling tube to test the samples. (Davies Tr. 334:2-3.) According to Dr. Linforth, one of the inventors of the MS Nose(R) APCI sample collection device, the MS Nose(R) APCI-GPA is a suitable technique for investigating the presence of TEA in a sample. (Linforth Dep. Tr. 165:24-166:4.) As will be discussed below, Lek disagrees.

FN46. Mass spectrometry is an analytical technique that allows the user to analyze compounds based on the molecular weight of their chemical species, and based on the atomic mass of the molecules, determine what chemicals are present in a sample. (Russell Tr. 4418:13-24, 4419:19-18, 4429:16-4430:12.) A mass spectrometer has three main components: the ionizer, the mass analyzer, and the ion detector. (*Id*. 4422:15-15.) The sample (in either liquid or gas form) is collected and introduced into the system and ionized, usually by an electric field. (*Id*. 4421:4-13.) The ionized molecules are pulled into a mass analyzer, which consists of four metal or metal-coated rods that act as electrodes. (*Id*. 4421:14-17, 4422:15-18.) A frequency voltage is then applied to the electrodes, which forces the ions to oscillate back and forth. (*Id*. 4422:18-22.) The mass analyzer can be programmed to allow only one mass-to-charge ratio (m/z) chemical species to pass through the analyzer into the ion detector. (*Id*. 4421:14-24.) Thus, by changing the applied

voltage, the mass analyzer can filter out all chemical species except those of a particular mass-to-charge ratio. (*Id*. 4422:23-25.)

The primary data obtained from a mass spectrometer is the mass spectrum. (Russell Tr. 4419:19-21.) The output is plotted as mass-to-charge ratio (m/z) on the horizontal axis and relative intensity or normalized (percent) abundance on the vertical axis. (*Id*. 4425:7-13; LEKTX 7455.) When a larger molecule reproducibly fragments into smaller molecules or fragments, the resulting set of peaks is called a fragmentation pattern, signature, or "fingerprint." (Russell Tr. 4430:3-8; Davies Tr. 679:18-680:1; LEKTX 456; *see also* Linforth Dep. Tr. 139:6-13, 157:17-24, Feb. 3, 2005.) The presence of chemical compounds is tested by comparing the fingerprints of mass spectra. (Russell Tr. 4430:8-12; Linforth Dep. Tr. 139:6-13.) If a mass spectrum creates a suspicion that a certain chemical species might be present, this can be tested by comparing the unknown chemical species with a known sample under the same conditions in the same system, to see if the fragmentation patterns or fingerprints match. (Russell Tr. 4430:8-12; Linforth Dep. Tr. 139:6-13.)

Another way of looking at the data obtained by the mass spectrometer is a chromatogram. (Russell Tr. 4423:6-10; LEKTX 7454.) A chromatogram is data acquired by the mass spectrometer over time. (Russell Tr. 4424:3-4, 4423:11-4424:4.) On a chromatogram, the y-axis is relative intensity or percent abundance just as for a mass spectrum, but the x-axis is time, or some temporal units such as scan number. (*See, e.g.,* LEKTX 7454; LEKTX 7487.) Dr. Russell testified that chromatogram traces are commonly used in practice to provide a basis for the reproducibility of the mass spectrometry system. (Russell Tr. 4423:22-24:15.) When identical samples are analyzed, the same number or abundance of ions should be detected at each time interval to establish reproducibility and a stable system. (Russell Tr. 4424:6-11.)
Dr. Linforth operated the equipment during the course of Dr. Davies's mass spectrometry testing. (Linforth Dep. Tr. 61:19-22, 76:25-77:2, 164:10-15, Feb. 3, 2005.) As described in Dr. Davies's lab notebook (PSWTX 1018), his expert report, and at trial, the 10-and 20-mg Lek product samples were prepared by placing the contents of six capsules into a 20-ml bottle and adding 5 ml of sodium hydroxide. (Davies Tr. 339:25-341:12; PSWTX 1018; PSWTX 1251-10.) Each sample was analyzed using the MS Nose(R) Micromass Platform II and the results were recorded at specific times. (Davies Tr. 339:25-341:12; PSWTX 1018; PSWTX 1275B; PSWTX 1275C.)

Dr. Davies also tested two sets of controls. (Davies Tr. 333:22-337:9; 340:19-21, 347:3-6; PSWTX 1018; PSWTX 1275A.) The first set of control samples Dr. Davies tested ("the TEA control") contained 1.12 ppm TEA in a sodium hydroxidesolution, a highly basic environment where TEA will predominately be in its neutral form. (Davies Tr. 333:22-335:8; PSWTX 1018 at Davies2W6019617.) The second set of control samples ("the no TEA control") contained only the sodium hydroxide solution. (Davies Tr. 340:19-21, 347:3-6, 349:1-9; PSWTX 1018 at Davies2W6019617.)

By systematically increasing the cone voltage, Dr. Davies determined that a cone voltage of 50V could be used to induce fragmentation of TEA in a controlled way. (Davies Tr. 640:7-25.) At a cone voltage 18V the TEA control exhibited a peak at m/z 102. (Davies Tr. 335:9-336:6; Linforth Dep. Tr. 166:5-22; PSWTX 1275A; PSWTX 1016A at 2W66019610; PSWTX 1251-9.) When the cone voltage was increased to 50V and controlled fragmentation was induced, the TEA control exhibited a peak at m/z 102, as well as peaks at m/z 74, 58, and 46. (Davies Tr. 336:7-337:9; Russell Tr. 4532:22-4533:8; Linforth Dep. Tr. 166:5-10; PSWTX 1275A; PSWTX 1251-9; *see also* Davies Tr. 346:13-347:2, 347:18-19, 349:10-12, 349:18-19; PSWTX 1275C; PSWTX 1251-12.) Dr. Davies's tests of sodium hydroxide solution alone did not show the peaks at m/z 102, 74, 58, or 46. (Davies Tr. 343:19-22, 345:14-19, 347:3-6, 349:1-9; PSWTX 1275A; PSWTX 1251-11; PSWTX 1251-12.)

Under the same environmental conditions, two samples of the same compound should produce the same

fragmentation patterns. (Linforth Dep. Tr. 139:6-13.) Like the TEA control, the mass spectra of Lek's fully formulated 10- and 20-mg samples detected a peak at m/z 102. (Davies Tr. 345:25-349:24; PSWTX 1275B; PSWTX 1275C; PSWTX 1251-11; PSWTX 1251-12; PSWTX 1018.) When the cone voltage was increased to 50 V and controlled fragmentation was induced, the signals at m/z 102 remained and signals at m/z 74 emerged. (Davies Tr. 345:13-349:24; PSWTX 1275B; PSWTX 1251-11; PSWTX 1275C; PSWTX 1251-12.) Dr. Linforth testified that the presence of mass spectrometry peaks at m/z 102 and 74, as detected in the TEA control tests, are strongly consistent with the presence of, and indicative of, TEA in Lek's fully formulated products. (Linforth Dep. Tr. 166:5-22.)

Lek disputes this assertion. Lek argues that the presence of only two of the four major ions in the TEA spectrum is not sufficient to establish the presence of TEA in Lek's product. According to Lek's Dr. Russell, to determine if TEA is present in Lek's samples, it is necessary to compare all four major peaks of the fingerprint, because they are all significant. (Russell Tr. 4438:10-17; 4533:1-8; 680:14-25; LEKTX 456.) The mass spectra of the 10-mg samples contained peaks at m/z 102, 74, and a very small peak at m/z 46, but the signal at m/z 58, which is found in the TEA control samples, was not present. (Davies Tr. 681:11-682:3, 682:18-22; Russell Tr. 4439:3-6, 4441:14-25; PSWTX 1275B at DAVIES2W6019585; LEKTX 7466; LEKTX 7467.) Likewise, for the 20-mg samples, the signals at m/z 102, 74, and 46 are present, but the signal at m/z 58 is either not present or is "weak[ly] disintegrating." (Linforth Dep. Tr. 141:13-142:13, 157:17-24; PSWTX 1275C at DAVIES2W6019589; LEKTX 189.) Dr. Russell concluded that because the peak at m/z 58 is absent, the mass spectrum of Lek's product does not match the fingerprint of the TEA control, and therefore, one cannot conclusively determine whether Lek's product contains TEA. (Russell Tr. 4439:7-12, 4441:14-4442:13.)

Dr. Davies attempted to explain the absence or weakness of the peak at m/z 58. He argued that in the tests of Lek's fully formulated product the signal of the peak at m/z 58 is weak or absent because the residual acetone in Lek's product produces a peak at 59 that masks the peak from TEA at 58. (Davies Tr. 681:11-682:22; Linforth Dep. Tr. 148:16-149:19.) However, in Dr. Davies's data, there are numerous instances of small peaks appearing one mass unit lower than a major peak. (Russell Tr. 4555:4-12; *e.g.,* LEKTX 186 at 5, 11, 12 (116 visible adjacent to 117); LEKTX 186 at 17 (86 visible adjacent to 87); LEKTX 186 at 21 (103 visible adjacent to 102); LEKTX 190 at 6 (73 visible adjacent to 74).) There are also instances of small peaks appearing one mass unit lower and one mass unit higher than a large peak. (*E.g.,* LEKTX 186 at 5, 17 (peaks identified at 116, 117, 118); LEKTX 190 at 6 (peaks identified at 73, 74, 75); LEKTX 190 at 9 (peaks identified at 142, 143, 144).) The Court finds that at the very least, the evidence is equivocal as to whether the 58 peak was present but masked, or not present at all-leaving Astra with only three out of the four peaks to rely upon.

In addition to disputing the results of Dr. Davies's mass spectrometry, Lek also argues that the data is not reproducible and therefore scientifically invalid. Dr. Russell testified that the TEA control samples tested by Dr. Davies produced identical mass spectra, but the mass spectra for Lek's 20-mg samples varied greatly. (Russell Tr. 4454:16-4457:13.) According to Dr. Russell, the large difference in the relative intensity of the peaks between the three 20-mg samples indicates that the tests may not be reproducible. (Russell Tr. 4453:13-4556:11; LEKTX 7484.) In addition, Dr. Russell testified that this is indicative of something going wrong with the experiment. (Russell Tr. 4454:16-4455:11.)

Dr. Davies attributes the variation in the results to the fact that the three 20-mg samples were mixed to different extents. (Davies Tr. 347:11-17; PSWTX 1275C.) Dr. Davies testified that within each sample the m/z 102, 74, and 46 signals each scale to each other (i.e., their respective peak heights rise and fall together), which shows that the peaks are related to each other and to the presence of TEA in Lek's product. (Davies Tr. 347:11-17, 1051:25-1056:5, 1058:4-19; PSWTX 2015; PSWTX 1275C.) Assuming scaling analysis is properly applied here-which Lek disputes-Dr. Davies only "scaled" three of the four major ions in the TEA spectrum. The Court is not persuaded that this incomplete analysis is sufficient to conclude that

the results are reproducible.

Lek also hypothesizes that acetone may be the source of the spectral peaks Dr. Davies identified as TEA. (Russell Tr. 4446:23-4447:6.) Acetone and acetone dimmer molecules are represented by signals at m/z 59 and 117-not m/z 102 and 74. (Russell Tr. 4434:21-4435:9.) Dr. Russell testified that the signal at m/z 102 may be produced by an acetone dimer that had lost a methyl group. (Russell Tr. 4533:9-4535:12; LEKTX 7463; LEKTX 7474.) An acetone dimer is formed by two acetone molecules that are hydrogen bonded together, while acetone's methyl group is covalently bonded to the carbon. (Russell Tr. 4533:9-19, 4535:25-4536:2; LEKTX 7463; Linforth Dep. Tr. 158:17-22.) Covalent bonds are much stronger than hydrogen bonds and it is much more difficult to break a covalent bond than a hydrogen bond. (Russell Tr. 4536:7-16.)

Dr. Linforth rejoined that it is more likely that as the cone voltage is increased the weaker hydrogen bond in the acetone dimer will break and the dimer will revert to the monomer, than it is for the acetone dimer to lose a covalently bonded methyl group. (Linforth Dep. Tr. 111:12-112:17, 158:17-22.) Dr. Russell did not consider the likelihood of one type of fragmentation occurring over the other. (Russell 4535:25-4536:2, 4537:3-7.)

Dr. Russell also testified that he did not consider the likelihood that an acetone dimmer could further fragment to produce a signal at m/z 74. (Russell Tr. 4540:4-4542:21.) For an acetone dimer to be responsible for the peak at m/z 74, the following steps would have to occur: (1) acetone dimer forms; (2) acetone dimer loses methyl group (an unlikely scenario as described above); (3) a C=O breaks in the middle of the molecule leaving two additional fragments; (4) the two additional fragments somehow recombine to form a molecule having a molecular weight of 74. (Russell Tr. 4540:4-4542:21.) Dr. Russell did not consider the likelihood of these steps occurring. (Russell Tr. 4540:4-4542:21). Accordingly, the Court is not persuaded that Lek's hypothesis that acetone is the alternative source of the peaks at m/z 102 and 74 is correct.

Lek also argues that Dr. Davies's testing is invalid because Dr. Davies failed to use readily available scientific techniques for addressing whether acetone was the alternative cause of the peaks at m/z 102 and 74. Lek argues that Dr. Davies should have performed a procedure known as "spiking" to eliminate acetone as a source of possible interference. (Russell Tr. 4450:13-4452:23.) However, Plaintiffs' experts are not required to perform every possible test-particularly when testing for alternative theories that are considered highly unlikely. *See, e.g.,* Zuchowicz v. United States, 140 F.3d 381, 385-87 (2d Cir.1998) (stating that it is not required that an expert categorically exclude each and every possible alternative cause in order to render the proffered testimony admissible); *see also* MicroStrategy Inc. v. Business Objects, S.A., 429 F.3d 1344, 1355 (Fed.Cir.2005) (stating that while an expert need not consider every possible factor to render a "reliable" opinion, the expert must consider enough factors to make his or her opinion sufficiently reliable in the eyes of the court). Thus, Plaintiffs' failure to perform alternative tests, such as "spiking," does not render Dr. Davies's testing invalid.

Lastly, Lek argues that Dr. Davies used entirely the wrong technique for analyzing Lek's products. According to Lek's Dr. Russell, gas chromatography-mass spectrometry ("GC-MS"), which is more common and widely available, would have been a better system than the MS Nose(R) APCI mass spectrometer for determining whether or not the samples of Lek's final product contain TEA. FN47 (Russell Tr. 4461:11-20, 4464:2-3, 4464:4-9.) According to Dr. Russell, the MS Nose(R) is not the preferable technique because the MS Nose(R) does not separate the individual volatile chemical species that are found in a single sample; instead it introduces all of the sample's chemical species simultaneously into the mass analyzer interface. (Russell 4461:11-4462:19, 4462:23-4464:8.) The resulting mass spectrum is representative of all of the sample's chemical species. (*See* Russell Tr. 4461:11-18; LEKTX 183.) "If there are a lot of compounds present from a sample which give a large number of ions, then it may be unclear as to which ions are associated with a particular compound ...." (Linforth Dep. 46:10-19.)

FN47. For a detailed explanation of gas chromatography-mass spectrometry, *see supra* note **Error! Bookmark not defined..**

Dr. Russell opined that gas chromatography-mass spectrometry is a better technique because a gas chromatograph separates the individual volatile chemical species before they are ionized, thereby producing a unique mass spectra for each chemical species. (Russell Tr. 4461:24-4462:4, 4462:25-4463:20; LEKTX 7496.) According to Dr. Russell, the mass spectra will be cleaner and simpler because there will be no interference from the other gas species present in the original sample. (Russell Tr. 4463:3-11.) In addition, the use of gas chromatography would eliminate the problem of assigning peaks to individual chemical species. (*Id*. 4463:17-20.) Lek and its experts could have, but did not, employ the use of GC-MS to test for TEA in its product. (*Id*. 4522:19-4523:2.)

Plaintiffs are not required to run every test suggested. In addition, the existence of an alternative test method, such as gas chromatography-mass spectrometry, does not render mass spectrometry using MS Nose(R) inadmissible or inherently unreliable. Libas, Ltd. v. United States, 193 F.3d 1361 (Fed.Cir.1999) ("If a test, methodology or procedure is clearly shown to be generally accepted and to test what is at issue in the case, a court is entitled to have confidence in its results unless some particular reason for doubt arises, such as failure under the other Daubert factors.").

The Court finds that Dr. Davies's results are clearly admissible expert opinions. However, Lek's criticisms of Plaintiffs' results and interpretations-including Plaintiffs' focus on only two of the four spectral fingerprints and failure to obtain consistent results-give the Court pause. Without more convincing and consistent results, the mass spectrometry evidence is insufficient to persuade the Court, by a preponderance of the evidence, that TEA is present in the fully formulated Lek product.

As for the presence of MA in Lek's fully formulated product, Plaintiff's expert, Dr. Klibanov failed to perform *any* tests to support his assertion that MA is retained in Lek's final formulation. (Klibanov Tr. 5398:12-5400:8.) Mere theorizing, without more, is insufficient to support finding by a preponderance of the evidence that MA is present in Lek's fully formulated product. *See* Astra v. Andrx, 222 F.Supp.2d at 516. It is within the discretion of the district court to prevent an expert from testifying where his or her methods or principles are speculative or unreliable. MicroStrategy Inc. v. Business Objects, S.A., 429 F.3d 1344, 1356 (Fed.Cir.2005). The Court has considered Dr. Klibanov's theories but gives them little weight. *See, e.g.*, Astra v. Andrx, 222 F.Supp.2d at 487 (citing Boucher v. United States Suzuki Motor Corp., 73 F.3d 18, 21 (2d Cir.1996) (stating that "contentions that the assumptions are unfounded go to the weight, not the admissibility, of the testimony")). Accordingly, the Court finds that Plaintiffs have failed to establish by a preponderance of the evidence that MA is present in Lek's full formulated product.

c. Effective Amount of TEA and MA

Even if Plaintiffs' mass spectrometry evidence was considered reliable and sufficient to show the presence of TEA in Lek's final product, Plaintiffs have failed to convince the Court that TEA and MA are present in an amount sufficient to stabilize the omeprazole.

Plaintiffs' Dr. Langer testified that because Lek's formulation is very dry-containing less than 1.5% water as taught by the '505 Patent-the acidic excipients in Lek's core are immobile and therefore have a hard time attacking the omeprazole. (Langer Tr. 1535:10-14, 1538:2-20.) Thus, even small amounts of TEA or MA in Lek's omeprazole are effective in creating the omeprazole microenvironment and protecting the omeprazole. (*Id*.) Dr. Langer's theory that a trace amount of MA or TEA stabilizes the omeprazole in Lek's product not only lacks factual support, but is also internally inconsistent.

According to Dr. Davies and Dr. Klibanov, TEA is entrained in the crystal lattice of omeprazole, and as the omeprazole crystal dissolves, TEA will be released. (Christian Tr. 3765:16-3766:16; Davies Tr. 296:18-20, 297:11-13; Klibanov Tr. 5260:21-5262:5, 5354:5-16.) According to Dr. Christian, if omeprazole with an impurity level of 30 ppm TEA is dissolved in water, the concentration of TEA in the solution will be one ten-thousandth that of the omeprazole in the solution, and that concentration of TEA will not change the theoretical pH of the omeprazole from 6.4. (Christian Tr. 3766:6-18; LEKTX 7357.) If there are only 5 ppm TEA in the omeprazole, the concentration of the TEA in the solution when the omeprazole is dissolved in water will be six times less than that; therefore, 5 ppm TEA would not even change the pH of pure water, and thus does not change the theoretical pH of omeprazole.FN48 (Christian Tr. 3766:19-3767:16; LEKTX 7357.)

FN48. If the amine does not dissolve proportionally with the omeprazole, as Dr. Christian's calculations assume, the calculations would perhaps change a little, but not in a significant way. (Christian Tr. 3799:4-16.)

While Plaintiffs presented evidence that small quantities of substances may "exert effects of technical importance," (PSWTX 2072), they did not present evidence sufficient to demonstrate that that is the case with TEA and MA. Nor is the Court persuaded by Dr. Klibanov's testimony that TEA/MA functions like preservatives in a food product:

Dr. Padwa asked rhetorically, how can one molecule of TEA protect 10,000 molecules of omeprazole? Well, paraphrasing, how can one molecule of a preservative protect 10,000 molecules of a food, whether it's canned nuts or jellies or whatever. One can ask exactly the same question. The answer is, however they do it, they do it.

(Klibanov Tr. 5369:7-12.) Indeed, Dr. Klibanov himself admitted that the mechanism by which preservatives protect food is different from the way an alkaline reacting compound might protect omeprazole. (Klibanov Tr. 5368:18-5369:2.) Likewise, the assumption of Apotex's expert, Dr. Robinson, that organic amine bases would provide an alkaline microenvironment does not rise to the level of proof required here. (Klibanov Tr. 5317:15-22 (quoting Robinson Dep. Tr. 99:6-99:16, Jan. 21, 2005).) The Court is more persuaded by the logic of Dr. Swenton's assertion that:

to have an effective amount of an alkaline reacting compound, TEA, it has to be close to the omeprazole that it is protecting. I can't tell you whether one triethylamine molecule can be close enough to 10 omeprazole molecules. I can certainly tell you that one in 10,000 won't do it.

(Swenton Tr. 2377:7-11.)

Therefore, even if TEA and MA survive into Lek's final product in very low ppm values, Plaintiffs have not proven by a preponderance that enough is present to protect the omeprazole from acid degradation. Omeprazole containing a hypothetical amount of 10 ppm TEA/MA would have one molecule of TEA/MA per 10,000 molecules of omeprazole. Thus, the Court finds that Plaintiffs have not shown by a preponderance of the evidence that this is enough to protect the omeprazole particles that can be attacked from any surface by acidic protons that might be present. (Padwa Tr. 2968:12-2969:25; LEKTX 7216.)

Furthermore, Plaintiffs' arguments concerning TEA/MA are internally inconsistent. Plaintiffs' experts testified that TEA and MA are tightly bound within the omeprazole crystal. (Langer Tr. 1546:10-16; Klibanov Tr. 5267:18-5269:13.) It is inconsistent to assert, as Plaintiffs' experts suggest, that allegedly tightly bound TEA/MA is nevertheless available to react with acidic protons that might approach the

omeprazole after being tightly sequestered within the omeprazole crystal during the purification process. (Padwa Tr. 2968:4-9; *see also* Swenton Tr. 2335:17-24.) This inconsistency is further highlighted by Dr. Klibanov's testimony that MA is an acid scavenger and that acid scavengers must be mobile in order to be effective. (Klibanov Tr. 5253:18-21.)

Accordingly, Plaintiffs have failed to show by a preponderance of the evidence that Lek's product literally contains an ARC.

d. Doctrine of Equivalents

Plaintiffs also argue that if not literally an ARC, TEA and MA in Lek's omeprazole formulations are equivalents of an ARC and that Lek knowingly uses omeprazole containing TEA and MA for its stabilizing effect. Plaintiffs argue that the TEA and MA in the omeprazole of Lek's product are the equivalent of an ARC because both compounds are alkaline, act as buffers, increase the pH of the omeprazole microenvironment to at least 7.0, and stabilize omeprazole used in the Lek formulation.

Because Plaintiffs have failed to show by a preponderance of the evidence that TEA and MA are present in an effective amount to stabilize the omeprazole by raising the micro-pH to 7 or above, Plaintiffs' claims under the doctrine of equivalents must fail.

e. Alkaline Omeprazole Salt Equivalent

Plaintiffs further assert that Lek's product infringes the '505 and '230 Patents because the Lek omeprazole (with MA) and Esteve omeprazole (with TEA) are the equivalent of an alkaline omeprazole salt. As stated above with respect to Mylan/Esteve's product, the conclusory statements of Drs. Langer and Klibanov are insufficient to support a finding under the preponderance of the evidence that Lek's product contains the equivalent of an alkaline omeprazole salt.

Moreover, Plaintiffs have not shown that Lek's omeprazole is substantially similar to an alkaline omeprazole salt. An alkaline omeprazole salt contains vastly more alkaline material. Dr. Padwa testified that an alkaline salt generally has a one-to-one ratio of basic counter-ion to omeprazole. (Padwa Tr. 2970:1-8.) Thus, a salt has thousands of times more molecules of base than Lek's omeprazole, which contains only trace amounts, if any, of TEA or MA. (Padwa Tr. 2970:1-8.) For example, assuming 10 ppm MA, there is only one molecule of MA per 10,000 molecules of omeprazole. In the case where an omeprazole salt forms with a one-to-one ratio of basic counter-ion to omeprazole, there will be 9,999 more molecules of base (counter-ion) present for 10,000 molecules of omeprazole. (Padwa Tr. 2970:1-8.)

Accordingly, the Court finds that Plaintiffs have not proven by a preponderance of the evidence that Lek's products contain an ARC as required by subpart (a) of claims 1 of the '505 and '230 Patents, either literally or under the doctrine of equivalents. Because all of the independent claims of the '505 and '230 Patents asserted against Lek require an ARC, the Court holds that Lek's products do not infringe any of the independent claims of those patents. Furthermore, it is axiomatic that any claims that depend from those independent claims also will not be infringed. Accordingly, the Court holds that Lek also does not infringe any of the dependent claims of the '505 and '230 Patents asserted against Lek. Wilson Sporting Goods Co. v. David Geoffrey & Assocs., 904 F.2d 677, 685 (Fed.Cir.1990).

3. Claim 1(b): An Inert Subcoating That is Soluble or Rapidly Disintegrating in Water

As explained above, claim 1(b) of the '505 Patent requires "an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of

materials selected from among tablet excipients and polymeric film-forming compounds." (PSWTX 1A 16:48-52.) Similarly, claim 1(b) of the '230 Patent requires "an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds." (PSWTX 2A 13:10-15.)

Plaintiffs allege that Lek's ANDA product contains a subcoating made of "povidone" or "polyvinyl-pyrrolidone" ("PVP"), which is specifically identified in the '505 Patent as an acceptable, water soluble, inert subcoating material. (PSWTX 1A 4:35-39, 8:58, 9:27.) FN49 According to Plaintiffs, the subcoating forms *in situ* by migration of PVP from the core of Lek's product to the core's surface during the enteric coating process. (Davies Tr. 625:16-23.) FN50

FN49. There is no dispute that *if* Lek's pellet contains a subcoating of PVP, it is inert for purposes of the claim 1(b) limitations.

FN50. The product claims of the '505 and '230 Patents do not limit the manner in which the product is made and cover subcoatings regardless of how they are formed-including subcoatings formed *in situ*. *See supra* Part II.B.1 (Claim Construction); *see also* Astra v. Andrx, 222 F.Supp.2d at 469.

Plaintiffs' infringement claim rests on three separate yet related groups of tests by its expert Dr. Davies. As explained further below, the first group tested Lek's enteric coated pellets using CLSM fluorescence,FN51 CLSM reflectance,FN52 wide-field UV fluorescence,FN53 and Atomic Force Microscopy (AFM).FN54 The purpose of this group of tests was to demonstrate the existence of a substantially continuous separating layer between the core and enteric coat of Lek's product. The second group of tests included CLSM fluorescence testing on Lek's washed pellets, *i.e.*, pellets that were washed in a solvent to remove most or all of the enteric coating. The purpose of these tests was to determine whether the alleged sublayer detected in the first group of tests was a discrete layer that remained intact after the enteric coat was washed off. The third group of tests consisted of ATR-FTIR FN55 and disintegration testing on Lek's washed pellets, the purpose of which was to show that the chemical and physical characteristics of the alleged subcoating render it inert and rapidly disintegrating. For the reasons below, Plaintiffs have not proven by a preponderance of the evidence that Lek's product infringes claim 1(b) of either Patent.FN56

FN51. In CLSM fluorescence, a laser is focused on a specific spot on a sample. Through the use of a pinhole, only the fluorescence from that portion of the sample will be detected. After passing through the pinhole, a prism and mirrors separate the light and different regions of light are directed to one of three detectors. (Davies Tr. 151:14-153:3; PSWTX 1250-5.) Because the sample is at a tilt when it is measured, fluorescence may be detected in only one portion of an optical slice ("Z section"). For that reason, to correctly interpret the CLSM data and understand the sample, it is necessary to look at all the Z sections. (Davies Tr. 153:4-155:1, 1045:24-1049:24; PSWTX 1250-6.)

FN52. CLSM reflectance measures the light reflected from a sample. It does not measure fluorescence. (Davies Tr. 155:2-24; PSWTX 1250-7.)

FN53. In widefield UV fluorescence, the sample is eradiated with light of 340-380 nanometers. Through the use of filters, only the fluorescent light beyond 425 nanometers is collected. (Davies Tr. 150:16-151:10; PSWTX 1250-4.) In contrast to CLSM fluorescence, which only captures information in the plane of focus, widefield UV fluorescence illuminates the entire sample and captures information from both above and

below the plane of focus. (Davies Tr. 150:16-151:10; Herman Tr. 4778:21-4779:2; PSWTX 1250-4.)

FN54. In AFM, a tip suspended from a cantilever scans over the contours of a surface and produces high resolution topographical information about the surface of the sample. (Davies Tr. 402:21-403:1.)

FN55. ATR-FTIR is a form of infrared spectroscopy that is widely used within the pharmaceutical industry to determine the chemical characterization of pharmaceuticals. *See supra* note 17.

FN56. In a letter dated July 12, 2006, Lek's attorneys objected to the admissibility of certain evidence presented by Dr. Davies. Even considering the evidence to which Lek objects, Plaintiffs have failed to meet their burden of proof. Accordingly, the Court need not reach the merits of Lek's objections.

In the first group of tests, Dr. Davies examined over 20 sectioned Lek pellets using CLSM fluorescence. (Davies Tr. 367:13-22). He analyzed the CLSM fluorescence data by viewing: (1) single optical slices ("Z sections") (Davies Tr. 364:19-365:2; PSWTX 899); (2) maximum intensity projections, whereby all of the Z sections are brought to the surface (Davies Tr. 365:5-8; PSWTX 895; PSWTX 905); (3) three-dimensional images, created by compiling Z sections with corresponding CLSM reflectance images (Davies Tr. 365:8-24; PSWTX 900); and (4) several Z sections from a sample which were laid on top of a CLSM reflectance image of the same sample (Davies Tr. 1047:16-1050:23; PSWTX 2012.)

The images presented by Dr. Davies from these analyses appear to evidence three regions of Lek's pellet: a core; an enteric coating layer; and a fluorescing band at the interface between the core and coat. (*See, e.g.*, PSWTX 894; PSWTX 895; PSWTX 899; PSWTX 901; PSWTX 905; *see also* Davies Tr. 363:17-367:12.) CLSM reflectance images alone did not reflect a separating layer because, according to Dr. Davies, CLSM reflectance lacks the resolution and does not exhibit the same level of contrast as CLSM fluorescence. (Davies Tr. 5627:18-5629:6; *compare* PSWTX 896; PSWTX 902 *with* PSWTX 899.) Dr. Davies nevertheless found CLSM reflectance images useful in locating the position of the fluorescence as being on top of the core. (Davies Tr. 363:24-364:2, 366:3-9.)

In addition to CLSM testing, Dr. Davies conducted AFM tests on Lek's bisected enteric coated pellets. (Davies Tr. 402:17-20, 5612:25-5613:14.) Dr. Davies looked at over ten different pellets with AFM and recorded images varying in size from 10 x 10 microns to 30 x 30 microns. (Davies Tr. 410:15-410:25.) Like the CLSM fluorescence images presented by Dr. Davies, his AFM images evidence three regions: a core region; an enteric coating layer; and what appears to be a separating layer in between. (Davies Tr. 405:18-407:1; PSWTX 915; PSWTX 916; PSWTX 918; PSWTX 918; PSWTX 919.)

From this data, Dr. Davies hypothesized that the purported separating region-measured on average to be between one and two microns thick (Davies Tr. 364:19-365:4, 406:14-19; PSWTX 918)-may be a subcoating. However, because Dr. Davies believed that the chemical properties of the separating layer could not be determined with the types of tests performed, other tests (discussed *infra*) were needed to verify that what appeared to be a separating layer in the CLSM and AFM images was in fact a subcoating having chemical properties and characteristics necessary to infringe claim 1(b) of the '505 and '230 Patents.

Before turning to those other tests, however, the Court notes that it has serious doubts about whether the goal of the first group of tests-to determine the existence of a continuous separating layer-was met. Indeed, the Court finds that Dr. Davies's analysis and conclusions in this regard were significantly undermined by Lek's well-credentialed experts. As explained below, those experts reviewed Dr. Davies's data, conducted

their own testing on Lek's coated pellets, and reached very different conclusions than Dr. Davies.

To begin, Lek's Dr. Herman presented wide-field UV fluorescent images of Lek's coated pellets in which no separating fluorescing layer is apparent; rather, the fluorescence appears to radiate throughout the entire enteric coating. (*See, e.g.,* LEKTX 1260-1; LEKTX 1260-2; LEKTX 1260-4; LEKTX 1260-5.) Dr. Davies conceded that the UV fluorescence data did not show a subcoating or layer between the enteric coat and core. (Davies Tr. 439:23-25.) His explanation for this was that UV fluorescence could not be used to analyze something with a translucent coat. (Davies Tr. 440:1-8.) Dr. Davies's explanation, however, is somewhat inconsistent with Dr. Davies's use of UV fluorescence to locate a layer in the Apotex product, which also has a translucent coat. (Cima Tr. 4209:2-7; APO 708. *But cf.* Davies Tr. 440:1-8 (distinguishing the analysis on the grounds that Lek's pellet is more translucent than Apotex's product).) Dr. Herman also testified that the source of any fluorescence cannot be PVP, because he believes that PVP does not fluoresce at UV excitation. (Herman Tr. 4740:19-4741:23; LEKTX 7541.) FN57

FN57. To the extent that the fluorescence appears brighter near the surface of the core in some of these images, Dr. Herman testified that this was the result of light refracting between the separate core and coating layers. (Herman Tr. 4635:23-4637:25, 4682:20-4684:7; LEKTX 7529; LEKTX 7530.)

In addition to wide-field UV fluorescence images, Dr. Herman presented CLSM fluorescence images where the fluorescence appears to shine through the entire width of the enteric coating in Lek's pellets. (Herman Tr. 4690:22-24, 4713:21-4714:15, 4720:23-4721:1; LEKTX 1267-4; LEKTX 1267-67.) Dr. Herman explained that this fluorescence cannot be from a layer at the interface between the coat and core because the fluorescence would fade away within microns of its origin, and well before it reached 40 or 50 microns away to the outside of the enteric coat. (Herman Tr. 4726:20-4730:12; LEKTX 7523; LEKTX 7527.)

Moreover-and contrary to Dr. Davies's opinion-Dr. Herman explained that CLSM reflectance does have the resolution to detect a sublayer that is thicker than one micron; especially if the sublayer's topography is as different from the core and the enteric coat as Dr. Davies suggested through his AFM presentation. (Herman Tr. 4739:19-4740:10.) Thus, the fact that Dr. Davies was unable to identify a separate sublayer using CLSM reflectance strongly suggests that no such sublayer exists. (*See* Garini Tr. 2691:4-2695:1; LEKTX 7134.) While Dr. Davies testified that CLSM reflectance images do not exhibit the same level of contrast as CLSM fluorescence and are of a lower resolution than AFM images (Davies Tr. 405:15-406:6, 5627:18-5629:6), that is not to say that CLSM could not detect a sublayer if one existed.

With respect to Dr. Davies's AFM analysis, Lek's Drs. Quate and Russell both emphasized the importance of seeing the context of an AFM scan because the individual images are so small. (*See* Quate Tr. 3128:21-3129:17; Russell Tr. 4372:1-4378:24; LEKTX 7012; LEKTX 7385; LEKTX 7388.) Lek's core has a circumference of about 3000 microns, of which Dr. Davies's AFM images show a very small fraction. (Davies Tr. 550:2-551:7.)

Moreover, Drs. Quate and Russell determined that Lek's core contains: (1) large smooth boulder-like structures; and (2) amorphous granular structure. (Quate Tr. 3118:16-21, 3119:20-3120:4, 3121:4-13; Russell Tr. 4411:15-19; LEKTX 291-7; LEKTX 291-10; LEKTX 7432; LEKTX 7439.) Their AFM images show that what appears to be a granular structure along the interface between the enteric coating and the core may very well be part of the core rather than a separate layer. (Quate Tr. 3128:21-3129:17, 3152:5-3154:12; Russell Tr. 4372:1-4378:24; LEKTX 7012; LEKTX 7377; LEKTX 7379; LEKTX 7385; LEKTX 7387; LEKTX 7388; LEKTX 7390; LEKTX 7392.) The Court finds that this evidence dramatically undermines the conclusions reached by Dr. Davies through his AFM testing.

Furthermore, Lek's Dr. Garini disagreed with Dr. Davies's hypothesis that CLSM fluorescence testing could

not be used to determine the chemical properties of the fluorescing layer. In fact, Dr. Garini provided quantitative and spectral analyses of his own CLSM data, as well as from data collected from Dr. Davies, showing that whatever was fluorescing was not PVP. (Garini Tr. 2650:13-2652:5, 2655:15-22, 2656:1-4; LEKTX 7107; LEKTX 7109.)

After considering the totality of evidence presented by Plaintiffs' and Lek's experts in connection with the first group of tests done on Lek's coated pellets, the Court is not at all convinced that Plaintiffs have demonstrated that a continuous separating layer exists between the core and the coat, much less a layer of PVP.

Unfortunately for Plaintiffs, the evidence that was-and was not-presented in connection with Dr. Davies second group of tests only compounds the Court's doubts. As noted above, the second group of tests included fluorescence testing on Lek's washed pellets (as opposed to coated pellets), for the purpose of determining whether the sublayer purportedly detected by Dr. Davies in the first group of tests was still intact after the enteric coat was washed away.

There is no dispute that Dr. Davies did not record the data from the second group of tests (Davies Tr. 543:10-13, 5922:9-5923:3), notwithstanding that he recorded and presented favorable data in connection with his analysis of Apotex's and Impax's products, which are also alleged to have an *in situ* subcoating. (*See* Davies Tr. 445:24-447:3; PSWTX 823; PSWTX 824; PSWTX 825 (Apotex); Davies Tr. 504:18-505:10, PSWTX 873 (Impax).) The Court need not draw an adverse inference from Dr. Davies's decision not to present CLSM data on Lek's washed pellets, as Lek urges the Court to do, because Dr. Davies's testimony alone is simply insufficient in itself. Specifically, Dr. Davies testified that while he observed fluorescence on the washed pellets, he did not observe a layer remaining on the surface of Lek's washed pellet as he had with the products of the other defendants. (Davies Tr. 5922:9-5923:3.) His testimony in this regard is neither convincing nor conclusive about what exactly was (or was not) detected in any fluorescent images taken of Lek's washed product.

The evidence from Dr. Davies's third group of tests on Lek's pellets falls short of curing the inadequacies of proof discussed above. This group of testing consisted of ATR-FTIR and disintegration tests on Lek's washed pellets: the former to determine the chemical properties of the alleged separating layer; the latter to determine whether the alleged separating layer rapidly disintegrates in water.FN58

FN58. Lek presented no expert testimony to rebut Dr. Davies disintegration testing. Because the Court ultimately finds that Plaintiffs have not met their burden of proving the existence of a subcoating, however, there is no need to address Dr. Davies's claim that any such subcoating rapidly disintegrates in water.

Dr. Davies used ATR-FTIR testing on Lek's pellets that he had first washed in a solution of acetone:IPA. (Davies Tr. 375:22-376:2.) Dr. Davies was unable to isolate the alleged PVP layer, but instead was left with traces of HPMCP on the surface of the washed pellet. (Davies Tr. 543:14-546:1, 605:3-22.)

Using ATR-FTIR spectroscopy, Dr. Davies found that the washed pellets exhibited peaks of about 1678 and 1286 cm^{-1}, which he believed were consistent with the presence of PVP. (Davies Tr. 378:10-14; PSWTX 908.) The washed pellets also exhibited peaks demonstrating the presence of residual HPMCP, which is a compound found in Lek's enteric coat. (Davies Tr. 378:10-14.) Dr. Davies also "scaled" and "subtracted" the ATR-FTIR spectra taken with the silicon and germanium crystals to confirm his belief that the composition of the alleged separating layer in Lek's product is PVP. (Davies Tr. 389:17-392:2.) Scaling is an analytical technique in which the information from different spectra is compared by applying a multiplication factor to adjust the peak in one spectrum to the peak in a second spectrum. Subtracting the results of one spectrum from the other provides a comparison of the remaining peak heights, which identify chemical compounds

and chemical composition in the two spectra. (Davies Tr. 389:17-392:2; Coates Tr. 3611:16-3612:15.)

The silicon and germanium crystals that Dr. Davies used to collect the data had different refractive indexes (about 3.4 and 4 respectively), and therefore collected information to different depths in the samples. (Davies Tr. 383:9-384:5.) Thus, according to Dr. Davies, comparing the spectra from the different crystals permitted an analysis of the chemical composition at different depths of Lek's washed pellets. (Davies Tr. 390:20-391:7.) The results of Dr. Davies scaling and subtraction analysis confirmed his belief that in the washed pellets he tested, a PVP layer was present under a thin layer of residual HPMCP from the enteric coat. (Davies Tr. 392:3-396:5; 5660:15-21; PSWTX 912; PSWTX 913; PSWTX 1251-26; PSWTX 1251-27; PSWTX 2625-10.)

Lek's Dr. Coates rejected Dr. Davies's ATR-FTIR analysis in its entirety, for a variety of reasons. First, Dr. Coates performed his own ATR-FTIR testing of Lek's pellets. (Coates Tr. 3441:17-3442:3, 3476:17-3477:16.) Using acetone as a solvent, Dr. Coates-unlike Dr. Davies-was able to completely remove the enteric coating from Lek's pellet. (Coates Tr. 3457:11-17, 3464:4-3465:11; LEKTX 7253.) All of Dr. Coates's ATR-FTIR data show that there is no PVP sublayer between the enteric coating and the core of Lek's pellets. (Coates Tr. 3634:1-3635:2; LEKTX 7346.)

Apart from his own testing, Dr. Coates also reviewed Dr. Davies's ATR-FTIR analysis. According to Dr. Coates, the washed-pellet spectral peak of 1678 cm^{-1} detected by Dr. Davies is evidence that PVP exists in a mixture with HPMCP, rather than as an isolated PVP sublayer. Dr. Coates surmises that the PVP was dissolved from the core and then was redeposited with HPMCP as a mixture on the surface of the core during Dr. Davies's washing process. (Coates Tr. 3610:7-14; 3631:12-3633:25; LEKTX 7345.)

Dr. Coates also opined that Dr. Davies's scaling and subtraction analysis was flawed because, pursuant to the Beer-Lambert Law, the germanium spectrum and silicon spectrum should have identical absorbance for the depth of penetration common to both crystals. (Coates Tr. 3505:15-3510:12, 3614:22-3615:3; LEKTX 7269; LEKTX 7270; LEKTX 7271; LEKTX 7272; LEKTX 7273; LEKTX 7274; LEKTX 7275; LEKTX1 7276; LEKTX 7337.) Assuming that Dr. Davies's tests were done correctly-which Dr. Coates says they were not FN59-the silicon and germanium scaled spectra should have been the same at or near the surface, with additional information for the deeper depths measured by the silicon crystal. (Coates Tr. 3613:9-3621:20; LEKTX 7337; LEKTX 7338; LEKTX 7339.)

FN59. One of Dr. Coates's criticisms of Dr. Davies's methodology relates to the varying contact between the sample and crystals in his testing. (Coates Tr. 3583:12-3584:20; 3593:14-3596:4; LEKTX 7321; LEKTX 7322.)

Perhaps the biggest shortcoming in Dr. Davies ATR-FTIR analysis is not the testing itself, but rather his failure to correlate it with much of the testing he performed in the first and second group of tests. Specifically, Dr. Davies did not correlate the ATR-FTIR data with any AFM testing on Lek's pellets. (Davies Tr. 547:18-548:2.) Without AFM data on Lek's washed pellets, Dr. Davies cannot adequately prove that the small granular material seen at the interface in the AFM images of the bisected coated pellets is the same material he measured by ATR-FTIR. Nor did Dr. Davies correlate his ATR-FTIR testing with his purported fluorescence findings on Lek's washed pellet. (Davies Tr. 543:10-13.) FN60

FN60. By contrast, Apotex and Impax, the other two Defendants whose product was alleged to have an *in situ* subcoating, Dr. Davies relied on the fluorescence images of the washed pellets to correlate the fluorescence testing results with the ATR-FTIR results. (Davies Tr. 448:17-451:22, 480:25-481:6, 508:25-510:20; PSWTX 1252-3; PSWTX 1252-4; PSWTX 1253-5.)

The Court also notes the lack of any separate empirical testing on Lek's product to prove Plaintiffs' theory that PVP somehow migrates to the surface of the core in a sufficient manner to form a subcoating.FN61 Plaintiffs presented no empirical evidence that there was a difference in the amount or location of PVP in the core of Lek's product before and after the enteric coating step. Rather than conduct any testing of their own in support of a PVP migration theory, Plaintiffs relied on two peer-reviewed articles in which PVP was found to migrate under certain conditions. (PSWTX 1841; PSWTX 1842.) Significant differences exist between the experiments that were the subject of those articles and the manufacturing of Lek's pellets that bear upon whether PVP migration (if it occurred at all) occurred in Lek's product to the extent necessary to form a substantially continuous subcoating around the core. (*See* Langer Tr. 1603:10-1603:3, 1609:14-1611:16.)

FN61. Plaintiffs' expert, Dr. Langer, testified that migration was "not impossible," but did not take a position on whether it was likely. (Langer Tr. 1188:9-11; 1189:13-14; 1604:1-2.)

For these reasons, Plaintiffs have failed to meet their burden of demonstrating that Lek's product infringes the claim 1(b) limitation in either the '505 or '230 Patent.

4. Claim 1(c): Enteric Coating and Enhanced Stability

The '505 Patent claim 1(c) requires "an outer layer disposed on said subcoating comprising an enteric coating." (PSWTX 1A 16:53-54.) The ' 230 Patent claim 1(c) requires, "an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced." (PSWTX 2A 13:15-20.) Lek's enteric coating layer includes hydroxypropyl methylcellulose phthalate. (PSWTX 1228A), and Lek admits that Lek's product contains an enteric coating as that phrase is used in the '505 and '230 Patents (PSWTX 1655 para. 138). Accordingly, Lek's product meets the limitation of claim 1(c) of the '505 and '230 Patents.

5. Conclusion

Although Lek's product meets the limitation of claim 1(c) of the patents, the Court finds that Plaintiffs have failed to prove by a preponderance of the evidence that Lek infringes, either literally or under the doctrine of equivalents, claim 1(a) and claim 1(b) of the '505 and '230 Patents. Accordingly, Lek does not infringe the '505 or '230 Patents.

E. *Apotex's Product*

[32] Apotex filed an ANDA with the FDA, seeking approval to manufacture, use and sell Apotex's 10-mg, 20-mg, and 40-mg products called "Omeprazole Delayed-Release Capsules" (collectively the "Apotex's product") as a generic version of Plaintiffs' Prilosec(R) product. (Second Am. Compl. Against Apotex para. 16.) On October 6, 2003, the FDA granted final approval of the 10-mg and 20-mg strengths of Apotex's product. (*Id*. para. 24a.) On October 6, 2003, the FDA granted tentative approval of Apotex's 40-mg product. (*Id*. para. 24b.) On or about November 12, 2003, Apotex started to sell its "Omeprazole Delayed-Release Capsules" 10-mg and 20-mg doses in the United States. (Apotex Answer & Countercls. to Second Am. Compl. para. 24c.)

Plaintiffs assert that Apotex committed an act of infringement under 35 U.S.C. s. 271(e)(2) with respect to the '505 Patent and the '230 Patent by filing an ANDA seeking FDA approval to engage in the commercial manufacture, use, or sale of Apotex's product prior to the expiration of the patents-in-suit (Second Am. Compl. Against Apotex para.para. 21, 33); that Apotex directly infringed the patents-in-suit under 35 U.S.C.

s. 271(a) by selling and offering for sale Apotex's FDA-approved 10-mg and 20-mg generic omeprazole products (*Id*. para.para. 24c, 36c, 36d); that Apotex's act was willful and deliberate (*Id*. para.para. 24e, 36e); and that Apotex has induced and contributed to infringement by others who administer or use Apotex's products 35 U.S.C. s. 271(b)-(c) (*Id*. para.para. 23, 35). Plaintiffs also assert that this case is exceptional under 35 U.S.C. s. 285 based on Apotex's lack of a meritorious defense and Apotex's litigation misconduct. (*Id*. para. 37.) FN62

FN62. The Court will not address willfulness or whether the case is exceptional under 35 U.S.C. s. 285 in this opinion.

Plaintiffs allege that Apotex's 10-mg, 20-mg, and 40-mg ANDA omeprazole products infringe claims 1, 5, 6, and 10 of the '505 Patent and claims 1, 6, 7, and 13 of the '230 Patent literally, and if not literally, under the doctrine of equivalents. The main infringement issue before the Court regarding Apotex's ANDA products is whether Apotex's products meet '505 and ' 230 Patent claims 1(b) and contain the claimed "subcoating."

1. Apotex's Formulation and Manufacturing Process

Apotex's ANDA generally describes the process for making Apotex's ANDA formulation.(Langer Tr. 1195:6-1196:7; PSWTX 1257-2; PSWTX 1257-3.) The 10-, 20-, and 40-mg products all use identical pellets; the only difference is the number of pellets in each capsule. (Langer Tr. 1196:8-16; PSWTX 1142H at No. 131; PSWTX 1257-4.)

In general, Apotex first makes extruded pellet cores. (Langer Tr. 1195:23-1196:3; PSWTX 1257-3; PSWTX 1170A; Barber Dep. 141:25-143:12, July 14, 2003.) Apotex's pellet cores contain omeprazole, povidone ("PVP"), magnesium hydroxide, and mannitol. (Langer Tr. 1195:23-1196:3; PSWTX 1257-3 (citing PSWTX 1170A at TM 7803).) Apotex mixes the core ingredients by adding water, extruding the core material to make it string-like, and then pelletizing it using a marumerizer. (Langer Tr. 1195:23-1196:3; Signorino Tr. 3856:17-3858:1; PSWTX 1257-3 (citing PSWTX 1170A).)

Apotex then applies an enteric coating to its pellet cores. (Langer Tr. 1195:23-1196:9; PSWTX 1257-3; PSWTX 1176A.) Apotex uses a methacrylic acid copolymer dispersion ("MACP") with 30% solids in its enteric coating solution, and uses water as a solvent to dilute the MACP to make the final coating suspension. (Davies Tr. 462:13-22; PSWTX 982; PSWTX 615A at TM 007518; *see also* Langer Tr. 1195:23-1196:9; PSWTX 1257-3; PSWTX 1176A.) Purified water, triethyl citrate, and MACP are mixed until a white dispersion is obtained. (PSWTX 615A at TM 007519 (steps 2-4).)

The core pellets are loaded into a fluid bed with a Wurster insert. (Barber Dep. 143:13-15; PSWTX 615A at TM 007520, step 7.) During spraying, the inlet air temperature is set to maintain the exhaust air temperature at 28-32 (deg.)C (not to exceed 35 (deg.)C). (PSWTX 615A at TM 007521, step 9.) Spray time for the sample batches was about eight hours. (PSWTX 1925 at TM 007868.) During drying the inlet air temperature is set to 45 (deg.)C until the exhaust reaches 40 (deg.)C. (PSWTX 615A at TM 007521, step 9; *see also* Barber Dep. 156:11-157:15.) The pellets are dried until the moisture content is not more than 1.5% by weight. (Barber Dep. 143:13-144:24; PSWTX 610 at TM 007726, step 17; *see also* Langer Tr. 1195:23-1196:9; PSWTX 1257-3; PSWTX 1176A.) The pellets are then cooled at an inlet air temperature set point of 0 (deg.)C until the exhaust reaches 30 (deg.)C. (PSWTX 615A at TM 007521, step 9.)

a. Claim 1 of the '505 and '230 Patents

Apotex's omeprazole delayed-release product is an "oral pharmaceutical preparation," as that phrase is used

in the '505 and '230 Patent claims. (Langer Tr. 1196:17-1197:2; PSWTX 1142A at No. 1; PSWTX 1648A.)

2. Claim 1(a): An Effective Amount of an Alkaline Reacting Compound (ARC)

Claim 1(a) of the '505 Patent calls for "a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline salt plus an alkaline reacting compound and an alkaline salt alone." (PSWTX 1A 16:43-47.) Similarly, claim 1(a) of the '230 Patent calls for "an alkaline reacting core." (PSWTX 2A 13:2.) Apotex admits that "[e]ach of the Apotex ANDA Products includes a core" and "[e]ach of the Apotex ANDA Products includes a core region," as the phrases "core" and "core region" are used in the '505 and '230 Patents. (Langer Tr. 1197:8-16 (citing PSWTX 1142B); *see* Barber Dep. 92:2-9.)

Apotex admits and the evidence shows that the magnesium hydroxide used in Apotex's product is an alkaline reacting compound ("ARC") as that phrase is used in the '505 and '230 Patent claims. (PSWTX 1142 at Nos. 31, 32.) Magnesium hydroxide is an alkaline substance with a pH greater than 7. (Langer Tr. 1197:19-1198:3 (citing PSWTX 1142B at Nos. 8, 9); PSWTX 1142C at Nos. 24, 25, 26, 27, 28; PSWTX 1142D at Nos. 28-36; PSWTX 1651.) Apotex further admits that "[e]ach of the Apotex ANDA Products includes a core region that contains, among other things, an alkaline reacting compound as that phrase is used in the '505 and '230 Patent claims." (PSWTX 1142 at No. 10.) Dr. Sherman, Apotex's formulator, testified that Apotex's ANDA product meets all of the limitations of claim 1, part (a). (Sherman Dep. 116:10-13, June 6, 2003.)

Specifically, Dr. Sherman admits that magnesium hydroxide is an alkaline agent which creates an alkaline microenvironment around the omeprazole and stabilizes the omeprazole in Apotex's product. (Sherman Dep. 36:23-37:7.) All pH values taken by Dr. Davies in investigating the omeprazole containing region of Apotex's pellet demonstrated that the core of Apotex's product is alkaline and has a microenvironment of pH 7-12. Dr. Davies tested the pH of the uncoated, omeprazole-containing pellet cores provided by Apotex and found a pH of 8.81-9.39. (Davies Tr. 487:13-490:8; PSWTX 998; PSWTX 844.) Dr. Davies confirmed that the cores were alkaline by testing the pH of extracted cores (removed from the fully formulated product). (Davies Tr. 488:14-491:1; PSWTX 844; *see also* Davies Tr. 486:25-488:9; PSWTX 998; PSWTX 844; PSWTX 1252-13.) Dr. Davies also found that as the amount of core material increases, there is an increase in the pH values for that particular batch, which, he testified, demonstrates that there is alkaline material in the core. (Davies Tr. 489:16-490:8; PSWTX 844 at Ex. 18-2; PSWTX 1252-13.) Apotex's expert, Dr. Signorino, measured the pH of a suspension containing the ingredients in Apotex's core and obtained results of 9.0-9.6, which are consistent with Dr. Davies' results. (Signorino Tr. 3960:13-18.)

Based on the foregoing, the Court finds that magnesium hydroxide is an ARC and stabilizes the omeprazole in the core of Apotex's ANDA formulation (Signorino Tr. 3850:22-25, 3960:7-12, 19-21; Langer Tr. 1198:4-9 (citing PSWTX 1142E at No. 34)) as required under claims 1(a) of the '505 and '230 Patents.

3. Claim 1(b): An Inert Subcoating That is Soluble or Rapidly Disintegrating in Water

The infringement issue, then, depends upon whether Apotex's product includes the subcoat required by claims 1(b) of the '505 and '230 Patents. As explained above, claim 1(b) of the '505 Patent requires "an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds." Similarly, claim 1(b) of the '230 Patent requires "an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group of tablet excipients, film-forming compounds and alkaline compounds." (PSWTX 2A 13:10-15.)

Plaintiffs allege that Apotex's product contains a sublayer comprised of an MACP:PVP complex, underneath the enteric coating and disposed on the core region. (Davies Tr. 435:16-436:9; PSWTX 1252-1.) Although Apotex's manufacturing process does not include directly applying a subcoating onto the core (Signorino Tr. 3881:5-8), Plaintiffs allege that the subcoating forms in the product, or "*in situ,*" during Apotex's enteric coating process (Davies Tr. 458:12-17). As a preliminary matter, the Court adopts its previous ruling that the product claims of the '505 and '230 Patents do not limit the manner in which the product is made and cover subcoatings regardless of how they are formed-including subcoatings formed *in situ*. (*See* Astra v. Andrx, 222 F.Supp.2d at 469 (holding that the claims cover subcoatings made of one or more materials); *see also* Langer Tr. 5465:10-24.)

a. Presence of A Continuous Subcoating

To show the presence of an *in situ* formed subcoating in Apotex's product, Plaintiffs rely largely on Dr. Davies' examination of the structure and chemical make-up of Apotex's enteric coated pellet using confocal laser scanning microscopy ("CLSM") reflectance and fluorescence, widefield UV fluorescence, attenuated total reflectance Fourier transform infrared spectroscopy ("ATR-FTIR"), solubility testing, pH testing, disintegration studies, and visual inspection.FN63 (Davies Tr. 436:10-15; 481:17-482:7; 486:3-487:4; PSWTX 1252-12.) UV fluorescence microscopy FN64 and CLSM FN65 are spatial analytical techniques that provide information about the spatial relationship among the components of the sample and, in some cases, certain physical characteristics of those components. ATR-FTIR provides information about the chemical composition of a substance.FN66

FN63. Apotex moves to exclude Dr. Davies' testimony based on *Daubert* on the grounds that: (1) Dr. Davies' ATR-FTIR spectra of Apotex's washed pellets are an unreliable indicator of the pellet composition prior to the wash; (2) Dr. Davies' washing procedure for removing the enteric coating from Apotex's pellets renders his data unreliable for the purposes of supporting a finding that there is a layer-like distribution of wash-resistant material surrounding the pellet core; (3) Dr. Davies' fluorescent images are not reliable evidence that there is a layer-like distribution of an MACP-PVP complex and Mg salt; and (4) Dr. Davies failed to consider an alternative hypothesis for the composition of the fluorescing region of Apotex's pellets. The Court finds these objections go to the weight-not the admissibility-of Dr. Davies' testimony. The Court also notes that Apotex's *Daubert* arguments are repeated as part and parcel of their non-infringement arguments (*i.e.,* as reasons why Plaintiffs have failed to meet their burden of proof). Accordingly, the Court has addressed those issues in its infringement analysis.

FN64. For a description of UV fluorescence microscopy, *see supra* note 53.

FN65. For a description of CLSM fluorescence, *see supra* note 51.

FN66. For a description of ATR-FTIR, *see supra* note 17.

Dr. Davies conducted CLSM fluorescence, CLSM reflectance, and widefield UV fluorescence studies on over twenty of Apotex's fully formulated pellets to determine the structure of Apotex's product. (Davies Tr. 436:10-13.) CLSM fluorescence, CLSM reflectance, and widefield UV fluorescence revealed three distinct structures in Apotex's product: a core region containing omeprazole, a fluorescent layer around the core region, and an enteric coating. (Davies Tr. 437:6-25; PSWTX 805-808; *see also* Langer Tr. 1198:15-1199:2.) PSWTX 805, for example, presents a clear image of the core (arrow labeled A), underneath a

bright fluorescence layer (arrow labeled B), underneath the enteric coating layer (arrow labeled C). (Davies Tr. 436:16-437:16; PSWTX 805; *see also* PSWTX 806 (same image without arrows).) Widefield UV fluorescence (using a wavelength of between 340 and 380) (Davies Tr. 150:8-151:8), also shows the presence of the three distinct regions of Apotex's pellet. (*See, e.g.,* PSWTX 807, PSWTX 808, PSWTX 811, PSWTX 815.) Similarly, PSWTX 807 demonstrates three distinct regions of the Apotex ANDA pellet- the core (arrow labeled A), underneath a bright fluorescent layer (arrow labeled B), underneath the enteric coating (arrow labeled C). (Davies Tr. 437:17-25; PSWTX 807; PSWTX 808 (same image without the arrows).) Apotex does not dispute the presence of a fluorescent band in Apotex's product. (Cima Tr. 4040:16-4041:6.)

Dr. Davies also used CLSM reflectance to ascertain where the fluorescence lies. (Davies Tr. 440:16-20.) When CLSM reflectance and CLSM fluorescence are overlaid, it demonstrates that the fluorescent layer hugs the surface of the Apotex core. (Davies Tr. 440:21-25; *see* PSWTX 813.) CLSM optical slices show the width of the fluorescing layer in Apotex's product measures 2-6 microns thick. (Davies Tr. 436:10-439:13, PSWTX 809; Langer Tr. 1198:25-1199:2; PSWTX 1257-12.) Dr. Davies also washed pellets in a 90:10 mixture of acetone and isopropanol ("acetone:IPA") to remove the enteric coating, and again observed a fluorescing layer under CLSM fluorescence (PSWTX 823) and widefield UV fluorescence (PSWTX 824), and observed a layer under CLSM reflectance (PSWTX 825). (Davies Tr. 444:23-447:3.)

Dr. Davies testified that a single optical slice of a CLSM fluorescence image overlaid on a CLSM reflectance image showed that the fluorescence is arising from the layer in the reflectance data (Davies Tr. 447:23-448:16; PSWTX 830; PSWTX 831), and that the fluorescing layer is continuous and distinct in both the enteric coated pellets and in the washed pellets (Davies Tr. 445:7-447:3, 886:1-3; PSWTX 823; PSWTX 824). Although Apotex's Dr. Cima also testified that the fluorescent band in Apotex's product is "more or less continuous or continuous" (Cima Tr. 4240:17-4241:5), Apotex claims that the alleged subcoat in at least one CLSM reflectance image (PSWTX 825) does not appear continuous toward the bottom of the image. Dr. Davies explained, however, that CLSM reflectance does not allow visualization of a subcoating that is not properly aligned with the detector. (Davies Tr. 5754:22-5755:4.) The Court is persuaded by Dr. Davies's explanation that, due to the angle of the knife used to bisect the pellet, the sublayer in PSWTX 825 is at an angle causing the light hitting the surface to be reflected away from the camera such that the subcoat in that area was not reflected. CLSM fluorescence of the same pellet (PSWTX 823), when shown in combination with CLSM reflectance, shows that the fluorescence is continuous around the entire core. (Davies Tr. 885:4-886:21; *compare* PSWTX 823 *with* PSWTX 825.) Dr. Davies also showed this occurrence with an Impax washed pellet, where CLSM fluorescence and a related 3D projection showed the subcoating sloping down the side of the pellet but CLSM reflectance did not show that same portion. (Davies Tr. 5755:22-5756:10; PSWTX 1483 (CLSM fluorescence); PSWTX 1484 (3D projection); PSWTX 1481 (CLSM reflectance).)

According to Dr. Davies, the enteric coating is soluble in a mixture of acetone:isopropanol but the fluorescent layer is not, further demonstrating that the layers are distinct. (Davies Tr. 446:23-447:3; 449:17-450:2, 451:9-22, 459:18-22; PSWTX 825; PSWTX 1252-3.) To wash off the enteric coating, therefore, Dr. Davies placed about 50 Apotex enteric coated pellets in 20 milliliters of a 90:10 mixture of acetone:isopropanol and agitated the mixture by hand for two minutes. (Davies Tr. 445:9-14 (citing PSWTX 1252-2).) Dr. Davies testified that he could observe the enteric coating coming off the samples during the washing procedure. (Davies Tr. 5793:23-5795:9.) The pellets were then dried and sectioned. (Davies Tr. 444:16-445:23 (citing PSWTX 1252-2); *see also* Davies Tr. 872:14-17.) FN67

FN67. Dr. Davies provided a complete description of the washing technique in his expert report and depositions. (Davies Tr. 5750:6-12.)

Dr. Davies also imaged 20 pellets obtained from Apotex prior to enteric coating using CLSM fluorescence,

CLSM reflectance, and widefield UV fluorescence-conducted in the same manner as on the fully formulated Apotex product (Davies Tr. 442:12-442:19, 443:14-444:15; PSWTX 819-822)-and did not observe the fluorescent region found in the enteric coated pellets. (Davies Tr. 443:14-444:15; PSWTX 819-822; Langer Tr. 1199:3-5.) From a comparison of this information, Dr. Davies concluded that the sublayer forms during the enteric coating process. (Davies Tr. 448:20-449:18; *compare* PSWTX 820 (pellet before enteric coating) *and* PSWTX 806 (pellet after enteric coating), *with* PSWTX 827 (washed pellet).)

Using ATR-FTIR, Dr. Davies obtained spectra from: (1) the surface of Apotex's enteric coated pellets; (2) the surface of Apotex's washed pellets; (3) the core of Apotex's pellets; (4) the PVP used by Apotex; and (4) the methacrylic acid copolymer:polyvinylpyrrolidone complex ("MACP:PVP complex") precipitates created by Dr. Davies. As described in detail above, ATR-FTIR spectra provide information about the structure and chemical identity of the sublayer. (Davies Tr. 451:7-12, 833:17-834:16; PSWTX 1252-5.) FN68

FN68. Dr. Davies used the same ATR-FTIR microscope that he used on the other Defendants' products and used a silicon crystal on the surface of the material to be sampled. As described in more detail above, the light from the crystal penetrates into the surface of the material and some light is absorbed by the molecules present in the layer and some light is reflected. The difference between the light absorbed and the light reflected creates a fingerprint of the chemical content present within that layer. (Davies Tr. 452:15-20; PSWTX 1252-5.)

Dr. Davies tested the enteric coating on the surface of Apotex's fully formulated pellets. Apotex's enteric coating contains MACP, which produces peaks at 1730 cm^{-1} and 1700 cm^{-1}, diagnostic of the ester and acid groups present within the polymer. (Davies Tr. 452:25-453:17, 834:20-835:12; PSWTX 832; PSWTX 1252-7.) Dr. Davies observed over 10 enteric coated pellets using ATR-FTIR and recorded the ATR-FTIR spectra of five enteric-coated pellets. (Davies Tr. 455:1-4.) Dr. Davies compared the ATR-FTIR spectrum for the Apotex enteric coated product (PSWTX 832) to the spectrum for a reference sample of MACP that Apotex uses to make its product and provided for testing (PSWTX 834). (Davies Tr. 453:18-20; PSWTX 1252-6; *compare* PSWTX 832 *with* 834.) Dr. Davies found that the spectra of the MACP reference sample also revealed diagnostic peaks at 1730 cm^{-1} and 1700 cm^{-1} comparable to the diagnostic peaks on the enteric coating of Apotex's pellets. (Davies Tr. 453:21-454:6; PSWTX 1252-6; *compare* PSWTX 832 *with* PSWTX 834.) A publication titled "The Infrared Spectra Atlas of Monomers and Polymers" lists the same peak assignments for MACP at 1700 cm^{-1} and 1730 cm^{-1}. (Davies Tr. 455:7-457:4; PSWTX 1161A at Davies2W6009218, Davies2W6009220.)

After confirming the peak assignments for the surface of the Apotex enteric-coated pellets, Dr. Davies analyzed the acetone:IPA washed pellets using ATR-FTIR (Davies Tr. 457:5-10), and found that the ATR-FTIR spectra of the washed pellets (with the enteric coat removed) are very different from the spectra for the enteric coating (Davies Tr. 457:5-10, 458:23-459:22; PSWTX 1252-7; *compare* PSWTX 833 *with* PSWTX 832). Dr. Davies recorded spectra for five washed pellets and testified that he observed consistent spectra for over ten different pellets. (Davies Tr. 459:23-460:6; *see, e.g.,* PSWTX 833.)

Dr. Davies identified the surface of the washed pellets as an MACP:PVP complex with a contribution from the magnesium salt of the MACP copolymer. (Davies Tr. 451:7-452:24.) In the spectra of the washed pellets, Dr. Davies observed a strong peak around 1633 cm^{-1} (Davies Tr. 457:11-18; PSWTX 833), which he testified is diagnostic of PVP in complex with the MACP copolymer (Davies Tr. 460:2-461:14-15, 464:23-24, 457:19-20). There is also a feature at 1550-1580 cm^{-1}, which Dr. Davies asserted is indicative of a small contribution of the MACP salt. (Davies Tr. 459:12-17, 835:18-836:6; PSWTX 833.) Dr. Davies stated that the peaks representing the MACP:PVP complex were observed in each instance. (Davies Tr. 460:2-6.)

To confirm the presence and availability of PVP to form a complex with MACP, Dr. Davies compared the ATR-FTIR spectra of Apotex's pellet cores with the PVP sample supplied and used by Apotex. Dr. Davies found that Apotex's PVP reference sample displays a peak around 1660 to 1680 cm^{-1},FN69 which is also observed in spectra of Apotex's pellet cores. (Davies Tr. 464:14-21; 465:22-466:8; PSWTX 1252-8; *compare* PSWTX 835 *with* 836.)

FN69. Dr. Davies confirmed his PVP peak assignment with authoritative treatises. (Davies Tr. 465:3-21; PSWTX 837 at 3.)

Dr. Davies testified that when the PVP complexes with the MACP, PVP undergoes a shift from 1660 cm^{-1} to 1633 cm^{-1}. (Davies Tr. 457:21-24; PSWTX 833.) Dr. Davies confirmed his peak assignments using a reference publication showing that the peaks were characteristic of a complex between PVP and acrylate co-polymers. (Davies Tr. 460:7-12.) In a publication in the *Journal of Applied Polymer Science,* the research team made a complex between PVP and polyacrylic acid and reported that ATR-FTIR showed the C=O stretching band was located at 1646 cm^{-1} for polyacrylic acid and 1670 cm^{-1} for PVP. (Davies Tr. 460:7-23; PSWTX 1144.) When the PVP complexes with the polyacrylic acid, the PVP peak shifts from 1670 cm^{-1} to 1630 cm^{-1}, which is evidence of the formation of a complex between the carboxyl groups (COOH) of the polyacrylic acid and the carbonyl groups of the PVP. (Davies Tr. 461:2-15; PSWTX 1144 at 4.)

Dr. Davies also mixed PVP and MACP in ethanol to demonstrate that the MACP:PVP complex can form and, using ATR-FTIR, compared the spectra of the MACP:PVP complex to the spectra of the surface of Apotex's washed pellets. (Davies Tr. 478:24-481:6; PSWTX 1252-11.) In Dr. Davies's Affirmative Report, he explained that PVP was mixed with MACP in ethanol and the resulting precipitate extracted by centrifugation; the precipitate was then washed in water with repeated dispersion and centrifugation. (Davies Tr. 5761:8-25; PSWTX 2549 at 13.) Dr. Davies's lab notebook also shows how he made the two different complexes at a 1:1 and 4:1 ratio of MACP to PVP. (Davies Tr. 469:19-473:17; 5762:9-5763:2; PSWTX 1006A; PSWTX 1007.)

Dr. Davies conducted ATR-FTIR on the 1:1 and 4:1 precipitates. These precipitates displayed the same diagnostic carbonyl peak (C=O) at 1630 cm^{-1}, which, according to Dr. Davies, shows that the precipitates are the MACP:PVP complex and that the MACP:PVP complex exhibits the same spectra found in Apotex's alleged sublayer. (Davies Tr. 476:10-478:19; PSWTX 843B.) Dr. Davies also measured the pHs of the precipitate, the PVP supplied by Apotex, and the MACP supplied by Apotex, and found that the pH of the individual components and the pH of the precipitate were different. (Davies Tr. 472:11-475:1; PSWTX 843A; PSWTX 1252-10.) The MACP film exhibited a mean pH of 2.75 and the MACP dispersion exhibited a mean pH of 2.86. PVP exhibited a mean pH of 3.41. (Davies Tr. 475:5-13; PSWTX 1252-10.) The MACP:PVP complex formed using a 4:1 and a 1:1 ratio of starting materials exhibited a pH of 5.51 and 5.53 respectively. (Davies Tr. 473:23-475:16; PSWTX 843A; PSWTX 1252-10.) Dr. Davies concluded that the pH differences between the individual components and the MACP:PVP complex/precipitate show that the complex has very different properties than the individual components. (Davies Tr. 475:8-24; PSWTX 1252-10.)

Apotex asserts that Plaintiffs have failed to meet their burden of proof to show that Apotex's product contains a subcoating because Plaintiffs provided no data showing that the alleged MACP-PVP complex is present in unwashed pellets. Rather, Apotex argues that: (1) the fluorescing region is actually omeprazole; (2) even if the fluorescing region is an MACP:PVP complex, it is formed during Dr. Davies acetone:IPA washing of the pellets and not during Apotex's enteric coating; and (3) even if MACP reacts with PVP

during Apotex's coating process, the MACP-PVP complex is not a subcoating within the meaning of the patents because it does not separate the omeprazole from the enteric coating in Apotex's product.

Apotex's Dr. Cima testified that the fluorescent layer is not a subcoating but rather omeprazole and/or its degradation products resulting from an interaction of the omeprazole in the pellets with the MACP enteric coating. (Cima Tr. 4116:21-4117:2; Signorino Tr. 3881:5-8.) Dr. Cima testified that his Raman spectroscopy FN70 data show the presence of omeprazole and/or its degradation products in the enteric coating of Apotex's product in or around the fluorescent band (at 95 microns, 90 microns, and 80 microns), but not near the surface of the enteric coating (at 10 microns). (Cima Tr. 4071:1-4073:3, 4074:8-4075:13, 4075:14-17; APO 942-30.) Dr. Cima concluded that his Raman results were consistent with omeprazole or its degradation products being the source of the fluorescence (Cima Tr. 4073:5-10) and, furthermore, no subcoating could be present because the active ingredient was not separated from the coating (Cima Tr. 4073:5-23).

FN70. Raman spectroscopy uses a monochromatic laser light to excite molecules in a small spot (approximately two microns) on the surface of a sample (Cima Tr. 4064:21-4065:8), and measures the differences in the energy of the light which is reflected from the sample. (Cima Tr. 4065:22-23.) The change in energy of the reflected light is controlled by the vibration of the molecules on the surface which is a function of the molecule's shape. (Cima Tr. 4065:23-4066:4.)

To test this theory, Dr. Signorino created so-called "ANDA Reproduction Pellets" based on the procedures in Apotex's ANDA specification. Using substantially the same procedure as used for the creation of his ANDA Reproduction Pellets (Signorino Tr. 3892:1-9, 3898:5-7, 3902:24-3903:15), Dr. Signorino also created modified ANDA Reproduction Pellets as follows: (1) without omeprazole in the cores (the "Pellets Without Omeprazole"); (2) without magnesium hydroxide in the cores (the "Pellets Without Magnesium Hydroxide"); (3) without omeprazole in the cores that were coated with a magnesium salt of MACP (the "Pellets Coated With MACP Salt"); and (4) without omeprazole in the cores, coated with MACP and Apotex's enteric coating suspension (the "Top Coated Pellets").FN71 Dr. Signorino also made pellets according to the disclosure of European Patent Application No. EP124495 with and without the magnesium salt of omeprazole (respectively, the "'495 Pellets With Omeprazole" and the "'495 Pellets Without Omeprazole").

FN71. The ingredients and procedure Dr. Signorino used to generate the cores of the modified ANDA Reproduction Pellets are described in his lab notebook. (*See, e.g.,* Signorino Tr. 3885:10-17, 3895:25-3896:4; APO 787 at TM00128368; APO 788 at TM00128371.) The cores of the Pellets Without Omeprazole were comprised of: magnesium hydroxide USP; mannitol USP; povidone USP; and purified water. (Signorino Tr. 3885:13-17; APO 787 at TM00128368.) The volume that was lost by the removal of the omeprazole was made up by adding an equal quantity of mannitol. (Signorino Tr. 3885:18-21; *compare* APO 787 at TM00128368 *with* APO 786 at TM00128369.) The cores of the Pellets without Magnesium Hydroxide were comprised of: omeprazole USP; mannitol USP; povidone USP; and purified water. (Signorino Tr. 3896:5-7; APO 788 at TM00128371.) The volume that was lost by the removal of the magnesium hydroxide was made up by increasing the omeprazole and mannitol in a proportionate quantity. (Signorino Tr. 3897:3-22; *compare* APO 788 at TM00128371 *with* APO 786 at TM00128369.)

Dr. Cima obtained UV fluorescent images from Dr. Signorino's Reproduction Pellets and found that the pellets containing omeprazole-including the ANDA Reproduction Pellets and the Pellets Without Magnesium Hydroxide-exhibit a fluorescent band, while the pellets that did not contain omeprazole-including the Pellets Without Omeprazole, the Pellets Coated With MACP Salt, and the Top Coated Pellets-did not exhibit a fluorescent band. (Cima Tr. 4053:10-4054:19, 4055:23-4057:16, 4059:5-4060:24; APO

942-18; APO 1182; APO 942-20; APO 1184; APO 942-21; APO 1187.) Similarly, Dr. Cima observed a fluorescent band in the '495 Pellets With Omeprazole but did not observe a fluorescent band in the '495 Pellets Without Omeprazole. (Cima Tr. 4061:25-4064:5; APO 942-22; APO 1188; APO 1189.)

This evidence is of little value, however, because Apotex did not demonstrate that Dr. Signorino's Reproduction Pellets were representative of Apotex's product. Dr. Signorino and Dr. Cima did not conduct any testing to show that the pellets Dr. Signorino manufactured are comparable to and representative of Apotex's product. (Signorino Tr. 3975:23-3976:3.) Apotex could have conducted studies on these samples that the FDA considers in determining bioequivalency-such as dissolution rate, stability, and gastric acid resistance-to show that they are representative of Apotex's product. (Langer Tr. 5474:16-25.)

Moreover, the FDA requires that a pilot scale batch be one-tenth of production scale, or 100,000 tablets or capsules, whichever is larger. (Langer Tr. 5472:11-5473:8; PSWTX 1628 at 18-19.) The samples produced for Apotex in Dr. Signorino's lab would not meet this requirement. Scaling down a manufacturing process may result in small effects on the chemical and physical properties of the pellets. (Signorino Tr. 3971:22-3972:9; Langer Tr. 5474:1-25.) For example, Plaintiffs presented evidence that Dr. Signorino's samples had an enteric coating half the size of Apotex's ANDA samples. (Cima Tr. 4143:7-15; 4145:9-15; PSWTX 2120-1.)

In addition, the *in situ* formation of a subcoating may depend on a number of process parameters, including but not limited to, enteric coating spray rate, inlet temperature, product temperature, air volume in a fluid bed, how long and how wet the surface will be, and the moisture content. (Langer Tr. 5474:1-25; PSWTX 1633 at 47.) Dr. Signorino did not know Apotex's product temperature and did not know if the pellets he made had the same product temperature as Apotex's pellets. (Signorino Tr. 3969:9-20.) Dr. Signorino also coated his sample pellets for half as long as Apotex coats its pellets (Signorino Tr. 3878:14-24; APO 796; APO 680B.), and Dr. Signorino added more water than called for in Apotex's ANDA (Signorino Tr. 3886:24-3887:15). Dr. Signorino's Pellets Without Omeprazole also had a higher solid content than specified in Apotex's ANDA. (Signorino Tr. 3892:18-3893:1; APO 793.) Furthermore, Plaintiffs presented evidence that Dr. Signorino did not follow the teachings of the '495 Patent, but instead modified certain ingredients and procedures in creating his reproductions.FN72 (Cima Tr. 4150:15-19; Signorino Tr. 3986:13-19; APO 791.)

FN72. Moreover, an infringement analysis requires a comparison of the accused product to the claims-showing that a phenomenon, like fluorescing omeprazole, may also be found in reproductions based on the '495 patent does little to advance Apotex's non-infringement defense. Therefore, the Court finds little value in Apotex's conclusory assertion that the fluorescence spectrum from the '495 Pellets With Omeprazole is consistent with omeprazole or its degradation products being the source of the fluorescence in Apotex's product. (Cima Tr. 4081:8-4083:14; APO 942-32; APO 1194.)

Apotex also argues that Dr. Davies's conclusions are flawed because the wash procedure chemically and physically alters the fluorescent region (Cima Tr. 4115:23-4116:1), and because Dr. Davies failed to do adequate controls regarding the effect of the wash, including determining whether the wash generated the MACP:PVP complex or salt. (Cima Tr. 4115:7-11; Davies Tr. 872:18-873:19; PSWTX 833; PSWTX 1252-5; PSWTX 1252-7.) Dr. Cima testified that a brief exposure of a 4:1 mixture of solid MACP and solid PVP to acetone:IPA (90:10) caused a reaction between the MACP and PVP. Using Fourier transform infrared spectroscopy ("FTIR"), Dr. Cima stated that he observed shoulder peaks at 1634 and 1652 cm^{-1} in the sample spectra. (Cima Tr. 4111:16-4113:22; APO 1199; APO 1217; *see also* Cima Tr. 4109:7-4110:10; APO 942-39; APO 1198 (mixture of MACP and magnesium hydroxide).) Dr. Cima presented three sets of FTIR reflectance data that he claims show that an MACP:PVP complex can form when MACP and PVP are exposed to acetone:IPA (the "first spot," the "second spot," and the "third spot"). (APO 1199; Davies Tr.

5763:11-15.)

Dr. Cima's attempt to create a MACP:PVP complex in acetone:IPA suffered from a number of inadequacies. First, Dr. Cima's procedure involved the use of extreme conditions that would not be used in pharmaceutical formulations, such as drying the mixture in a vacuum for 11 hours or heating the mixture at 100 (deg.)C for 25 minutes. (Cima Tr. 4280:22-4281:7.) Dr. Cima admitted that an omeprazole formulation would not be exposed to such conditions. (Cima Tr. 4281:13-16.)

In addition, Dr. Davies compared Dr. Cima's reflectance FTIR data to that of PVP and MACP and found that Dr. Cima's spectra for the second and third spot look like PVP, while Dr. Cima's spectrum from the first spot looks like the MACP polymer. (Davies Tr. 5763:25-5674:13; PSWTX 2650-9.) Dr. Davies also compared the MACP-PVP complex precipitate he made against Dr. Cima's results, and found that Dr. Cima's spectrum do not show the diagnostic carbonyl peak at 1630 cm^{-1} that is "classic of the PVP-MACP complex." (Davies Tr. 5764:18-5765:11; PSWTX 2120-6; PSWTX 1298.1; PSWTX 1299-1302.)

Moreover, Dr. Cima relied on peaks observed at 1652 cm^{-1} and 1634 cm^{-1} to conclude that exposure to acetone:IPA causes a reaction between MACP and PVP. (Cima Tr. 4113:12-4114:4; APO 942-040.) According to the testimony of Dr. Davies, however, Dr. Cima was actually relying on artifacts resulting from his use of atmospheric suppression. (Davies Tr. 5766:24-5767:3; PSWTX 2120-7.) Atmospheric suppression is a correction algorithm used if water is in the optical path in the instrument. (Cima Tr. 4297:5-9.) In other words, it tries to suppress water vapor peaks and the effect of water. (Davies Tr. 5767:22-5768:2; PSWTX 2161.) The OMNIC software printout warns, however, that if atmospheric suppression is used, one must "keep in mind that a tradeoff exists; the benefit, removing gross atmospheric signals from the spectra data is offset to some extent by the introduction of minor artifacts." (Cima Tr. 4298:5-10; PSWTX 2161 at 3.)

Dr. Cima testified that when he conducted his reflectance FTIR on the alleged MACP-PVP complex, he made corrections to the data in order to take into account the humidity or water that was present in the atmosphere (Cima Tr. 4297:5-6; Davies Tr. 5766:6-11; PSWTX 2120-7), including atmospheric suppression, Kramers-Kronig correction, automatic baseline correction, and automatic smoothing. (Davies Tr. 5767:13-21; PSWTX 2161 at 2).FN73 Dr. Davies testified that when the data was displayed without atmospheric suppression, the alleged MACP-PVP diagnostic peaks disappeared FN74 (Davies Tr. 5769:12-25; PSWTX 2120-7) and, in the absence of the artifacts induced by atmospheric suppression, the spectrum was that of PVP without any MACP contribution (Davies Tr. 5766:16-23; PSWTX 2120-7). Dr. Davies concluded that Dr. Cima was not observing an MACP-PVP complex, but rather he was observing only unreacted PVP and MACP. (Davies Tr. 5766:20-23.)

FN73. PSWTX 2161 is the collection and processing information from Dr. Cima's FTIR machine generated for reflectance FTIR set out in Exhibit APO 942-040. (Cima Tr. 4296:5-12.) Dr. Cima's technician, Mr. Rigione, collected this data on June 17, 2004. (Davies Tr. 5767:4-12; PSWTX 2161.)

FN74. Dr. Davies was able to do this because when Mr. Rigione performed his reflectance FTIR of the MACP-PVP mixtures, he saved the interferograms. (Davies Tr. 5769:4-11, 6043:15-6044:3, 6048:18-6049:18; PSWTX 2712; PSWTX 2650-2; PSWTX 2717 at 5-7.) Contrary to Plaintiffs' assertion, the Court finds that Apotex did not engage in misconduct in questioning the source and reliability of the data used by Dr. Davies.

The Court has carefully and thoroughly examined the evidence on this issue and finds that Dr. Cima's

conclusions more than likely were based on artifacts introduced through his improper use of atmospheric suppression and smoothing. Apotex provides no other evidence to support their theory that the MACP:PVP complex is formed by Dr. Davies's use of an acetone:IPA solvent.

Finally, the Court is unpersuaded by Apotex's argument that the alleged MACP-PVP complex cannot be a subcoating within the meaning of the '505 and '230 Patents because: (1) omeprazole and/or its degradation products are present in the alleged subcoating; (2) the alleged subcoating does not separate omeprazole from the enteric coating; and (3) the alleged subcoating does not prevent the interaction of omeprazole with MACP. Contrary to Apotex's assertions, the presence of some omeprazole or its degradation products in the enteric coating is not inconsistent with the presence of a subcoating. As the Court stated in the First Wave:

Where, as here, the specification as a whole, and the claims in particular, contain no temporal limitation to the claimed product, product claims as properly interpreted are entitled to a broad scope that is not time-limited. Exxon Chem. Patents v. Lubrizol Corp., 64 F.3d 1553, 1558 (Fed.Cir.1995). Accordingly, if at any time from the date of their manufacture Defendants' ANDA products meet the claim limitations as recited in the product claims of the '505 and '230 Patents, then Defendants infringe.

Astra v. Andrx, 222 F.Supp.2d at 540. Here, as in the First Wave, whether the MACP:PVP layer in Apotex's ANDA products forms during the enteric coating process or after manufacture, Apotex's product still infringes the '505 and '230 Patents. The Court also reiterates its previous finding that the patents do not require that the subcoating be "perfect," Astra v. Andrx, 222 F. Supp 2d at 470-72. Accordingly, the Court finds that inconsequential amounts of omeprazole or its degradation products in the enteric coating does not necessarily preclude the presence of a subcoating within the meaning of the '505 and '230 Patents.

Nor has Apotex presented evidence that there is anything other than an inconsequential amount of omeprazole or its degradation products in the enteric coating. Dr. Cima acknowledged that the Raman spectrometry he used is not quantitative (Cima Tr. 4075:18-24), and Dr. Davies's ATR-FTIR analysis did not detect omeprazole or its degradation products in the area of the fluorescent band (Davies Tr. 481:11-14). Many of the First and Second Wave Defendants' ANDAs described their products as containing less than 2% degraded omeprazole in the pellets. (Langer Tr. 5463:21-5464:23; *see also* ITX 34650 at Langer 2W4008939; PSWTX 631A at TM 009318; LEKTX 88 at LK 521787.) In addition, Plaintiffs presented evidence that Dr. Cima may have relied on "normalized" data that does not accurately reflect the position or intensity of the materials present across the interface of Apotex's product.FN75 (*E.g.,* Davies Tr. 5739:11-17, 6032:2-10; PSWTX 2168 at 1.)

FN75. Because Dr. Cima's Raman original analyses did not make sense in the context of Apotex's product (PSWTX 2547 Fig. 5 (showing mannitol (a core ingredient) spread equally throughout the core and the enteric coating); Davies Tr. 5733:15-18) and more omeprazole in the enteric coating than in the core (Davies Tr. 5733:15-18), Dr. Cima re-analyzed and normalized his data (PSWTX 2168). According to Dr. Davies, by normalizing all peaks in Raman data, even though one material exhibited an extremely intense peak in comparison with the peak intensity for the other materials, the contribution of peaks which are of low intensity becomes distorted. (Davies Tr. 5740:14-19.) Because in Dr. Cima's data, the mannitol peak is much more intense than omeprazole or MACP peaks, normalization causes a dramatic shifting of peaks from the core to the enteric coating (shifting of peaks along the x-axis) as well as overemphasized features within the analysis (shifting in peak intensity) and thus renders distorted results. (Davies Tr. 6031:19-6032:1; PSWTX 2168). Notably, in Dr. Cima's non-normalized data, the omeprazole and mannitol are in the core and the MACP is shown to be in the enteric coating. (Davies Tr. 5739:22-23; PSWTX 2168 at page 2 (top graph).) Dr. Davies also testified that Raman spectrometry is not well suited to detect an MACP-PVP complex layer in a bisected pellet. (Davies Tr. 5720:2-12; PSWTX 2212-A.) Because the Court finds Dr. Cima's Raman results to be of limited relevance to the question of whether Apotex's product contains a subcoating, it does not reach the issue of whether Dr. Cima's use of Raman spectrometry was appropriate or

reliable.

Apotex's assertion that Plaintiffs provided no data showing that the alleged MACP-PVP complex is present in unwashed pellets is belied by the totality of the evidence presented. Circumstantial evidence may be sufficient to prove that an accused product infringes. *See* Moleculon Research Corp. v. CBS, 793 F.2d 1261, 1272 (Fed.Cir.1986) ("It is hornbook law that direct evidence of a fact is not necessary. 'Circumstantial evidence is not only sufficient, but may also be more certain, satisfying and persuasive than direct evidence.' " (quoting Michalic v. Cleveland Tankers, Inc., 364 U.S. 325, 330, 81 S.Ct. 6, 5 L.Ed.2d 20 (1960))); *see also* San Huan New Materials High Tech, Inc. v. ITC, 161 F.3d 1347, 1360-61 (Fed.Cir.1998) (finding that a test of one batch of infringing product was sufficient circumstantial evidence that other batches infringed). Dr. Davies's CLSM fluorescence, CLSM reflectance, and UV fluorescence, along with the ATR-FTIR and disintegration testing evidence, all show a distinct subcoating all the way around the core of Apotex's ANDA pellets.

In sum, Plaintiffs demonstrated the presence of a subcoating in Apotex's product through the following evidence: (1) CLSM reflectance, CLSM fluorescence, and widefield UV fluorescence of enteric coated and acetone: IPA washed pellets show a continuous subcoating; (2) Differences in the solubility between the enteric coating and sublayer shows the presence of a distinct and continuous sublayer; (3) Visual observation during disintegration testing shows the presence of a continuous, rapidly disintegrating, inert subcoating; (4) ATR-FTIR testing of enteric coated, uncoated, and washed pellets shows the presence of a continuous, inert subcoating; (5) ATR-FTIR testing of Dr. Davies' reference MACP:PVP complex precipitate and Apotex's washed pellets show the sublayer is an MACP:PVP complex containing an MACP/Mg salt; and (6) pH testing of MACP-PVP complex shows the complex has properties different than MACP and PVP alone. (*See* Davies Tr. 485:14-486:24; PSWTX 1252-12.)

Having considered the evidence and arguments presented by both parties, the Court finds that a preponderance of the evidence supports Plaintiffs' assertion that Apotex's product contains an *in situ* formed subcoating.

b. Inert

The Court also finds that Apotex's subcoating is inert. (Langer Tr. 1198:15-1199:12; PSWTX 1257-11.) ATR-FTIR spectra of Apotex's washed pellets did not detect omeprazole or its degradation products in the subcoating. (Davies Tr. 5702:21-5704:10; PSWTX 2650-10; PSWTX 2650-11.) Visual inspection of the washed pellets also did not exhibit discoloration suggestive of the presence of degraded omeprazole. (Davies Tr. 481:7-16.)

Nevertheless, as discussed above, small amounts, like .05%, of degraded omeprazole are inconsequential. (Langer Tr. 5463:21-5464:12; Cima Tr. 4158:23-4159:7.) In addition, Apotex admits that "[i]n each of the Apotex ANDA Products, magnesium methacrylic acid copolymer salt does not substantially adversely affect omeprazole." (PSWTX 1142 at No. 74.) The Court therefore finds that Apotex's subcoating is inert within the meaning of the patents.

c. Water Soluble or Rapidly Disintegrating in Water

Apotex's subcoating is rapidly disintegrating within the meaning of claim 1(b) of the '505 and '230 Patent. (Langer Tr. 1199:13-24.) Dr. Davies testified that visual observation and time lapse photography during disintegration testing shows the presence of a continuous, rapidly disintegrating subcoating. (Davies Tr. 481:17-482:7, 485:18-486:24; PSWTX 1252-12.)

Dr. Davies placed washed pellets into a dish under the same microscope as used for confocal and UV fluorescence, added water and then took pictures every 1.784 seconds for approximately twenty minutes. (Davies Tr. 481:17-482:7, 483:20-23.) The time lapse video shows that the sublayer in Apotex's product begins to disintegrate after two minutes. (Davies Tr. 484:20-23, 485:2-16; PSWTX 1060A; PSWTX 838-842.) By 4 minutes and 36 seconds the entire subcoating layer has come off. (Davies Tr. 484:23-25, 485:10-13; PSWTX 1060A; PSWTX 841; PSWTX 842.) Dr. Davies performed disintegration tests on over ten different pellets which yielded similar results of rapid disintegration. (Davies Tr. 482:8-13.)

The Court is not persuaded by Apotex's argument that what Dr. Davies characterized as a disintegrating subcoating was actually the disintegration of the enteric coating. Dr. Davies used the same procedure of washing the pellets for his disintegration tests as he used for his CLSM and UV tests-which clearly showed that no enteric coating remained after the washing. Thus, the evidence presented by Dr. Davies and described in detail above, supports the Court's finding that the subcoating of Apotex's product is rapidly disintegrating.FN76

FN76. The disintegration videos also provide additional evidence that the subcoating is continuous. The fact that the subcoating material follows the contours of the underlying core and, at one point separates in one large piece, suggests the presence of a substantially continuous sublayer. (Davies Tr. 5760:10-19; PSWTX 1060A; *see also* PSWTX 838 (image at 4 minutes, 36 seconds).)

4. Claim 1(c): Enteric Coating and Enhanced Stability

Apotex's product also meets the limitations of claims 1(c) of the '505 and ' 230 Patents. The '505 Patent claim 1(c) requires, "an outer layer disposed on said subcoating comprising an enteric coating." (PSWTX 1A 16:53-54.) '230 Patent claim 1(c) requires, "an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced." (PSWTX 2A 13:15-20.)

Apotex admits that each of its ANDA products contains an enteric coating layer that includes MACP and triethyl citrate. (PSWTX 1142F at No. 113; Langer Tr. 1196:4-7, 1199:25-1200:9.)

The subcoating in Apotex's product meets the enhanced stability requirement of '230 Patent claim 1(c), because "the subcoating layer isolates or separates the core from the enteric coating sufficiently to enhance the formulation's stability." Astra v. Andrx, 222 F.Supp.2d at 475. Comparative testing is not required to show that a subcoating results in enhanced stability. (Jan. 12, 2006 Order at 13.) As explained, Apotex's product has a continuous, inert MACP:PVP layer that hugs the surface of the core and separates the core from the enteric coating. Thus, Apotex's product meets the limitations of claims 1(c) of the '505 and '230 Patents.

For the reasons stated above, the Court finds that Apotex's products meet all the claim limitations of claim 1 of the '505 Patent and claim 1 of the '230 Patent.

5. Claim 5 of the '505 Patent and Claim 6 of the '230 Patent

Claim 5 of the '505 Patent calls for "[a] preparation according to claim 1 wherein the alkaline core comprises omeprazole and pH buffering alkaline compound rendering to the microenvironment of omeprazole a pH of 7-12." (PSWTX 1A 16:65-68.) As this Court previously found, '505 Patent claim 5 expressly requires that: (1) omeprazole be present; and (2) that the ARC result in an omeprazole micro-pH of 7-12 (as opposed to a micro-pH of 7 or greater-up to pH 14). Astra v. Andrx, 222 F.Supp.2d at 476-79.

Apotex meets the limitations of claim 5 of the '505 Patent. (Langer Tr. 1201:2-8). As discussed above, Apotex's products contain omeprazole plus the alkaline reacting compound magnesium hydroxide, and the microenvironmental pH of Apotex's core containing magnesium hydroxide is between 7 and 12. (Langer Tr. 1201:2-8.) Dr. Davies's studies further show that the materials comprising Apotex's omeprazole containing pellet cores exhibit a pH range between 8.82 and 9.36. (Langer Tr. 1201:2-8 (citing PSWTX 1257-18); PSWTX 844 at 18-1 & 18-2.)

Claim 6 of the '230 Patent does not materially differ from claim 5 of the ' 505 Patent. This claim calls for: "[a] preparation according to Claim 1, wherein an alkaline core comprises the acid labile compound and a pH-buffering alkaline reacting compound which renders the micro-environment of the acid labile compound a pH of 7-12." (PSWTX 2A 14:4-8.) The proof of infringement for claim 6 of the '230 Patent is the same as that for claim 5 of the ' 505 Patent. (Langer Tr. 1201:9-11.) The acid labile pharmaceutically active substance (the acid labile compound) in '230 Patent claim 6 is omeprazole, and the pH buffering alkaline reacting compound in ' 230 Patent claim 6 is magnesium hydroxide. (Langer Tr. at 1201:2-11.) As demonstrated above, the micro-pH in Apotex's product is between 7 and 12. (Langer Tr. at 1201:2-6, PSWTX 1257-18.)

Accordingly, this Court finds that Apotex's products meet all the claim limitations of claim 5 of the '505 Patent and claim 6 of the '230 Patent.

6. Claim 6 of the '505 Patent and Claim 7 of the '230 Patent

Claim 6 of the '505 Patent calls for "[a] preparation according to claim 5 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide, or carbonate ...." (PSWTX 1A 17:1-8.) Apotex admits that each of its ANDA products contains a core region that contains the alkaline reacting compound magnesium hydroxide. (PSWTX 1142 at Nos. 7, 8, 10, 31, 32.) Thus, the Court finds that Apotex infringes claim 6 of the '505 Patent. (*See* Langer Tr. 1201:12-19; PSWTX 1257-20.)

Claim 7 of the '230 Patent calls for "[a] preparation according to claim 6 wherein the alkaline reacting compound comprises one or more of magnesium oxide, hydroxide, or carbonate ...." (PSWTX 2A 14:9-14.) The proof of infringement for this claim is the same as for '505 Patent claim 6. (Langer Tr. 1201:20-23; PSWTX 1257-20.)

Thus, Apotex's products meet all the claim limitations of claim 6 of the '505 Patent and claim 7 of the '230 Patent.

7. Claim 10 of the '505 Patent and Claim 13 of the '230 Patent

Claim 10 of the '505 Patent is directed to "[a] method for the treatment of gastrointestinal disease comprising administering to a host in need of such treatment a therapeutically effective amount of a preparation according to claim 1." (PSWTX 1A 17:23-26.) Apotex's product contains a therapeutically effective amount of omeprazole. Apotex's product insert shows that Apotex's ANDA products are to be used for treating gastrointestinal disease and are bioequivalent to Prilosec(R). (Langer Tr. 1201:24-1202:13 (citing PSWTX 1257-22, PSWTX 1648 & PSWTX 1649).) Accordingly, Apotex has induced and contributed to infringement by others who administer or use Apotex's product and claim 10 of the '505 Patent is met.

Claim 13 of the '230 Patent calls for "[a] method for the treatment of gastrointestinal disease characterized in that a preparationaccording to claim 1 is administered to a host in the need of such treatment in a therapeutically effective amount." (PSWTX 2A 14:42-45.) The proof of infringement for this claim is the same as for '505 Patent claim 10. (Langer Tr. 1193:10-13.)

For the reasons stated above, Apotex's products meet all the claim limitations of claim 10 of the '505 Patent and claim 13 of the '230 Patent.

8. Conclusion

Apotex's 10-, 20-, and 40-mg ANDA omeprazole products infringe claims 1, 5, 6, and 10 of the '505 Patent and claims 1, 6, 7, and 13 of the '230 Patent. (Langer Tr. 1202:14-1203:5; PSWTX 1257-24; PSWTX 1257-25.)

By filing ANDAs seeking FDA approval to engage in the commercial manufacture, use or sale of Apotex's products prior to the expiration of the patents-in-suit Apotex has committed acts of infringement. (Second Am. Compl. Against Apotex para.para. 21, 32). Apotex has directly infringed the patents-in-suit by manufacturing, selling and offering for sale Apotex's FDA-approved 10-mg and 20-mg generic omeprazole product (*Id*. para.para. 24c, 36c, 36d); and Apotex has induced and contributed to infringement by others who administer or use Apotex's product (*Id*. para.para. 23, 35).

F. *Impax's Product*

[33] Impax is a manufacturer of generic pharmaceutical products in the United States. Impax submitted ANDA No. 75-785 to the FDA, seeking the FDA's approval to sell Impax's proposed 10- and 20-mg products called "Omeprazole Delayed Release Capsules, 10 and 20 mg" as a generic version of Plaintiffs' Prilosec(R) product. (Impax's Answer & Countercls. to Second Am. Compl. para. 11; PSWTX 1127A.) In September 2004, the FDA had granted final approval for Impax's 10-, 20-, and 40-mg omeprazole products, and Impax commenced commercial sales of its ANDA product in conjunction with its marketing partner, Teva Pharmaceutical Industries Ltd. ("Teva"). (Second Am. Compl. Against Impax para.para. 19a, 19b, 31a, 31b.)

Plaintiffs assert that Impax committed an act of infringement under 35 U.S.C. s. 271(e)(2) with respect to the '505 and '230 Patents by filing an ANDA seeking FDA approval to engage in the commercial manufacture, use or sale of Impax's products prior to the expiration of the patents-in-suit (Id. para.para. 16, 28); that Impax has directly infringed the patents-in-suit under 35 U.S.C. s. 271(a) by selling and offering for sale Impax's FDA-approved "Omeprazole Delayed Release Capsules, 10 and 20 mg," (*Id*. para.para. 19c, 31c); and that Impax has induced and contributed to infringement by others who administer or use Impax's products under 35 U.S.C. s. 271(b)-(c) (*Id*. para. para. 18, 19, 30, 31). Plaintiffs further assert that Impax had knowledge of the ' 505 and ' 230 Patents before the infringement referred to above, and such infringement has been willful and deliberate. (Id. para.para. 19d, 31d.) Additionally, Plaintiffs claim this case is exceptional under 35 U.S.C. s. 285 based on Impax's litigation misconduct and lack of a meritorious defense. FN77 (*Id*. at para.para. 20, 32.)

FN77. The Court will not address willfulness or whether the case is exceptional under 35 U.S.C. s. 285 in this opinion.

Plaintiffs allege that Impax's 10-mg, 20-mg, and 40-mg ANDA omeprazole products infringe claims 1, 5, 6, 8, and 10 of the '505 Patent and claims 1, 6, 7, 10, and 13 of the '230 Patent literally, and if not literally, under the doctrine of equivalents.

1. Impax's Objections to Plaintiffs' Exhibits

As a preliminary matter, pursuant to the Court's June 14, 2006 oral order, Impax provided Plaintiffs with a

list of its objections to certain exhibits, demonstratives, and citations included in Plaintiffs' Proposed Findings of Fact. (Letter from Impax to Plaintiffs, July 12, 2006 ("Impax July 12 Letter").) For the reasons outlined below, the Court finds that Impax's objections are without merit.

First, Impax lodges a general objection to twenty-nine demonstratives that were used at trial and cited in Plaintiffs' Proposed Findings of Fact regarding Impax. (Id. at 1). The demonstratives are included in Plaintiffs' submission for the convenience of the Court, and Plaintiffs properly rely on the expert testimony concerning each demonstrative that was discussed at trial and exhibits that were listed on the demonstrative and properly admitted at trial. FN78

FN78. In addition, to the extent the Court cites to demonstratives in this Opinion, it is just for convenience. The Court is not relying on the demonstratives in its analysis or conclusions.

Second, Impax complains about Astra's citation of the prosecution history of the '505 Patent, found at PSWTX 3B. (Id.) Plaintiffs have not introduced new arguments or portions of the prosecution history that were not previously before the Court. Instead, Plaintiffs properly include the prosecution history of the '505 Patent to refer to rulings made by the Court in its January 12, 2006 Order Denying Defendants' Summary Judgment Motions.

Third, Impax broadly objects to citations to Plaintiffs' Proposed Findings of Fact and Conclusions of Law that relate to other Second Wave Defendants. (Id. at 2.) The Second Wave proceedings were consolidated for discovery and trial for patent liability issues, and, while there may be material differences between each Defendants' product, there are many overlapping issues in this case that may relate to more than one Defendant. Therefore, Plaintiffs have properly cross-referenced the sections of its post-trial submissions that relate to two or more Defendants.

Accordingly, the exhibits, demonstratives, and citations identified by Impax in its letter are admitted over Impax's objections.

2. Impax's Formulation and Manufacturing Process

Impax's 10-, 20-, and 40-mg products have identical pellets. The only difference is the number of pellets in each capsule. (PSWTX 1258-5; Langer Tr. 1204:23-1205:10; Shaw Dep. Tr. 260:23-261:24, Aug. 8, 2005.) Impax makes its core by spray-coating an omeprazole-containing drug layer on a sugar sphere. (Langer Tr. 1204:7-13; PSWTX 1258-3; PSWTX 521A.) The omeprazole containing layer includes omeprazole, dibasic sodium hydrogen phosphate, Poloxamer 338, and hydroxypropyl methylcellulose ("HPMC"). Impax mixes into purified water the HPMC followed by the Poloxamer, followed by the disodium hydrogen phosphate. Then, Impax slowly disperses the omeprazole into the solution. The sugar spheres are then charged into a fluid bed coater and the omeprazole dispersion is sprayed onto the sugar spheres. The drug coated pellets are then dried. (Langer Tr. 1204:7-13; PSWTX 1258-3; PSWTX 521A.)

The pellets are then coated with enteric coating polymer hydroxypropyl methylcellulose phthalate ("HPMCP") HP-55, acetyltributyl citrate, and talc. (Langer Tr. 1204:14-22; PSWTX 1258-4; PSWTX 521A; PSWTX 522A.) First, the acetone and HPMCP are mixed, then the acetyltributyl citrate is added and mixed, and finally talc is added and mixed. The omeprazolecore seeds are charged into the fluid bed coater and heated. The enteric coated pellets are then dried and cooled. (Langer Tr. 1204:14-22; PSWTX 1258-4; PSWTX 521A; PSWTX 522A.)

3. Claim 1 of the '505 and '230 Patents

Impax's 10-, 20-, and 40-mg omeprazole capsules are designed for an oral route of administration, and therefore, Impax's ANDA product is an "oral pharmaceutical preparation" as that phrase is used in claim 1 of the '505 Patent. (Langer Tr. 1205:11-22; PSWTX 1210; PSWTX 1512B.)

a. Claim 1(a): An Effective Amount of an Alkaline Reacting Compound (ARC)

Claim 1(a) of the '505 Patent calls for "a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone." (PSWTX 1A 16:43-47.) Similarly, claim 1(a) of the '230 Patent calls for "an alkaline reacting core." (PSWTX 2A 13:2.) Impax refers to its pellets prior to enteric coating as "core seeds" (PSWTX 1258-8; Langer Tr. 1205:23-1206:5), and according to Impax's manufacturing and processing instructions, Impax adds omeprazole during the manufacturing of Impax's "core seeds" (*id*.). Impax's ANDA states that the active drug layer is part of the core region. (Langer Tr. 1206:6-11; PSWTX 37A; PSWTX 578A.) The Court finds, therefore, that Impax's product contains a core as required by claim 1(a) of the '505 and '230 Patents.

As stated above, the Court previously construed the claim phrase "alkaline reacting compound" ("ARC") to be "(1) a pharmaceutically acceptable alkaline, or basic, substance having a pH greater than 7 that (2) stabilizes the omeprazole or other acid labile compound by (3) reacting to create a micro-pH of not less than 7 around the particles of omeprazole or other acid labile compound." Astra v. Andrx, 222 F.Supp.2d at 453. An "effective amount" of an ARC, expressly required in claim 1(a) of the '505 Patent and implicit in the '230 Patent, id. at 462, is the amount required to raise the micro-pH to not less than pH 7, which thereby stabilizes omeprazole, id. at 463-464. The amount of an ARC sufficient to be "effective" in relation to the omeprazole depends on the nature of the formulation and how it was made. *Id*. at 463-464; *see also* Langer Tr. 5453:22-5457:1.

Impax uses disodium hydrogen phosphate (also referred to as dibasic sodium phosphate or "DHP") in its drug layer. (Davies Tr. 492:22-493:14; PSWTX 1035.) The '505 Patent explicitly teaches that DHP is an ARC that stabilizes omeprazole. (Langer Tr. 1207:10-18; PSWTX 1258-11; PSWTX 1517B; PSWTX 1A 6:44, 7:64, 9:18, 9:68, 17:1-8; *see also* Astra v. Andrx, 222 F.Supp.2d at 526.) DHP is an alkaline material and can have a pH of up to 9.4. (PSWTX 1258-10; Langer Tr. 1206:24-1208:10; PSWTX 1070; PSWTX 1217; PSWTX 1517B; PSWTX 1258-11; PSWTX 1258-12.) Impax's ANDA specification for DHP provides for a pH of 8.7-9.3 (PSWTX 1258-10; PSWTX 1217; PSWTX 1517B; Langer Tr. 1206:24-1207:9), and the DHP used to make Impax's ANDA product has a pH of 9.1 (PSWTX 1217; PSWTX 1258-10). Impax's expert Dr. Chambliss acknowledged that DHP has a pH greater than 7 in water. (Chambliss Tr. 5054:5-11.) Impax represented to the FDA that the DHP is added to the drug layer as a buffer. (PSWTX 1258-9; PSWTX 519A (I0002536); PSWTX 1516B (I0034580); Chambliss Tr. 5054:5-7.) Therefore, the Court finds that the DHP in Impax's drug layer is an ARC.

Because the omeprazole in Impax's active drug layer is mixed with DHP (PSWTX 1258-3; PSWTX 1258-4; PSWTX 521A; PSWTX 522A), the pH of the active drug layer represents the micro-pH of the omeprazole in Impax's product.FN79 *See supra* Part II.D.2.a (discussion of micro-pH in Lek's Product); see also Astra v. Andrx, 222 F.Supp.2d at 517. Dr. Davies tested the pH of the active drug layer, and found it to be alkaline. (Davies Tr. 535:20-537:6; PSWTX 1000A; PSWTX 890A; PSWTX 1253-16.) Using Impax pellets coated only with the active layer, Dr. Davies incubated the pellets in a humid environment. (Davies Tr. 535:9-19) Using a sharp scalpel, Dr. Davies then pressed on the layer, which cracked off. (*Id*.) Dr. Davies checked the cracked-off material to ensure that there was no sugar seed in that material and then tested its pH.FN80 (*Id*.)

FN79. The Court is utterly unpersuaded by Impax's argument that there is no such thing as a micro-pH of a solid. (Chambliss Tr. 5039:5-19; Meyer Dep. Tr. 104:12-105:5, Jan. 21, 2005.) As discussed above with

respect to Lek's product, the patents provide clear instructions for how to test the micro-pH of a solid core (or, in this case, active layer).

FN80. Dr. Davies used a similar method to test the microenvironment of Andrx's drug layer during the First Wave litigation. Astra v. Andrx, 222 F.Supp.2d at 526.

Dr. Davies found that Impax's drug layer exhibits mean pH values of 8.32-8.47, over a range of concentrations and a two month period. (Davies Tr. 535:20-537:6; PSWTX 1000A; PSWTX 890A; PSWTX 1253-16; Langer Tr. 1207:19-1208:4; PSWTX 1258-12.) The mean pH value for the supernatant (pH 8.35) was consistent with these results. (PSWTX 890A.) Dr. Davies's testing on a suspension containing HPMC, omeprazole, DHP, and Poloxamer in the same proportions as present in Impax's drug layer exhibits a mean pH value of 8.58, further demonstrating that the active layer of Impax's ANDA product is alkaline. (Davies Tr. 537:7-539:15; PSWTX 1000B; PSWTX 1002; PSWTX 890B; PSWTX 1253-17.)

As shown above, the Impax formulation contains a sufficient amount of DHP to raise the pH of the omeprazole to 7.0 or greater. Contrary to Impax's arguments, having established that Impax's product contains an ARC that successfully creates a micro-pH of not less than 7, Plaintiffs were not required to separately test for stability. (*See, e.g.,* Langer Tr. 5455:4-12; 5456:5-11) Impax attempts to read the patents to require that the ARC-and only the ARC-completely and perfectly stabilizes the omeprazole. This is obviously incorrect, because the patents themselves require an additional source of stability, i.e., an inert subcoating. (*See* PSWTX 1A 16:48-52; PSWTX 2A 13:10-15.)

Accordingly, because the DHP in Impax's formulation has a pH greater than pH 7, creates a micro-pH of 7 or greater, and stabilizes the omeprazole in Impax's drug layer, the Court finds that Impax's products contain an effective amount of an ARC, as required by claim 1(a) of the '505 and '230 Patents.

b. Claim 1(b): An Inert Subcoating That is Soluble or Rapidly Disintegrating in Water

Claim 1(b) of the '505 Patent requires "an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film forming compounds." (PSWTX 1A 16:48-52.) Similarly, claim 1(b) of the '230 Patent requires "an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group of tablet excipients, film-forming compounds and alkaline compounds." (PSWTX 2A 13:10-15.)

As with Apotex's Product, Impax's manufacturing process does not involve a separate application of a subcoating. Rather, Plaintiffs assert that Impax's Product contains an inert subcoating that is formed *in situ*. (Davies Tr. 526:4-12.) As stated above, the Court adopts its previous ruling that the product claims of the '505 and '230 Patents do not limit the manner in which the product is made and cover subcoatings regardless of how they are formed. FN81 Astra v. Andrx, 222 F.Supp.2d at 469-70; *see also* Langer Tr. 5465:20-5466:14. Having considered the evidence presented by Plaintiffs and Impax and for the reasons stated below, the Court finds that Plaintiffs have shown by a preponderance of the evidence that Impax's Product contains an inert subcoating which is water soluble or rapidly disintegrating in water disposed on the Product's core region.

FN81. Contrary to Impax's argument, Plaintiffs are not estopped from arguing that the patents-in-suit cover *in situ* formed subcoatings based on the content of an affidavit from its expert, Dr. Rees, submitted to the

Canadian Federal Court in the matter of *Astrazeneca AB v. Apotex Inc.,* No. T-766-03. In that action, which concerned the validity of Canadian Patent No. 2,186,037 (the "'037 Patent"), Dr. Rees explained that "none of the ['505 or '230] patents discloses or suggests forming a water soluble separating layer *in situ* by reaction between the enteric coating polymer and an alkaline reacting compound in the core." (ITX 90 para. 40.) However, the Federal Court of Canada did not rely on Plaintiffs' position with respect to the statement at issue in paragraph 40 of the Rees Affidavit. In fact, the Canadian Court expressly declined to reach validity of the ' 037 Patent, stating that "[e]ither of my alternative findings [on infringement] is sufficient to dispose of the application. It is therefore not necessary to deal with the allegation of invalidity and I decline to do so." *Astrazeneca AB v. Apotex, Inc.,* 2006 F.C. 7 (ITX 3466 para. 125). Because the Canadian court did not adopt Astra's position, Plaintiffs are not estopped from advancing that argument. See New Hampshire v. Maine, 532 U.S. 742, 750-51, 121 S.Ct. 1808, 149 L.Ed.2d 968 (2001) (noting that there is no risk of inconsistent court determinations absent a court's adoption of a party's prior position).

i. Presence of A Continuous Subcoating

Dr. Davies examined the structure and chemical make-up of Impax's enteric coated pellet using CLSM fluorescence and CLSM reflectance, widefield UV fluorescence microscopy, ATR-FTIR, solubility testing, disintegration testing, pH testing and visual inspection. (Davies Tr. 495:12-16, 509:25-510:6, 514:18-20, 526:16-527:7, 527:8-12, 535:5-8.) Dr. Davies bisected over 20 Impax enteric coated pellets and observed the cross section using CLSM fluorescence, CLSM reflectance, and widefield UV fluorescence. (Davies Tr. 495:17-496:5; PSWTX 1253-3.)

Dr. Davies compared the CLSM images to the widefield UV images and found they were consistent-showing a sugar seed, a drug layer, a continuous, fluorescent ring on top of the drug layer, and an enteric coating. (Davies Tr. 496:9-14; 499:4-21; PSWTX 848; PSWTX 850; PSWTX 855-859.) Dr. Davies determined the location of the fluorescent layer by overlaying the fluorescence images onto a CLSM reflectance image, revealing that the fluorescent layer in Impax's ANDA pellets sits on top of the active layer, and underneath the enteric coating. (Davies Tr. 496:15-497:5; PSWTX 853 (an overlay of the CLSM fluorescence image in PSWTX 851 on the CLSM reflectance image in PSWTX 852).) The thickness of the fluorescing layer was shown to range from two to four microns. (Davies Tr. 499:22-501:9; Langer Tr. 1209:5-24; PSWTX 860.)

Dr. Davies testified that every Impax enteric coated pellet examined with CLSM and widefield UV fluorescence exhibited the fluorescent layer which was not present in Impax's active pellets prior to enteric coating. (Davies Tr. 503:5-504:4; PSWTX 864-67; *see, e.g.,* PSWTX 864 (a CLSM fluorescence image of Impax's active pellet prior to enteric coating, showing the presence of the sugar seed and the active layer, but not the bright fluorescing layer).) Dr. Davies testified that the presence of the fluorescing layer in Impax's enteric coated pellets, but its absence in the uncoated active pellets, demonstrates that the layer is due to the enteric coating process. (Davies Tr. 503:11-504:4.)

Because Impax's enteric coating material (HPMCP), is soluble in acetone (Davies Tr. 504:5-15), Dr. Davies washed approximately 50 of Impax's pellets in 20 milliliters of acetone to remove the enteric coating, as he did with other defendants' products.FN82 (Davies Tr. 504:5-17.) Dr. Davies observed the presence of the fluorescing layer both before and after the washing procedure. (Davies Tr. 504:18-505:10; *compare* PSWTX 851 (Impax enteric coated pellet) *with* PSWTX 873 (Impax enteric coated pellet after acetone washing).) PSWTX 868 is a side-by-side comparison of representative UV fluorescence (PSWTX 869), CLSM fluorescence (PSWTX 870), and CLSM reflectance (PSWTX 871) images of Impax's washed pellets, all of which show the fluorescing layer (or the region in the CLSM reflectance that corresponds to the fluorescing layer) on top of the drug layer.FN83 (Davies Tr. 505:15-506:3; *see also* PSWTX 879-81.) Furthermore, because Dr. Davies observed that the fluorescing layer is not present in Impax's uncoated pellet, but is

present in Impax's enteric-coated pellet and acetone-washed pellet, Dr. Davies concluded that the layer forms as a result of the enteric coating process. (Davies Tr. 508:25-509:13; PSWTX 1253-5.)

FN82. Impax moves to exclude Dr. Davies' testimony and evidence (and Dr. Langer's related testimony) regarding Dr. Davies' acetone-washing procedure and his ATR-FTIR studies (discussed below) based on *Daubert* on the grounds that these procedures were unreliable and inappropriately tailored to address the factual issues in this case. (*See, e.g.,* Meyer Tr. 5117:14-5136:22, 5157:2-24.) The Court finds that the evidence and arguments put forward by Impax in support of its *Daubert* motions do not warrant exclusion of the expert testimony at issue.

FN83. At trial, Impax attacked the credibility of Dr. Davies's fluorescence and CLSM data, arguing through Dr. Piston that he had (1) failed to identify appropriate Z slices; (2) failed to obtain fluorescence spectra for his HPMCP/DHP salt film and a DHP sample; (3) improperly used the Leica machine and Imaris software; and (4) improperly altered his CLSM data. Impax raised many of these issues improperly for the first time at trial, and such late disclosure was undoubtedly prejudicial to Plaintiffs. The Court finds that Dr. Davies properly used UV fluorescence and CLSM reflectance. (Davies Tr. 954:15-25.) In addition, Impax's arguments against Dr. Davies's use of maximum projection images and stacked Z-slices go to the weight, not the admissibility of the evidence. The Court also finds that Impax failed to produce any credible evidence of data manipulation or inappropriate data processing, and Impax's allegations of data manipulation are without merit. (*See* Davies Tr. 5525:3-5527:12.)

An overlay of CLSM fluorescence and CLSM reflectance clearly shows the position of the fluorescence on the surface of the active layer (Davies Tr. 506:16-25; PSWTX 872), and three-dimensional projections of Impax's pellets also show that the fluorescing layer is continuous within the meaning of the patents (PSWTX 1481-84; Davies Tr. 510:21-514:17).FN84 Impax's experts misconstrue the claims of the patents in their arguments that Impax's product does not contain a subcoating under the terms of the patents because (1) an *in situ* subcoating would not be perfectly continuous (*see, e.g.,* Chambliss Tr. 5021:6-20) and (2) Dr. Davies has not shown that the alleged subcoating in Impax's product is perfectly continuous. The Court disagrees. In the Court's First Wave Opinion, it construed the term "subcoating" according to its ordinary meaning as:

FN84. PSWTX 876-78 contain more high-resolution CLSM fluorescence, reflectance, and UV fluorescence data showing a continuous layer around the surface of the active pellet. (Davies Tr. 507:10-19.)

a layer of material that "coats" and is "disposed on" the core region; therefore, it must be physically on or in contact with that core region. The plain meaning of the noun "coating" requires a "material that will form a continuous film over a surface".

. . . . .

... Thus, the patent contemplates, and the court construes the claims to cover, subcoatings that are less than perfect, including subcoatings that contain inconsequential amounts of omeprazole or permit inconsequential contact between portions of the core and the enteric coat. The claims do not require a perfectly continuous, exactly uniform subcoating.

Astra v. Andrx, 222 F.Supp.2d at 464, 471; *see also* Langer Tr. 5461:22-5462:15. Furthermore, because there is no real world formulation, including the Prilosec(R) formulation, which could satisfy a perfect subcoating standard, the patents could not require a perfect subcoating. Astra v. Andrx, 222 F.Supp.2d at 471; *see also* Langer Tr. 5462:7-15. The Court's claim construction controls on this issue.

Dr. Davies also used ATR-FTIR FN85 to chemically identify the sublayer in Impax's product and concluded that the sublayer is an HPMCP salt. (Davies Tr. 515:22-516:12; Langer Tr. 1210:1-5.) ATR-FTIR spectra were obtained from (i) the surface of Impax's enteric coated pellet (PSWTX 882); (ii) the fluorescing layer that remains after removing the enteric coating (PSWTX 883); (iii) an HPMCP reference film (PSWTX 758); and (iv) HPMCP salt reference films. Dr. Davies determined that the ATR-FTIR spectra for the HPMCP enteric coating material exhibits peaks at about 1727 and 1280 cm^{-1} (PSWTX 882; Davies Tr. 515:8-21, 1010:23-1011:19), which reflect the acid-ester in HPMCP (Davies Tr. 517:20-519:10; PSWTX 776.).FN86 The Impax enteric coating spectra also exhibit peaks that match the spectra of the HPMCP reference film. (Davies Tr. 520:13-521:25; PSWTX 882; PSWTX 758; PSWTX 1253-8.) However, the spectra of Impax's enteric coating did not correlate to the spectra of the surface of Impax's washed pellets-, i.e., the fluorescing layer. (PSWTX 882; PSWTX 883; PSWTX 1253-7; Davies Tr. 516:21-517:8.) Rather, Dr. Davies testified that the spectra of the fluorescing layer in Impax's product exhibits peaks which correlate with the HPMCP salt reference film, but are distinct from the enteric coating. (PSWTX 883; PSWTX 759; PSWTX 1253-10; Davies Tr. 515:22-517:8; *see also* Davies Tr. 5562:4-15, 5563:9-5564:9.)

FN85. For an explanation of ATR-FTIR, *see supra* note 17.

FN86. The Aldrich Library of Infrared Spectra (PSWTX 776) shows two peaks associated with an acid-ester (C=O at about 1725 and C-O near 1250) (Davies Tr. 517:20-519:10; PSWTX 776 at 1017).

Based on further testing, Dr. Davies concluded that an HPMCP salt may form as a result of a reaction between DHP and HPMCP. (Davies Tr. 508:16-20; 521:22-523:19, 944:15-947:5; *compare* PSWTX 883 *with* PSWTX 761, PSWTX 758 *with* PSWTX 759, and PSWTX 759 *with* PSWTX 883.) Although the process by which the HPMCP salt subcoating forms need not be articulated to prove infringement, Dr Davies testified that during Impax's enteric coating process, the DHP and HPMCP in Impax's Product interact in the presence of water FN87 to form an HPMCP salt layer. (Davies Tr. 525:18-526:12, 994:15-945:3; PSWTX 1253-12; PSWTX 1258-20.)

FN87. Dr. Davies recorded mean water content in Impax's final product of 2.36, 2.41, 2.58, and 2.42 percent. (Davies Tr. 539:19-540:11; PSWTX 1001; PSWTX 892.) DHP is highly soluble in water, whereas omeprazole is only very slightly soluble in water. (PSWTX 1259-49; PSWTX 1615; PSWTX 1639; PSWTX 1103B.)

ii. Inert

Dr. Davies testified that the ATR-FTIR spectra taken from different samples of Impax's 10-mg ANDA product do not show the presence of omeprazole or its degradation product (Davies Tr. 5561:16-5563:8; PSWTX 2600-11 to -14), and two of the five spectra taken from Impax's 40-mg product show very weak peaks (Davies Tr. 5565:15-5567:19; PSWTX 2600-16 to -19). According to Dr. Davies, these weak peaks are coincident with omeprazole at the deepest sampling depths, but do not appear at higher wavenumbers (or more shallow sampling depths). (Davies Tr. 5566:25-5567:19.) Considering the sampling depth and the measured width of the subcoating layer,FN88 Dr. Davies concluded that the omeprazole peaks were coming from the core. (Davies Tr. 1020:14-1021:16.)

FN88. Dr. Davies testified that at approximately 800 cm^{-1}, where the omeprazole-related peaks are found, the silicon crystal he uses has a sampling depth of around 3 microns. (Davies Tr. 5567:20-5568:12; PSWTX

2222-1 (citing PSWTX 1534A at 136).) He also calculated a subcoating width of 2-4 microns in Impax's product. (Davies Tr. 5568:13-17, 499:22-500:17.)

However, even if trace amounts of omeprazole or its degradation products were found at shallower sampling depths (i.e., outside of the active layer), the subcoating found in Impax's product may still be inert. Under the patents, a subcoating may be inert and still contain inconsequential amounts of omeprazole or omeprazole degradation products. As the Court stated above with respect to Apotex, the patents do not require the subcoating to protect against *all* adverse effects, no matter how inconsequential. Nor do the patents require perfect storage stability:

The patent specifications describe the properties the subcoating should have in terms of stability. The subcoating must provide increased gastric resistance and storage stability. Thus, the patent teaches that the subcoating must be inert under those conditions, which allows for the possibility that some inconsequential amounts of different components may react under some conditions or to such a limited extent that gastric acid resistance and storage stability remain uncompromised for practical purposes.

Astra v. Andrx, 222 F.Supp.2d at 474 (citation omitted). Accordingly, the preponderance of the evidence supports this Court's finding that the subcoating in Impax's product is inert within the meaning of the patents.

iii. Water Soluble or Rapidly Disintegrating in Water

Dr. Davies also demonstrated that HPMCP salt is a polymeric film forming compound and is soluble in water. (PSWTX 1253-13; PSWTX 762; Davies Tr. 526:13-527:7.) The HPMCP salt film dissolves in water in about 15 seconds and is rapidly disintegrating. (Davies Tr. 526:16-24, 27:8-529:22.) Dr. Davies placed acetone-washed Impax pellets in water and, using time lapse photography, showed that within seconds the water penetrates the HPMCP salt film and after a minute and a half the sugar seed is exposed. (Davies Tr. 527:13-529:11; PSWTX 1061A; PSWTX 884-87; PSWTX 973.) The results, taken as a whole, indicated that the Impax subcoating disintegrates in under 5 minutes (Langer Tr. 1214:21-1215:5), and ATR-FTIR of the surface of the remaining pellet showed that only the sugar seed remained (Davies Tr. 529:12-22; PSWTX 888). Accordingly, the Court finds that Impax's subcoating is rapidly disintegrating within the meaning of the patents.

iv. Representativeness

Both Astra and Impax have requested that the Court find that the samples each has tested are representative of Impax's ANDA product.

In September 1999, in preparation for its ANDA submissions, Impax manufactured samples of its 10-mg and 20-mg ANDA products, and in November 1999, Impax manufactured samples of its 40-mg ANDA product. (Impax's Opp'n to AstraZeneca's Motion to Determine Whether the Impax Samples are Representative, June 23, 2004, hereinafter "Opp'n," at 6.) Impax proposed a two-year expiration date in its ANDA, and set the expiration date for the samples at September 2001 and November 2001, respectively. (*Id.*)

On August 25, 2000, Plaintiffs requested all documents and things concerning Impax's delayed-release capsules. (AstraZeneca's Reply Mem. in Support of its Motion to Determine Whether the Impax Samples are Representative, July 2, 2004, hereinafter "Reply," at Ex. 1.) Impax failed to produce samples at that time. On April 16, 2001, the Court stayed discovery pending resolution of the First Wave litigation. (Reply at Ex. 3.)

In December 2002, Plaintiffs sent Impax its Second Request for Production of Documents and Things, expressly requesting production of samples of Impax's ANDA product. (Plaintiffs' Motion to Determine Whether the Impax Samples Are Representative, June 8, 2004, hereinafter "Motion," at Ex. 1.) Impax did not produce the requested samples, arguing that the ANDA samples were irrelevant because they were expired and not representative. (Motion at Ex. 2.) Impax also informed Plaintiffs that it had commissioned testing on the ANDA samples while they were still representative. In February 2003, Impax agreed to produce the ANDA samples but not the results of its testing. (Opp'n at Ex. 6.) Impax produced ANDA samples in March 2003. (Motion at Ex. 5.) In May 2003, Impax was ordered to produce the withheld testing. In September 2003, Impax produced the testing documents, but reversed its position, and informed Plaintiffs that the testing was not performed on representative samples. (Motion at Ex. 5.)

In February 2004, Plaintiffs submitted their affirmative expert reports, which relied on testing performed on Impax's ANDA samples (the only samples Impax had produced at that time). Plaintiffs allege that although Impax started preparations for commercial-scale production before the scheduled due date for affirmative expert reports, Impax did not inform them of the availability of these commercial-scale pellets or their forthcoming small-scale samples.

In June 2004, Plaintiffs filed a Motion to Determine Whether the Impax Samples Are Representative, which Impax timely opposed. Plaintiffs requested a hearing on the representativeness of the tested ANDA samples, and, if the Court found the samples were not representative, Plaintiffs requested a delay in proceedings until representative samples were available. At this time, Impax notified Plaintiffsof its production of small-scale samples, and provided Plaintiffs with samples from this production. (Motion at 5.)

In mid-June 2004, Impax completed its first commercial-scale 10mg and 20mg production of enteric-coated pellets and conducted internal stability testing on these pellets. (Sept. 23, 1004 Letter Motion at Ex. 1, Ex. 3.) On June 14, 2004, Impax provided an expert with samples of this production (*Id*. at Ex. 3), but Impax did not provide Plaintiffs with samples from this production, nor did it notify Plaintiffs of the samples' existence. On September 9, 2004, Impax notified Plaintiffs' counsel that its marketing partner Teva had launched commercial sales of Impax's ANDA omeprazole product. (Oct. 7, 2004 Reply Letter Motion at Ex. A.)

On December 1, 2005, the Court heard oral argument on Plaintiffs' Motion to Determine Whether the Impax Samples are Representative. After further briefing on the issue, the Court ruled that representativeness was a question of fact to be decided at trial rather than in pre-trial proceedings. (Order, Jan. 18, 2006 at 6.) In addition, the Court denied Plaintiffs' request that the Court sanction Impax for its litigation misconduct by precluding Impax from arguing that the samples are not representative. (*Id*. at 7.)

At trial, Impax argued that Plaintiffs' evidence showing a subcoating is not reliable because Dr. Davies tested samples that were more than two years beyond their expiration date, and are therefore not representative of Impax's ANDA product. (Chambliss Tr. 5036:12-13.) Impax asserts that an ANDA product ceases to be representative for commercialization if it is past its expiration date, or FDA-required shelf life. (Lovgren Dep. Tr. 173:2-175:2, July 2, 2003.) However, the Court sees no reason to assume that on the date a product is no longer within the FDA-required shelf life for the purposes of commercialization, it also ceases to be structurally representative of the product. As an initial matter, the Court credits the testimony of Drs. Langer and Davies that the subcoating on Impax's product forms during the enteric coating process. (Davies Tr. 531:14-20, 531:21-532:1; Langer Tr. 1210:6-1213:7.) Specifically, Dr. Davies explained that the subcoating forms during the production process through the interaction of HPMCP and DHP, thus the subcoating is present from that point forward. (Davies Tr. 531:18-20.) As Drs. Davies and Langer concluded, the subcoatings in the samples were representative of Impax's product as of the time that they were manufactured.

Moreover, the samples Dr. Davies tested were taken from Impax's ANDA batches. (Davies Tr. 531:14-535:4.) Dr. Davies tested the samples for acid resistance, dissolution, assay, and related substances (or impurities), and found that the tested products met all stability criteria for an extended expiration date as set forth in Impax's stability evaluation protocol. FN89 (*Id.*) In addition, Dr. Davies's results were comparable to the stability testing Impax submitted to the FDA as representative. (Langer Tr. 1220:9-24.)

FN89. Impax's ANDA sets forth an FDA approved Stability Evaluation Protocol for determining the expiration date of Impax's ANDA product. (Davies Tr. 532:2-533:12; Langer Tr. 1218:23-1219:6; PSWTX 1141 at DAVIES2W4003605; PSWTX 555A.) If the criteria in the Stability Evaluation Protocol are met, then the expiration date will be extended. (Langer 1218:23-1219:6.)

Nor is the Court is persuaded by Impax's Dr. Chambliss's testimony that the samples Dr. Davies tested were susceptible to dissolution and aging. In his expert report, Dr. Chambliss referred to an article in *Modern Pharmaceuticals,* which states that aging is likely to affect dissolution characteristics (i.e., drug release amount over time) of a dosage form. (ITX 223 (citing ITX 414 at 187); *see also* Langer Tr. 5471:10-5472:6.) Dr. Chambliss stated that the dissolution data "shows that the decreased dissolution rate ... was due to a physical change in the dosage form" (ITX 223 at G-4), which in his opinion illustrates an "aging effect in the samples" (*id.*). However, Dr. Langer testified that the dissolution studies conducted by Dr. Davies showed that the dissolution characteristics were still within the FDA specifications.FN90 (Langer Tr. 5472:3-13.) In addition, Dr. Langer testified that the mean dissolution values obtained by Dr. Davies did not decrease as a function of storage, which suggests that contrary to Dr. Chambliss's assertion, there is no physical change in the dosage form. (Langer Tr. at 1219:18-1220:5.) The Court is not persuaded that the possibility of aging renders the samples unrepresentative.

FN90. Dr. Chambliss suggested for the first time at trial that Dr. Davies did not use the correct method to test dissolution. (Chambliss Tr. 5037:8-15.) However, he did not explain how the difference in methods is significant and, therefore, the Court gives his unsupported testimony little weight.

Accordingly, the Court finds that the samples tested by Dr. Davies are representative of Impax's ANDA product.

As to the samples that Impax tested, the Court finds that these samples are not representative of Impax's ANDA products. In April of 2004, in accordance with a request from Impax's attorneys, an Impax employee manufactured samples on a small-scale. (Ting Tr. 4843:3-7, 4845:8-13, 4846:9-11; Lin Dep. Tr. 16:20-17:21.) The small-scale production differed in several respects from Impax's ANDA procedures. (Langer Tr. 5472:14-5473:4; PSWTX 2502-7; Lin Dep. Tr. 152:11-153:10.) For example, the inlet temperatures of Lot A of the small-scale samples differed from those used in the ANDA product: the small-scale samples ranged from 52-58 (deg.)C whereas the ANDA product ranges between 70-75 (deg.)C. (Ting Tr. 4851:12-4852:5; *compare* PSWTX 2531 at I00045533 *with* PSWTX 1222 at I0003000.)

Impax relies on the testing of its small-scale samples in support of its argument that its product does not have a subcoating as claimed in the patents. However, making the product on a smaller laboratory scale could influence the factors that lead to formation of Impax's *in situ* subcoating. (Langer Tr. 5473:9, 5474:1-5475:3, PSWTX 2502-8 (quoting PSWTX 1633); *see also* PSWTX 1633A.) According to an article in *Pharmaceutical Technology* entitled "Scale-Up Considerations in the Fluid-Bed Process for Controlled-Release Products," an *in situ* subcoating formation is dependent on as many as 20 variables, including enteric coating spray rate, inlet temperature, product temperature, air volume in a fluid bed, how long and how wet the surface will be, and the moisture content. (PSWTX 1633.) Dr. Langer explained that the

changes in scale result in changes in the many variables affecting the formation of a subcoating, which makes a scaled-down manufacture unrepresentative. (Langer 5474:1-5475:3.) Impax has provided no evidence to support its assertion that these small-scale samples are representative of Impax's ANDA product. (Ting Tr. 4844:1-4845:7, 4846:20-22, 4847:5-12.) Moreover, the FDA would not recognize these laboratory litigation samples as representative of the ANDA products because the FDA requires a pilot scale that, at a minimum, is equal to one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is larger. (Langer Tr. 5473:1-8; PSWTX 2502-7.) Accordingly, the Court finds that Impax's small-scale samples are not representative of its ANDA products.FN91

FN91. Finally, just as with production of its commercial product samples, Impax delayed in producing these small-scale samples: although the samples were made in early April 2004 (Lin Dep. Tr. 69:7-13; Ting Tr. 4843:3-7), Impax did not produce them to Astra until early June 2004.

c. Claim 1(c): Enteric Coating and Enhanced Stability

Claim 1(c) of the '505 Patent requires "an outer layer disposed on said subcoating comprising an enteric coating." (PSWTX 1A 16:53-54.) Claim 1(c) of the '230 Patent requires "an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced." (PSWTX 2A 13:16-20.)

Impax's ANDA products contain an enteric coating disposed on the subcoating. (Langer Tr. 1215:10-24; PSWTX 37B; PSWTX 520B; PSWTX 578B; PSWTX 563A.) Impax's enteric coating layer includes HPMCP, which the '505 Patent teaches may be used as an enteric coating material. (Langer Tr. 1215:13-17; PSWTX 1A 4:66-67.) Impax's enteric coating has good gastric acid resistance, i.e., it does not dissolve in the stomach acid or disintegrate until it reaches the small intestine. (Langer Tr. 1290:22-1291:6.)

Through its experts, Impax argues that its product is only stable when packed with extremely large amounts of dessicant and, therefore, Plaintiffs cannot show that the alleged subcoating, or an "effective amount" of an ARC, enhances the stability of Impax's formulation. (Ting Tr. 4811:24-4812:17, 4813:24-4814:5; ITX 3465G; ITX 3465H; ITX 3465N; ITX 3465O.) However, the formulations included in the patents-in-suit may benefit from stabilization techniques that are not claimed in the patents, including the use of dessicant or, for example protection from light and heat. Having shown that Impax's product contain all of the elements of claims 1 of the '505 and '230 Patents, Plaintiffs are not required to refute Impax's assertion that its product is also stabilized through the use of dessicant.

The patents teach that the presence of an ARC and a subcoating enhances the stability of the formulation. The term "enhanced stability" refers to the intended result of a subcoating and does not require comparative testing. (Jan. 12, 2006 Order at 13-14.) Contrary to Impax's assertion, the fact that Dr. Davies did not conduct comparative testing with and without dessicant or with and without the alleged ARC (DHP) (Davies Tr. 957:5-19, 959:3-961:7) is irrelevant to a determination of infringement. Whether Plaintiffs could have performed these tests, or did perform these tests on their own product, is also irrelevant. Likewise, a finding of infringement is not precluded by the fact that accelerated stability testing on Impax's original ANDA batches, its experimental laboratory batches, the 2004 samples, and the process validation samples show degradation in the absence of dessicant. (Ting Tr. 4824:18-4829:20; *see also* Lin Dep. Tr. 36:10-38:24, 68:12-69:24, 77:18-80:25, 90:2-99:18; ITX 295; PSWTX 2539 at IMPAX00000414.) Thus, Impax's ANDA product meets claim 1(c) of the '230 Patent in that the HPMCP-salt subcoating "isolates the alkaline reacting core from the enteric coating such that the stability of the preparation is enhanced." (PSWTX 2A 13:17-20; see Davies Tr. 959:3-10.)

As demonstrated above, Impax's products meet all the limitations of claim 1 of the '505 and claim 1 of the

'230 Patent.

d. Claim 5 of the '505 Patent and Claim 6 of the '230 Patent

Claim 5 of the '505 Patent calls for "[a] preparation according to claim 1 wherein the alkaline core comprises omeprazole and pH-buffering alkaline compound rendering to the micro-environment of omeprazole a pH of 7-12." (PSWTX 1A 16:65-68.) As this Court previously found, '505 Patent claim 5 expressly requires that: (1) omeprazole be present; and (2) that the ARC result in an omeprazole micro-pH of 7-12. Astra v. Andrx, 222 F.Supp.2d at 479. Claim 6 of the '230 Patent does not materially differ from claim 5 of the '505 Patent. This claim calls for: "[a] preparation according to claim 1, wherein an alkaline core comprises the acid labile compound and a pH-buffering alkaline reacting compound which renders the micro-environment of the acid labile compound a pH of 7-12." (PSWTX 2A 14:4-8.) The proof of infringement for claim 6 of the '230 Patent is the same as that for claim 5 of the '505 Patent. (Langer Tr. 1201:9-11.)

The Court finds that the micro-environmental pH of Impax's core is between 7 and 12, and the DHP in Impax's omeprazole containing region is clearly "pH buffering." (Langer Tr. 1216:10-22.) Accordingly, Impax's products meet all the limitations of claim 5 of the '505 Patent and claim 6 of the '230 Patent.

e. Claim 6 of the '505 Patent and Claim 7 of the '230 Patent

Claim 6 of the '505 Patent calls for "[a] preparation according to claim 5 wherein the alkaline compound comprises one or more of ... sodium or potassium carbonate, phosphate or citrate." (PSWTX 1A 17:1-5.) Claim 7 of the ' 230 Patent similarly calls for "[a] preparation according to claim 6 wherein the alkaline reacting compound comprises one or more of ... sodium or potassium carbonate, phosphate or citrate." (PSWTX 2A 14:9-13.) The proof of infringement for this claim is the same as for '505 Patent claim 6. (Langer Tr. 1201:20-23.)

Impax's product contains the alkaline compound dibasic sodium phosphate, or DHP. (Langer Tr. 1216:23-1217:12; PSWTX 1258-28.) DHP is a sodium phosphate. (Langer Tr. 1217:8-9.) Accordingly, Impax's products meet all the limitations of claim 6 of the '505 Patent and claim 7 of the '230 Patent.

f. Claim 8 of the '505 Patent and Claim 10 of the '230 Patent

Claim 8 of the '505 Patent calls for "[a] preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer." (PSWTX 1A 17:13-19.) Claim 10 of the '230 Patent calls for "[a] preparation according to claim 1, wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing plasticizer." (PSWTX 2A 14:24-29.) The proof of infringement for this claim is the same as for '505 Patent claim 8. (Langer Tr. 2117:20-22.)

Impax's ANDA products include an enteric coat comprising hydroxypropyl methylcellulose phthalate. (Langer Tr. 1217:13-19; PSWTX 1258-30.) The enteric coating also contains acetyltributyl citrate, a pharmaceutically acceptable plasticizer. (Langer Tr. 1217:13-19; PSWTX 1258-30.) Accordingly, Impax's products meet all the limitations of claim 8 of the '505 Patent and claim 10 of the '230 Patent.

g. Claim 10 of the '505 Patent and Claim 13 of the '230 Patent

Claim 10 of the '505 Patent is directed to "[a] method for the treatment of gastrointestinal disease

comprising administering to a host in need of such treatment a therapeutically effective amount of a preparation according to claim 1." (PSWTX 1A 17:23-26.) Claim 13 of the '230 Patent also calls for "[a] method for the treatment of gastrointestinal disease characterized in that a preparation according to claim 1 is administered to a host in the need of such treatment in a therapeutically effective amount". (PSWTX 2A 14:42-45.) The proof of infringement for this claim is the same as for '505 Patent claim 10. (Langer Tr. 1218:12-15.) Impax's product provides a method of treatment of gastrointestinal disease by administering a therapeutically effective amount of a preparation according to claims 1 of the '230 and '505 Patents. (Langer Tr. 1217:23-1218:15; PSWTX 1212A; PSWTX 1515; PSWTX 1209A; PSWTX 1521; PSWTX 1258-32.) Prilosec is a therapeutically effective treatment for gastrointestinal disease. (PSWTX 1521.) Impax's omeprazole delayed release capsules are bioequivalent to Prilosec and identical with respect to "conditions of use, active ingredient, route of administration, dosage form, and strength." (PSWTX 1209A.) Impax's proposed package insert for its 10, 20, and 40 mg omeprazole delayed release capsules instructs in the "Indications and Usage" section that its products can be used for duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, erosive esophagitis, and pathological hypersecretory conditions. (PSWTX 1212A; PSWTX 1515.) In other words, Impax instructs patients in need of treatment for gastrointestinal disease to administer a therapeutically effective amount of its products. Impax's products therefore meet all the limitations of claim 10 of the '505 Patent and claim 13 of the '230 Patent.

h. Conclusion

Impax's 10-mg, 20-mg, and 40-mg ANDA omeprazole products infringe claims 1, 5, 6, 8, and 10 of the '505 Patent and claims 1, 6, 7, 10, and 13 of the ' 230 Patent. By filing ANDAs seeking FDA approval to engage in the commercial manufacture, use or sale of Impax's product prior to the expiration of the patents-in-suit Impax has committed acts of infringement. Impax has directly infringed the patents-in-suit by manufacturing, selling and offering for sale Impax's FDA-approved omeprazole product; and Impax has induced and contributed to infringement by others who administer or use Impax's product.

III. *Invalidity*

Apotex, Impax, and Mylan/Esteve raise several invalidity counter-claims and defenses to the '505 and '230 Patents. (*See* Apotex Answer & Countercl. para.para. 5-19, 53-68 (Countercl.); Impax Answer & Countercl. para.para. *34*-35, 177-80, 186-89; Mylan Answer & Countercl. para.para. 41-42, 148-53; Esteve Answer & Countercl. para.para. 80-81, 190-95.) Collectively, these Defendants claim that the Patents are invalid: (1) under 35 U.S.C. s. 112, para. 1, for failing to satisfy that provision's best mode, enablement and/or written description requirements; (2) under 35 U.S.C. s. 102(b), for being in the public use or described in a printed publication more than one year prior to the date of the application for patent in the United States; and (3) under 35 U.S.C. s. 103(a), for obviousness. For the following reasons, these invalidity claims are denied.

A. *Presumption of Validity*

As a general matter, every patent is presumed valid, and each claim of any patent is presumed valid irrespective of the validity of any other claim. *See* 35 U.S.C. s. 282 (2000); Apple Computer, Inc. v. Articulate Sys., Inc., 234 F.3d 14, 24 (Fed.Cir.2000); Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 446 (Fed.Cir.1986). Given this statutory presumption, a patent challenger has the burden of proving invalidity by clear and convincing evidence. Robotic Vision Sys. Inc. v. View Eng'g Inc., 189 F.3d 1370, 1377 (Fed.Cir.1999); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1375 (Fed.Cir.1986). "Clear and convincing" evidence is that which gives the finder of fact "an abiding conviction that the truth of [the proponent's] factual contentions [is] 'highly probable'." Colorado v. New Mexico, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984) (citation omitted). The burden of showing invalidity of each claim individually and by clear and convincing evidence rests on Defendants.

Am. Hoist & Derrick Co. v. Sowa & Sons, 725 F.2d 1350, 1358-60 (Fed.Cir.1984).

[34] [35] [36] [37] When, as here, a party asserts invalidity of a patent and bases that assertion on evidence, including prior art references, that was before the patent examiner when he allowed the patent claims, the difficulty of overcoming the presumption of validity is greater than it would be if the evidence relied on was not before the examiner. *See* Am. Hoist & Derrick Co., 725 F.2d at 1358-60. The party attacking validity has the burden of overcoming the deference that is due to a governmental agency presumed to have done its job properly. Id. at 1359. In determining whether to allow the application, the patent examiner is also presumed to have considered each reference that was before him individually and in combination with every other reference before him. In re Portola Packaging, Inc., 110 F.3d 786, 790 (Fed.Cir.1997). Deference must be given to the findings of fact of the USPTO on the issues of validity, identity of invention, and enablement with respect to the prior art that was before the patent examiner. *See* Am. Hoist, 725 F.2d at 1359-60. References are not material to patentability if they are merely cumulative of references that were already before the examiner. Mentor H/S, Inc. v. Medical Device Alliance 244 F.3d 1365, 1378 (Fed.Cir.2001) (citing Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1574-75 (Fed.Cir.1997)).

B. 35 U.S.C. s. 112

The first paragraph of 35 U.S.C. s. 112 provides:

The [patent] specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. s. 112, para. 1. This provision distills into three related, yet independent, requirements. The patent specification must: (1) provide a written description of the invention; (2) "enable" another to use the invention; and (3) provide the "best mode" contemplated for the invention. Contrary to Defendants' claims, the Court finds that the specifications of the '505 and '230 Patents satisfy these requirements.

1. The Written Description and Enablement Requirements

[38] Impax claims that the '505 and '230 Patents are invalid on the grounds that the patents' specifications do not satisfy the "written description" and "enablement" requirements under 35 U.S.C. s. 112, para. 1, with respect to Plaintiffs' claim to *in situ* subcoatings. The Court disagrees.

The written description requirement exists "to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *See* Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345 (Fed.Cir.2000). The written description requirement is broader than merely explaining how to make and use the invention; the applicant must also convey with reasonable clarity to those of skill in the art that, as of the filing date, he or she was "in possession" of the invention. Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323 (Fed.Cir.2000) (citation omitted). To do so, the patent specification must "describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention.' " Eli Lilly, 119 F.3d at 1566 (citation omitted).

Impax's written description challenge is meritless. Contrary to Impax's suggestion, the Patents do not "teach away" from use of an *in situ* subcoating. Indeed, in the First Wave, this Court held in the context of construing the Patents' term "disposed on," that "the product claims are not limited in the manner in which the product is made and so would include products in which the subcoating was formed *in situ*." Astra v. Andrx, 222 F.Supp.2d at 469-70.

Impax's enablement challenge is equally meritless. The "enablement" requirement is met if the description enables a person skilled in the art of making and using *any mode* of the invention without having to undertake undue experimentation. Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1361 (Fed.Cir.1998); Warner-Lambert Co. v. Teva Pharms. USA, Inc., 418 F.3d 1326, 1337 (Fed.Cir.2005). Here, the patents at issue describe at least one mode of making the claimed inventions. These processes are described generally (*see* PSWTX 1A 4:31-35, PSWTX 2A 9:26-30),FN92 and then specifically with reference to each example listed in the '505 and ' 230 Patents (*see* PSWTX 1A 6:28-12:36; PSWTX 2A 10:66-12:68).

FN92. Both the '505 and '230 Patents provide that the "separating layer(s) can be applied to the cores-pellets or tablets-by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution." (PSWTX 1A 4:31-35, PSWTX 2A 9:26-30.)

Accordingly, Impax's written description and enablement challenges fail.

2. Best Mode

Apotex alleges that the '505 and '230 Patents are invalid under 35 U.S.C. s. 112, para. 1, on the ground that the patent specifications fail to disclose Plaintiffs' manufacturing process of micronizing omeprazole to 2.5 m^2/g-a process that Apotex believes the inventors considered to be the best mode of carrying out the patents' claimed inventions. Apotex has failed to present clear and convincing evidence that the patents are invalid on this basis. To be valid, a patent specification "must set forth the best mode contemplated by the inventor for carrying out his invention." 35 U.S.C. s. 112, para. 1. The best mode requirement is intended to "restrain inventors from applying for patents while at the same time concealing from the public preferred embodiments of their inventions which they have in fact conceived." In re Gay, 50 C.C.P.A. 725, 309 F.2d 769, 772 (Cust. & Pat.App.1962).

[39] The test for whether a best mode exists involves a two-prong factual inquiry. *See* High Concrete Structures, Inc. v. New Enter. Stone & Lime Co., 377 F.3d 1379, 1382 (Fed.Cir.2004). "The first prong is subjective, focusing on the inventor's state of mind at the time he filed the patent application, and asks whether the inventor considered a particular mode of practicing the invention to be superior to all other modes at the time of filing." FN93 *Teleflex,* 299 F.3d at 1330 (citing *N.* Telecom Ltd. v. Samsung Elecs. Co., 215 F.3d 1281, 1286 (Fed.Cir.2000)). "The second prong is objective and asks whether the inventor adequately disclosed the mode he considered to be superior." *Id.*

FN93. This prong is not satisfied unless the inventor both "knew of and concealed a better mode than was disclosed for making and using the claimed invention." *Cardiac Pacemakers, Inc.,* 381 F.3d at 1378. However, "specific intent to deceive is not a required element of the best mode defense." Graco, Inc. v. Binks Mfg. Co., 60 F.3d 785, 789-90 (Fed.Cir.1995). Thus, "[a]ny concealment of the best mode, whether accidental or intentional, is a violation of the best mode requirement." DiscoVision Assocs. v. Disc Mfg., Inc., 25 F.Supp.2d 301, 347 (D.Del.1998).

As noted above, the allegedly undisclosed best mode at issue here pertains to the micronization of omeprazole in a core to a size of 2.5 m^2/g. There is no dispute that micronization to this size was a manufacturing specification in Plaintiffs' Phase III formulation, and was ultimately utilized in the commercialized 20-mg Prilosec(C) dosage form. (Pilbrant Dep. Tr. 217:19-219:9, 312:19-313:22, Sept. 10,

2003.) There also is no dispute that the patents do not disclose 2.5 m^2/g micronization as a manufacturing specification, either expressly or by incorporation of any prior literature or art. Rather, the dispute focuses on the subjective first prong of the best mode inquiry; namely, whether the inventors considered micronization to 2.5 m^2/g to be the best mode of carrying out the inventions claimed in the '505 and '230 Patents.

In support of its best mode claim, Apotex relies on: (1) excerpts from deposition testimony of Dr. Pilbrant; (2) excerpts from pre-application reports written by two of the claimed inventors, Drs. Lovgren and Pilbrant; and (3) the fact that Plaintiffs micronized omeprazole in their commercialized formulation. For the reasons explained below, the Court finds that this evidence does not establish that 2.5 m^2/g micronized omeprazole was a best mode. Rather, 2.5 m^2/g micronization was a nonessential manufacturing preference relating to a particular (and non-exhaustive) formulation within the patents' many possible embodiments, and beyond the scope of the claimed invention.

At most, Dr. Pilbrant's deposition testimony establishes that micronization of omeprazole to 2.5 m^2/g was "suitable" for the Phase III formulation, in part because the process made it "easier" to get the required properties of that particular formulation. (*See* Pilbrant Dep. Tr. 217:19-219:9, Sept. 10, 2003.) FN94 While micronizationof omeprazole to 2.5 m^2/g may have represented the "best manufacturing process" for "this particular" Phase III dosage form (*see* Pilbrant Dep. Tr. 312:19-313:22, Sept. 11, 2003), it is not necessarily the best mode of carrying out the many alternative embodiments of the claimed invention. Thus, contrary to Apotex's assertion, Dr. Pilbrant's testimony does not establish by clear and convincing evidence that he (or any other inventor) contemplated that micronized omeprazole was a best mode.

FN94. Dr. Pilbrant testified during his deposition, in relevant part, as follows:
Q: Why did you choose that particular [2.5 m^2/g] particle size?

A: It was suitable to be used in the particular formulation we have.

Q: Well, could you have used other particle sizes?

A: Yes.

Q: Why did you choose this particular one?

A: Because it suited the purpose being included in the dosage form that we have on the market.

. . . . .

Q: .... Based on the studies that were done at Astra, did they come to a conclusion as what the preferred way was to size the omeprazole for purposes of the patent?

. . . . .

A: For the purpose of the patent, taking into account the different examples, I don't think there is necessary [sic] any preferred particle size.

(Pilbrant Dep. Tr. 217:19-219:9, Sept. 10, 2003) (objections omitted).

Q. Okay. So at some point in time, it was determined that it-and it was prior to 1986 apparently that you wanted to have the omeprazole milled to a surface area of at least 2.5 square meters (sic, meters squared) per gram?

. . . . .

A. I would say for that particular product for which we applied for marketing approval, we wanted to have omeprazole milled to a surface area of 2.5 square meters per gram (sic) because that gave us the best manufacturing process for this particular single formulation.

. . . . .

Q. Let me ask you this: Did you know of a better particle size distribution for the omeprazole to be used in the formulation for the Phase III for a marketable product of the omeprazole?

A. For that particular dosage form as we used in the Phase III formulation and we aimed to have it on the market for that particular single dosage form, we found that a particle size of 2.5 grams (sic) made it easier to get the required properties of the final dosage form and that a particular manufacturing process for that particular dosage form ran better if you had micronized omeprazole.

(Pilbrant Dep. Tr. 312:19-313:22, Sept. 11, 2003) (objections omitted).
Excerpts from Dr. Lovgren's 1984 report (PSWTX 2855) and Dr. Pilbrant's 1986 report (PSWTX 2856) prove to be no more availing. Indeed, Dr. L ovgren's report notes "alternative way[s]" to reduce the amount of residual solvents, of which 2.5 m^2/g micronization was one such method. (*See* PSWTX 2855 at 9549436.) FN95 While Dr. Lovgren acknowledged that micronization resulted in "good absorption characteristics" (PSWTX 2855 at 9549437), FN96 there is no indication that he believed micronization afforded the best absorption, or that other processing methods would not be equally suited. Likewise, Dr. Pilbrant's subsequent recognition that micronization of omeprazole could "achieve[ ]" "adequate bioavailability" (PSWTX 2856 at 9872563),FN97 falls far short of demonstrating that 2.5 m^2/g micronizationprovided the best mode of achieving bioavailability.

FN95. In Dr. Lovgren's report entitled "Preliminary Process Report Omeprazole Capsules, 20 mg," he notes in his "Comments on Manufacture, Omeprazole raw material," that:
To improve the stability of the drug the amount of residual solvents must be reduced to levels as low as possible. This is achieved in wet-milling operation in the production of uncoated granules. An alternative way to reduce the amount of residual solvents is to dry-mill the substance in an air jet mill down to a particle size corresponding to a surface area of 2.5 m^2/g. This micronized substance [micronized omeprazole] has a much better stability (18 months at refrigerated temperature) due to reduced amount of residual solvent.

(PSWTX 2855 at 9549436.)
FN96. Dr. Lovgren's stated in his report, in a section entitled "Omeprazole Uncoated Granules," that: "In order to obtain good absorption characteristics of the drug the omeprazole substance must be micronized." (PSWTX 2855 at 9549437.)

FN97. In Dr. Pilbrant's 1986 report entitled "Expert Report on Omeprazole Capsules 20 mg," Dr. Pilbrant stated in a section devoted to "Production of omeprazole pellet cores," that: "Results from studies in healthy volunteers showed that an adequate bioavailability was obtained when the surface area of the omeprazole substance used in the formulation was greater than 2.5 m^2/g." (PSWTX 2856 at 9872544.) Dr. Pilbrant further stated in a section of the Conclusion entitled "Dosage form," that: "A rapid release of omeprazole in the small intestine is achieved by using micronized substance [i.e., micronized omeprazole]." (PSWTX 2856 at 9872563.)

Further, Plaintiffs' use of 2.5 m^2/g micronized omeprazole in its 20-mg commercial dosage form is insufficient evidence that the inventors considered this a best mode of the invention. *See, e.g., Teleflex,* 299 F.3d at 1329 (finding that commercial embodiment was insufficient evidence of best mode); Fonar Corp. v. General Elec. Co., 107 F.3d 1543, 1550 (Fed.Cir.1997) (same); Minco, Inc. v. Combustion Engineering, Inc., 95 F.3d 1109, 1116 (Fed.Cir.1996) (same). *But cf. Dana Corp.,* 860 F.2d at 418 (best mode violation evidenced in part by commercial embodiment, considered in conjunction with other probative and persuasive evidence). Upon consideration of the body of evidence discussed above, the Court finds that Apotex has failed to meet its burden of proving that micronization of omeprazole to 2.5 m^2/g was considered by the inventors to be the best mode for processing omeprazole.

[40] In any event, disclosure of Plaintiffs' preference for using 2.5 m^2/g micronized omeprazole in its Phase III and commercial dosage form was not required because this process condition does not fall within the scope of the claimed inventions in the '505 and '230 Patents. In general, "[s]ubject matter that is not part of the invention that is claimed need not be included in the specification, and thus is not subject to the best mode requirement." Cardiac Pacemakers Inc. v. St. Jude Medical, Inc., 381 F.3d 1371, 1378-79 (Fed.Cir.2004); *accord* Teleflex, Inc. v. Ficosa N. America Corp., 299 F.3d 1313, 1331 (Fed.Cir.2002) (collecting cases); Bayer AG v. Schein Pharms., Inc., 301 F.3d 1306, 1315 (Fed.Cir.2002); *see also* Eli Lilly & Co. v. Barr Lab., Inc., 251 F.3d 955, 963 (2001) ("[T]he extent of information that an inventor must disclose depends on the scope of the claimed invention."). While claim 1 of the '505 Patent calls for a core that includes omeprazole, neither the particle size nor the manufacturing process for the omeprazole is part of the subject matter of the claimed limitations. (*See* PSWTX 1A at 16:42-54.) Moreover, the core described in claim 1 of the '230 Patent does not even require omeprazole, much less require a process for preparing it. (*See* PSWTX 2A at 13:1-20.)

The Court rejects Apotex's assertion that disclosure of micronization of omeprazole to 2.5 m^2/g-even if not strictly within the bounds of the claims-was required given the strong relationship between this manufacturing process and the invention. *See* Bayer, 301 F.3d at 1319 (best mode requirement is violated if "the patentee failed to disclose aspects of making or using the claimed invention and the undisclosed matter materially affected the properties of the claimed invention"). While the Federal Circuit has recognized such an exception where the undisclosed best mode was "necessary to satisfactory performance" of the invention, *see* Dana Corp. v. IPC Ltd. P'ship, 860 F.2d 415, 420 (Fed.Cir.1988); *accord* Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1537 (Fed.Cir.1987), was "critical to the production" of the invention, *see* Nobelpharma AB v. Implant Innovations, Inc., 141 F.3d 1059, 1065 (Fed.Cir.1998); *accord* Great N. Corp. v. Henry Molded Prods., Inc., 94 F.3d 1569, 1572 (Fed.Cir.1996), or was "essential to improving" the invention, *see* United States Gypsum Co. v. Nat'l Gypsum Co., 74 F.3d 1209, 1213 (Fed.Cir.1996), Apotex has not proven any of those to be the case here.

While stability and bioavailability of the active ingredient are clearly related to the intended purposes of the claimed inventions, the evidence relied upon by Apotex (discussed *supra*) does not demonstrate that micronization of omeprazole to 2.5 m^2/g was necessary or critical to obtaining these desired characteristics. *See, e.g., Applied Med. Resources,* 147 F.3d at 1377-78 (no best mode violation where preferred lubricant for seal was not "necessary" to the functioning of the claimed inventions). Indeed, Dr. Pilbrant testified that 2.5 m^2/g micronized omeprazole was not selected by Plaintiffs for stability purposes, but rather because micronizing omeprazole made it easier to get a good dissolution rate. (Pilbrant Dep. Tr. 229:21-230:3, Sept. 10, 2003; Pilbrant Dep. Tr. 313:9-22, Sept. 11, 2003.) Moreover, Drs. Pilbrant and Lovgren testified that 2.5 m^2/g micronized omeprazole also does not necessarily improve the bioavailability of omeprazole in the patented formulation. (*See, e.g.,* Pilbrant Dep. Tr. 230:4-6, Sept. 10, 2003; Lovgren Dep. Tr. 540:1-12, July 2, 3003); *see also* Bayer, 301 F.3d at 1320-23 (no best mode violation where "preferred way" of making intermediate starting materials for chemical compound "had no material effect on the properties of the claimed ... end product").

Accordingly, the '505 and '230 Patents are not invalid under Section 112, para. 1, for failure to disclose a best mode of carrying out the claimed inventions.

C. *Public Use*

[41] Impax separately claims that the '505 and '230 Patents are invalid under 35 U.S.C. s. 102(b), which renders a patent invalid if "the invention was ... in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. s. 102(b); *see also* In re Katz, 687 F.2d 450, 454 (Cust. & Pat.App.1982) (inventor's own work may be used to invalidate patents protecting his own later inventive activities if he places it on sale or uses it publicly more than a year before filing). There is no dispute that the critical date for this analysis is April 20, 1986, as both the '505 and '230 Patent applications were filed one year later on April 20, 1987. (PSWTX 1A; PSWTX 2A.)

[42] An inventor's experimentation may negate either the "invention" or "public use" requirements under s. 102(b), thereby defeating an invalidity challenge under that statute. *See* Invitrogen Corp. v. Biocrest Mfg., L.P., 424 F.3d 1374, 1379-1380 (Fed.Cir.2005); EZ Dock v. Schafer Sys. Inc., 276 F.3d 1347, 1351 (Fed.Cir.2002) ("[E]vidence of experimental use ... operates to negate application of section 102(b)."). Use is generally considered experimental, and thus beyond the scope of s. 102(b)'s validity bar, if the use is to "perfect[ ] or complet[e] an invention to the point of determining that it will work for its intended purpose." RCA Corp. v. Data Gen. Corp., 887 F.2d 1056, 1061 (Fed.Cir.1989); *accord* EZ Dock, 276 F.3d at 1352. Because the experimental use doctrine is not an exception to the public use bar, but rather negates its applicability, the challenging party bears the burden of overcoming a defense based on experimental use. *See* EZ Dock, 276 F.3d at 1351.

1. Ready for Patenting

[43] The "invention" requirement under 35 U.S.C. s. 102(b) is not satisfied until the invention is "ready for patenting." Pfaff v. Wells Elecs., 525 U.S. 55, 67-68, 119 S.Ct. 304, 142 L.Ed.2d 261 (1998); *see also* Invitrogen, 424 F.3d at 1379. An invention is deemed ready for patenting if it had been "reduce[ed] to practice" or the inventor had prepared descriptions of the invention that were sufficiently specific "to enable a person skilled in the art to practice the invention." Pfaff, 525 U.S. at 67-68, 119 S.Ct. 304; *see also* Invitrogen, 424 F.3d at 1379.

While Plaintiffs assert that the claimed inventions were still under experimentation and not ready for patenting as of the critical date, April 20, 1986, Impax contends otherwise. Specifically, Impax claims that: (1) the bioavailability of omeprazole in Plaintiffs' pharmaceutical Phase III formulation had been demonstrated and reduced to practice in the preceding Phase II formulation (*see* ITX-302 at SWN0000624; Carlsson Dep. Tr. 81:6-82:6, 82:25-83:10, Aug. 6, 2003); FN98 and (2) the stability of the Phase III formulations was sufficiently demonstrated prior to the critical date. In support of its claims, Impax relies on the in-house reports of Dr. Pilbrant (ITX 365) and Dr. Lovgren (ITX 371), which indicate that the Phase II and Phase III formulations were bioequivalent in "healthy volunteers" (ITX 365 at A00031469), and that the Phase III formulations were tested and found to have "good stability" before the critical date (ITX at A00031489; ITX 371 at A0068189).

FN98. The Phase II formulation was the predecessor to the formulation ultimately adopted by Plaintiffs in the Phase III formulation. "The Phase II formulation consisted of a core containing omeprazole mixed together with some excipients and alkaline reacting compounds ('ARCs') and an enteric coating that covered the core and included hydroxypropyl methylcellulose phthalate ('HPMCP')." Astra v. Andrx, 222 F.Supp.2d at 436 (citing Lovgren Dep. Tr. 1747:22-1748:6, Jan. 2, 2002.) This formulation had inferior gastric acid resistance, resulting in too much of the omeprazole degrading before it reached the small intestine (*see id.*), and poor long-term storage stability, (*see id.;* Cederberg Dep. Tr. 308:22-309:5, Sept. 17, 2003). To rectify these shortcomings, Plaintiffs adopted the Phase III formulation in or around 1983, *see* Carlsson Dep. Tr. 477:16-22, Aug. 8, 2003, which added a water soluble subcoating. Andrx, 222 F.Supp.2d at 437. "The Phase III formulation is the same as the one that Astra ultimately has used on the market, except that the amount of enteric-coating polymer is slightly increased in the market formulation." *Id.*

Contrary to Impax's assertion, however, reduction to practice was not achieved simply upon conception and initial testing of a subcoated omeprazole formulation that the inventors believed *might* solve the twin problems of in vivo stability and long-term storage. Rather, the Phase III formulation still required extensive clinical and real-time stability testing to determine whether it could treat gastric acid diseases safely and effectively. (*See* Carlsson Dep. Tr. 536:9-537:6, Aug. 8, 2003.) To this end, Plaintiffs commissioned four clinical trials of the Phase III formulation prior to the critical date.FN99

FN99. Specifically, Trial I-403 was conducted primarily to evaluate the long-term efficacy and safety of omeprazole in patients with a rare and often fatal gastric disease called Zollinger-Ellison syndrome. (ITX 0317 at SWN202779, 202782.) Trial 499 was an open-label study to evaluate the use of omeprazole in patients with Zollinger-Ellison syndrome and other hypersecretory states resistant or intolerant to H2-receptor antagonists. (ITX 0310 at SWN18365.) Protocol 1 was a double-blind study that purportedly evaluated the safety, efficacy, and tolerability of a 20-mg daily dose of omeprazole-as compared to a placebo-in patients with acute duodenal ulcers. (ITX 0309 at SWN17952, 17956.) Finally, Protocol 2 was a double-blind study to evaluate the safety and effects of a 20-mg daily dose of Omeprazole-as compared to ranitidine-on the healing of acute duodenal ulcers. (ITX 6279 at SWN18091.) Plaintiffs' licensee-Merck, Sharp & Dohme Research Laboratories ("Merck")-conducted all of these United States based trials, with the

exception of Trial I-403, which was conducted by one of Plaintiffs' subsidiaries (Hassle). (*See* ITX 309; ITX 310; PSWTX 1900; ITX 6279.)

The clinical study reports for three of these trials were not completed until after the critical date. (ITX 0310 at SWN18358 (Trial 499 report dated November 24, 1987); ITX 0309 at SWN17952 (Protocol 1 reports dated October 30, 1987); ITX 6279 at SWN18083 (Protocol 2 study report dated November 19, 1987).) Dr. Carlsson testified that it is only after all the information is collected and results are determinedfrom the Phase III clinical trials and the results are discussed with the FDA can it then be determined that the safety and efficacy has been documented. (Carlsson Dep. Tr. 547:11-22, Aug. 8, 2003.)

Impax has not met its heavy burden of demonstrating by clear and convincing evidence that the claimed inventions had been reduced to practice during the clinical trials of the Phase III formulation and prior to the critical date. Indeed, the trials demonstrate the opposite; namely, that Plaintiffs were still in the process of determining whether the Phase III formulation could safely and effectively be used as a "method of treatment of gastrointestinal disease." (PSWTX 1A 16:42-54, 17:23-26; PSWTX 2A 13:1-20, 14:42-45.) Because critically relevant experimentation was still ongoing and data was still being analyzed as of the critical date, the Court finds that Impax has failed to demonstrate that the inventions were ready for patenting prior to the critical date, April 20, 1986.

2. In Public Use

Impax's Section 102 claim also fails for the independent reason that Plaintiffs' invention was not in public use prior to the April 20, 1986 critical date. To qualify as "in public use" under s. 102(b), an invention must have been either "accessible to the public[ ]" or "commercially exploited," as evidenced by whether the use was for experimentation; the nature of the activity that occurred in public; public access to the use; and confidentiality obligations imposed on members of the public who observed the use. Invitrogen, 424 F.3d at 1380; *accord* Egbert v. Lippmann, 104 U.S. 333, 336, 14 Otto 333, 26 L.Ed. 755 (1881) (to qualify as "public," a use must occur without any "limitation or restriction, or injunction of secrecy."); Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 550 (Fed.Cir.1990) (use is not likely to be deemed "public" if the inventor has done nothing to make the public reasonably believe that the invention is in the public domain); *cf.* Netscape Comm. Corp. v. Konrad, 295 F.3d 1315, 1321 (Fed.Cir.2002) (claimed invention shown to computer personnel who could easily demonstrate the invention to others was a public use).

a. Public Accessibility

Although Plaintiffs' clinical trials resulted in some public disclosure of the inventions at issue, such disclosure was the result of experimental use, and is thus beyond s. 102's public use bar. The Court rejects Impax's claim that the experimental use doctrine does not apply.

First, Impax claims that the doctrine does not apply because the trials were aimed at testing attributes of the Phase III formulation outside the limitations of the '505 and '230 Patents. While the clinical trials tested the Phase III formulation's pharmacokinetics and bioavailability, safety and efficacy, dosing schedules, and utility in treating certain gastric disorders, such testing was within the '505 and '230 Patents' claims expressly directed to a "method of treatment of gastrointestinal disease" by administering the subcoated formulations. (*See* PSWTX 1A 16:42-54, 17:23-26; PSWTX 2A 13:1-20, 14:42-45.) Thus, a sufficient nexus exists between the claimed inventions and the experimental trials.

Second, and contrary to Impax's assertion, the trials were sufficiently controlled and monitored. *See* Lough v. Brunswick Corp., 86 F.3d 1113, 1120 (Fed.Cir.1996) (In determining whether a use is experimental, the "factor of control is critically important, because, if the inventor has no control over the alleged

experiments, he is not experimenting. If he does not inquire about the testing or receive reports concerning the results, similarly, he is not experimenting."). Specifically, clinical investigatorswere required to monitor the amount of the drug administered (ITX 0309 at SWN0017966; ITX 6279 at SWN18185-86), and patients were required to keep diaries recording their gastrointestinal pain as well as how many tablets they had taken (ITX 6279 at SWN18185; ITX 0309 at SWN17964). These diaries were read by clinical investigators who would then dispense more drugs if the patient continued to participate in the trial. (ITX 0309 at SWN18045; ITX 0310 at SWN18371.) These protocols comported with FDA regulations requiring investigators to strictly control the administration and disposition of the drugs, including the dates, quantity and use by the subjects. *See* 21 C.F.R. s. 312.61 (2005). Further, the patients who participated in the clinical trials were also carefully selected.FN100 The restricted patient population is evidence that the experiments were sufficiently controlled, such that that the public would not reasonably believe that the invention was in the public domain. *See* Manville Sales Corp., 917 F.2d at 550.

FN100. Protocol 1 and Protocol 2 selected only patients who had a primary diagnosis of acute duodenal ulcer documented by endoscopy (ITX 0309 at SWN17957 (Protocol 1); ITX 6279 at SWN18091 (Protocol 2)), and were not otherwise excludable (ITX 0309 at SWN17957-17959; ITX 6279 at SWN18091-18093). Trial 403 was available only to patients diagnosed with Zollinger-Ellison syndrome having elevated serum gastrin concentration and a certain minimum base levels of gastric acid secretion, depending on whether the patient previously had surgery. (ITX 0317 at SWN202782.) Trial 499 was available only to patients with a diagnosis of Zollinger-Ellison Syndrome or other hypersecretory states resistant to H2-receptor antagonists, and could nevertheless be excluded on other grounds. (ITX 0310 at SWN18365 (exclusion for pregnancy, late start, anatomic impediment to endoscopy).)

Equally meritless is Impax's claim that the inventions were not kept sufficiently confidential. All information and communication between Plaintiffs and Merck (which conducted some of the trials) was confidential. (Lovgren Dep. Tr. 175:13-16, 185:22-186:12, Feb. 3, 2004.) Moreover, all of the clinical investigators were told that the information given to them was confidential in nature (ITX 0310 at SWN18412; Carlsson Dep. Tr. 543:6-14, Aug. 8, 2003), and were required to sign protocols which mandated that investigators maintain that confidentiality (ITX 0310 at SWN0018412; ITX 6279 at SWN18194).

While Impax tries to make much of the fact that patients were not required to sign confidentiality agreements, the lack of a confidentiality agreement is not dispositive as a matter of law, especially where Impax has come forth with no evidence to demonstrate what material confidential information the patients were privy to. *See Allied Colloids,* 64 F.3d at 1576. For example, Impax has not claimed, much less demonstrated, that the patients were cognizant of the nature and processing methods of the formulations they were provided. (Cederberg Dep. Tr. 354:10:355:23, July 17, 2003.) Neither the clinical investigators nor the informed consent forms provided to the patients disclosed specific information relating to the structure of the formulation. (Cederberg Dep. Tr. 354:10:355:23; PSWTX 1901; ITX 6279 at SWN18198-99.) Moreover, while Impax suggests that patients could have disseminated the medicine to others, Impax has provided no evidence that the patients did anything with the medication other than take it as directed, under the supervision of the clinical investigators. *See* Bernhardt, L.L.C. v. Collezione Europa USA, Inc., 386 F.3d 1371, 1381 (Fed.Cir.2004) (stating that confidentiality agreements were unnecessary to permit sufficient control over the invention by the inventors when access to the invention was tightly controlled and there was no effective means for other parties to divulge the designs that they viewed).

b. Commercial Exploitation

Moreover, contrary to Impax's assertion, there simply is no evidence that Plaintiffs or its licensees commercially exploited the invention through the clinical trials. The relatively few patients in these studies did not pay for the medication they received. (Carlsson Dep. Tr. 543:15-17, Aug. 8, 2003.) Nor is there any

evidence that Plaintiffs were using the trials for the purpose of testing the market. Rather, Impax merely theorizes that the trials constitute invalidating commercial exploitation, insofar as the trials were a means of obtaining the FDA approval required to enter into the United States market. The Court rejects this proposition.

Any experiments toward the development of an invention that is ultimately sold are commercially beneficial or advantageous in retrospect. When a pharmaceutical company tests a formulation in clinical trials, it does not know whether the trials will be successful or enable it to file an application for FDA approval. (*See* Cederberg Dep. Tr. at 356:12-357:13.) Clinical trial testing is uncertain and many drugs and formulations fail, even after successful prior trials. Even after an FDA application is filed, there is no assurance that approval will be granted. Impax's proposed theory, if accepted, would unduly force the hand of inventors of new pharmaceutical formulations to file for patents prior to sufficiently testing the safety and efficacy of the formulation. There is simply nothing in the patent law or its underlying policy which requires or supports this.

Contrary to Impax's assertion, 35 U.S.C. s. 156 does not change the analysis or result. Section 156 provides a specific procedure for extending a patent's protection for the regulatory review period. Section 156 was designed, in part, "to accommodate the delay caused by the FDA's testing process," SmithKline Beecham Consumer Healthcare, LP v. Watson Pharm., Inc., 211 F.3d 21, 28 n. 4 (2d Cir.2000), and to create an incentive for increased expenditures for research and development of certain products that are subject to pre-market government approval, *see* Pfizer Inc. v. Dr. Reddy's Labs., 359 F.3d 1361, 1364 (Fed.Cir.2004) (citing H.R.Rep. No. 98-857, pt. 1, at 15 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2670).

Nothing in s. 156 itself, or in the legislative history behind it, suggests that Congress intended to displace the experimental safe-harbor that otherwise exists under s. 102(b)'s public use law. Nor would s. 156 be rendered "redundant and utterly meaningless," as Impax claims, if inventors could both experiment with formulations prior to patenting and still receive an extension of the patent time under the statute. Section 156 is intended to provide a limited incentive to pursue commercialization of certain regulated products by extending the term of an already issued patent, *see* Pfizer Inc., 359 F.3d at 1364, whereas the public use doctrine of s. 102(b) creates an incentive to file patent applications soon after efforts to commercialize the invention are begun, *see* TP Labs., Inc. v. Prof'l Positioners, Inc., 724 F.2d 965, 968 (Fed.Cir.1984). These statutory provisions are if anything complementary, not redundant.

Lastly, the Court rejects Impax's argument that section 102(b)'s bar was triggered by a "sale of" Plaintiffs' inventions to Merck, its licensee. As the Federal Circuit explained: "An assignment or sale of the rights in the invention and potential patent rights is not a sale of 'the invention' within the meaning of section 102(b)." Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1267 (Fed.Cir.1986). Such a result comports with the policies underlying the on sale bar ... and with the business realities ordinarily surrounding a corporation's prosecution of patent applications for inventors .... *Id*. Impax has simply come forth with no persuasive evidence that Merck was anything other than Plaintiffs' licensee.

Thus, Impax has failed to show that Plaintiffs sold or otherwise commercially exploited its invention prior to the critical date. Accordingly, Impax's public use claim fails in its entirety.

D. *Anticipation Under* 35 U.S.C. s. 102(b)

[44] Impax argues that Plaintiffs' European Patent Application No. 0 124 495 A2 (the "'495 Patent") renders claims 1, 5, and 6 of the '505 Patent and claims 1, 6, 7, 10, and 13 of the '230 Patent invalid for lack of novelty under 35 U.S.C. s. 102(b). Impax further asserts that U.S Patent No. 2,991,226 (the "'226 Patent") and Shin-Etsu's JP 59-20219 (the "'219 Patent") each render claims 1, 6, 7, 10, and 13 of the '230 Patent invalid for lack of novelty under s. 102(b). Apotex argues that the '226 Patent renders claims 1, 6, and 7 of

the '230 Patent invalid for lack of novelty and that the EP 0 122 815 A1 (the "'815 Application") and U.S. Patent No. 4,470,980 (the "'980 Patent") each render claim 1 of the '230 Patent invalid for lack of novelty. Finally, Mylan/Esteve argues that claims 3, 4, 7, 11, and 14 of the '505 Patent and claims 8, 9, 12, and 15 of the '230 Patent are rendered anticipated by various prior art references.FN101

FN101. Mylan/Esteve also asserts that these claims are invalid for obviousness, as discussed infra.

1. Applicable Law

[45] A patent may not issue, or is rendered invalid as anticipated, where the claimed invention "was patented or described in a printed publication in this or a foreign country ... more than one year prior to the date of the application for patent in the United States." 35 U.S.C. s. 102(b). Such publications are referred to as "prior art." *See, e.g.,* Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1376 (Fed.Cir.2003). It is well settled that if a single prior art reference discloses each and every limitation set forth in a claim, or if any limitation not expressly disclosed is necessarily inherent in such reference, the claim is invalid. *See, e.g.,* Id. at 1377; In re Schreiber, 128 F.3d 1473, 1477 (Fed.Cir.1997). Under these circumstances, the invention is said to be "anticipated" by the prior art, and any claim purporting to patent the invention is deemed invalid. *See* Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347 (Fed.Cir.1999) (citing Titanium Metals Corp. v. Banner, 778 F.2d 775, 781 (Fed.Cir.1985)).

[46] [47] To anticipate a claim in a formulation patent, a prior art reference must have placed the claimed invention "in the possession of the public" more than one year before the date of the patent application. Eli Lilly & Co. v. Zenith Goldline Pharms. Inc., 471 F.3d 1369, 1375 (Fed.Cir.2006) (citing In re Brown, 51 C.C.P.A. 1254, 329 F.2d 1006, 1011 (Cust. & Pat.App.1964)); *see also* 35 U.S.C. s. 102(b). An invention is placed "in the possession of the public" only where (1) the reference "describes" the claimed invention-the "identity of invention" requirement-such that (2) a person possessing ordinary skill in the art would have been able to make it as of that time based on his own knowledge and the teaching of the publication-the "enablement" requirement. *See* In re Elsner, 381 F.3d 1125, 1128 (Fed.Cir.2004); Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1565 (Fed.Cir.1992); In re Yale, 58 C.C.P.A. 764, 434 F.2d 666, 668-69 (Cust. & Pat.App.1970).

[48] To determine whether a patent is invalid because it was anticipated by a prior art, a court must first construe the claims of the patent and then compare those claims, as construed, to the alleged prior art. For a patent to be held invalid because it has been described in a prior art reference, there must be identity of invention between what is disclosed in the reference and the invention as claimed. *See* Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 302 (Fed.Cir.1995). Identity of invention is a question of fact. Finnigan Corp. v. Int'l Trade Comm'n, 180 F.3d 1354, 1362 (Fed.Cir.1999); Minn. Mining, 976 F.2d at 1565. All of the claimed elements must be found within the four corners of that single publication, either expressly or inherently, as it is understood by the hypothetical person of ordinary skill in the art. *See* ATD Corp. v. Lydall Inc., 159 F.3d 534, 545 (Fed.Cir.1998).

The person of ordinary skill in the art is a hypothetical person who is presumed to have the skill and experience of an ordinary worker in the field, and is deemed to have knowledge of all pertinent prior art. *See* Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed.Cir.1986). "[A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference .... The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field, not to fill gaps in the reference." Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed.Cir.1991) (citations omitted).

[49] [50] "Under the principles of inherency, if the prior art necessarily functions in accordance with, or

includes, the claimed limitations, it anticipates.... [Furthermore,] 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." Atlas Powder Co., 190 F.3d at 1347 (citations omitted). Thus, newly discovered results of known processes directed to the same purpose are inherent and unpatentable. *See* Bristol-Myers Squibb Co. v. Ben Venue Labs., 246 F.3d 1368, 1376 (Fed.Cir.2001) (citing In re May, 574 F.2d 1082, 1090 (Cust. & Pat.App.1978)). Whether a person of ordinary skill in the art would have recognized the inherent characteristics of the functioning of the prior art is irrelevant, if those inherent characteristics indeed exist. *See* Atlas Powder Co., 190 F.3d at 1349 ("Insufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." (citing Titanium Metals, 778 F.2d at 782)).

2. The Construed Claims as Compared to the Allegedly Anticipating Prior Art

As the meaning of claim language remains the same for both infringement and validity, *see* SmithKline v. Helena Labs., 859 F.2d 878, 882 (Fed.Cir.1988), the Court has already completed the first step by construing the claims of the patents at issue. *See* Claim Construction, *supra* Part II.B.1. Therefore, the Court must now compare the construed claims to the allegedly anticipating prior art.

The Court finds that Apotex, Impax, and Mylan/Esteve have failed to prove facts that show by clear and convincing evidence that any single reference, read as one of ordinary skill in the art at the time of the invention would read it, describes each and every element of any claim of the '505 or the '230 Patents.

a. The '495 Patent

In the First Wave litigation, this Court previously found that the '495 Patent does not anticipate any of the claims of the '505 or '230 Patents. Astra v. Andrx, 222 F.Supp.2d at 573. Here again, Impax has failed to show by clear and convincing evidence that the '495 Patent describes each and every element of any claim in the '505 or '230 Patents.

Impax argues that the '495 Patent "inherently discloses" an *in situ* subcoating which anticipates the subcoating in claim 1(b) of the '505 and '230 Patents. "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." Trintec Indus., Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1295 (Fed.Cir.2002) (citing In re Robertson, 169 F.3d 743, 745 (Fed.Cir.1999)).

Unlike the '505 and '230 Patents, the '495 Patent does not expressly disclose a subcoating-rather, it discloses an enteric coating sprayed directly on the alkaline core. (*See* Chambliss Tr. 6203:20-21; ITX 225.) Impax argues that the '495 Patent "inherently disclose[s]" a subcoating, because a subcoating "can develop *in situ*" once an enteric coating is applied to the alkaline material in the core. (Chambliss Tr. 6203:1-6207:2.) Therefore, according to Impax, any subcoating that may develop in the '495 Patent anticipates the subcoatings in the '505 and '230 Patents.

The Court is not persuaded that the '495 Patent "inherently discloses" an inert subcoating disposed on the core. First, Impax has failed to show that a subcoating would necessarily form in the '495 Patent formulation. Indeed, Impax's own expert, Dr. Chambliss, testified to the contrary. (*See* Chambliss Tr. 6203:18-6204:10 ("My opinion is that an *in situ* subcoat does not occur ....").) Second, even if an *in situ* subcoating were to form, Impax has failed to show that it would be inert. (*See* Chambliss Tr. 6205:17-6206:22 ("I don't think [an *in situ* subcoating] would be inert because it's using omeprazole to form ....").) The mere possibility that an inert *in situ* subcoating *may* develop after applying the enteric coating is insufficient to constitute inherent anticipation, because Impax has not shown that an inert, *in situ* subcoating is necessarily present in the '495 Patent. *See* Trintec, 295 F.3d at 1295.

The Court finds that the '495 Patent does not explicitly or inherently disclose an inert subcoating disposed on the core and therefore does not anticipate claims 1 in the '505 or '230 Patents. (*See* Langer Tr. 7024:1-7025:14; Astra v. Andrx, 222 F.Supp.2d at 572.) All remaining claims of the '505 and '230 Patents are dependent claims or, in the case of the process claims, require application of such a subcoating. Accordingly, Impax has not shown by clear and convincing evidence that the '495 Patent anticipates any claims of either the '505 or '230 Patents. *See* Hartness Int"l, Inc. v. Simplimatic Eng'g Co., 819 F.2d 1100, 1107 (Fed.Cir.1987); Langer Tr. 7027:4-7028:23.

b. The '226 Patent

Impax and Apotex argue that the '226 Patent anticipates claim 1(a) of the ' 230 Patent. The '226 Patent discloses tablets of penicillin and penicillin salts. (*See* ITX 335.) Impax and Apotex assert that penicillin is an "acid labile pharmaceutically active substance" as that term is used in claim 1(a) of the '230 Patent, based on evidence demonstrating that penicillin is unstable in an acidic environment. (*See, e.g.,* Block Tr. 6576:5-6, 6578:12-15; Chambliss Tr. 6146:6-8, 6149:14-15.) The Court disagrees. As explained in more detail above, the term "acid labile pharmaceutically active substance" as used in the '230 Patent refers to a compound that is unstable in acidic conditions and has better stability in alkaline conditions. *See* Claim Construction, *supra* Part II.B.1. In the First Wave, the Court recognized that the active ingredient in the prior art should be an acid-sensitive ingredient like omeprazole and other substituted benzimidazole proton pump inhibitors. *See* Astra v. Andrx, 222 F.Supp.2d at 484. The claimed substances in the '230 Patent exhibit a stability profile like omeprazole and other substituted benzimidazoles, namely they are "labile in acid media, but have better stability in neutral to alkaline media." (PSWTX 2A 1:23-27.) The reverse is true for penicillin-it has better stability in acid media than alkaline media. Penicillin has optimal stability at pH 6.5, a slightly acidic pH, and is equally unstable in both acidic and basic environments to either side of this pH value. (*See* APO 1255 at 1121; Langer Tr. 7142:25-7145:11.)

Apotex and Impax also argue that potassium penicillin G as used in Example I of the '226 Patent is an "alkaline salt." As stated above, the Court construes the term "alkaline salt" in claim 1 of the '230 Patent as a salt with a basic pH. *See* Claim Construction, *supra* Part II.B.1. A three percent aqueous solution of potassium penicillin G has a pH range from 5.0 to 7.5. (PSWTX 2589 at 7042.) Apotex argues that potassium penicillin G actually has a pH greater than 7, and that the range of pH below 7 is due to an acidic byproduct of potassium penicillin G degradation. (*See* Chambliss Tr. 6222:18-6223:5; Block Tr. 7298:4-23.) However, Apotex failed to show that the potassium penicillin G in the '226 Patent contains these byproducts, or that the portion of the pH range below 7.0 for potassium penicillin G is due to an acidic byproduct rather than the pH of the potassium salt itself. (*See* Chambliss Tr. 6222:18-6223:5; Block Tr. 7298:4-23.)

Apotex and Impax have failed to present clear and convincing evidence that potassium penicillin G in the '226 Patent has an alkaline pH such that the '226 Patent discloses an "alkaline salt" as that phrase is used in the '230 Patent. Therefore, the '226 Patent does not anticipate claim 1 of the '230 Patent because (1) penicillin is not an "acid labile pharmaceutically active substance," and (2) the potassium and calcium salts of penicillin are not "alkaline salt[s]" as those terms are used in the '230 Patent. Because all other claims in the '230 Patent are dependent on claim 1, the '226 Patent does not anticipate any claims in the '230 Patent. FN102

FN102. The Court finds that the '226 Patent does not anticipate any claims in the '505 or '230 Patents for the aforementioned reasons. Therefore, the Court does not address whether the '226 Patent discloses the subcoatings of the '505 and '230 Patents or the limitations in the dependent claims.

c. The '219 Patent

Impax argues that the '219 Patent anticipates claim 1 of the '230 Patent because it discloses the use of an inert subcoating between the core and enteric coating.FN103 The '219 Patent teaches the use of a hydroxypropyl methylcellulose ("HPMC") undercoating with a higher fatty acid, such as stearic acid to avoid interactions between an enteric coat and alkaline core. (ITX 53 at 134-35; PSWTX 2821-31; Langer Tr. 6996:10-6997:5.) Impax asserts that the '219 Patent anticipates the inert subcoating claimed in the ' 230 Patent. However, Impax has failed to show that the subcoating in the ' 219 Patent is "inert." The term "inert" in claims 1 of the '505 and ' 230 Patents, when modifying "subcoating," means that the subcoating must be chemically, pharmaceutically, and pharmacologically inactive such that the subcoating does not adversely affect the properties of the active ingredient or the enteric coating material in the formulation. *See* Claim Construction, *supra* Part II.B.1. Plaintiffs presented evidence that stearic acid, one of the undercoating examples in the '219 Patent, is not inert and probably degrades omeprazole. (*See* Langer Tr. 6993:6-14; PSWTX 2758; PSWTX 2759; Block Tr. 6852:21-6854:8.) Impax's expert, Dr. Chambliss, acknowledged that the only coatings disclosed in the '219 Patent contained fatty acids and that he would have to test them to determine if they would degrade an acid labile active ingredient like omeprazole. (Chambliss Tr. 6235:16-6237:6.) Impax presented no such tests.

FN103. The '219 Patent does not disclose omeprazole or an omeprazole salt or an acid labile pharmaceutically active substance or an alkaline salt of an acid labile pharmaceutically active substance.

In light of this failure of proof, the Court finds that Impax has failed to show by clear and convincing evidence that the undercoat in the '219 Patent is inert. Accordingly, the '219 Patent does not anticipate claim 1 or any dependent claims of the '505 and '230 Patents, as each claim has an inert subcoating limitation, either explicitly or by dependent reference.

d. The '815 Application

Apotex asserts that the '815 Application anticipates claim 1 of the '230 Patent because the '815 Application discloses a drug formulation comprising a core, a subcoat, and an enteric coating. (Block Tr. 6536:4-24.) The cores of Example 1 and Comparative Example 1 in the '815 Application include the sodium salt of M-4 carboxylic acid. (Block Tr. 6537:14-6538:7; APO 281 at 18.) Apotex claims that M-4 carboxylic acid is an "acid labile pharmaceutically active substance" because it tends to decompose on contact with acid, as stated in the '815 Application's specification. (*See* APO 281 at 20.) However, the term "acid labile pharmaceutically active substance" as used in the '230 Patent refers to a compound that is unstable in acidic conditions and has better stability in alkaline conditions. *See* Claim Construction, *supra* Part II.B.1. The goal of the '815 Application is "to release M-4 carboxylic acid at a really low pH," which implies that M-4 carboxylic acid is stable in acid. (Langer Tr. 7057:12-7058:4.) Accordingly, Apotex has failed to show by clear and convincing evidence that M-4 carboxylic acid is more stable in an alkaline environment than an acidic environment, and the '815 Application does not anticipate the claims of the '230 Patent.

e. The '980 Patent

Apotex argues that the '980 Patent anticipates claim 1 of the ' 230 Patent because Example 54 of the '980 Patent discloses a recipe for the preparation of a drug formulation containing sodium cefoxitin comprising a core, a subcoat, and an enteric coat. (Block Tr. 6560:24-6561:24; APO 1268.)

Apotex asserts that the sodium salt of cefoxitin is an "alkaline salt" as used in claim 1(a) of the '230 Patent. Apotex's expert, Dr. Block, assumed that the sodium salt of cefoxitin was alkaline simply because it is a sodium salt, and he admitted that he did no research and consulted no references in reaching that

conclusion. (Block Tr. 6806:19-21; 6566:6-7; 6568:16-21.) Apotex presented no direct evidence that the sodium salt of cefoxitin has an alkaline pH, while Plaintiffs presented evidence that cefoxitin is essentially acidic, with a pH between 4.2 and 7.0. (Langer Tr. 7060:14-7061:16; PSWTX 2755 at 844.) Therefore, Apotex has not met its evidentiary burden and has failed to show that the '980 Patent discloses an "alkaline salt" as that term is used in the '230 Patent.

Apotex also asserts that cefoxitin is an "acid labile pharmaceutically active substance" as that phrase is used in claim 1 of the ' 230 Patent. Upon examining the degradation rate of cefoxitin in acidic and alkaline environments, Dr. Block admitted that cefoxitin is more stable in acidic environments than in alkaline environments. (*See* Block Tr. 6814:2-6814:8, 6812:22-25, 6813:7-6813:14; PSWTX 2757; APO 432; PSWTX 1108 at 114.) FN104 The term "acid labile pharmaceutically active substance" as used in the ' 230 Patent refers to a compound that is unstable in acidic conditions and has better stability in alkaline conditions. *See* Claim Construction, *supra* Part II.B.1. Because cefoxitin is more stable in acidic conditions than alkaline conditions, the Court finds that Apotex has not shown that cefoxitin is an "acid labile pharmaceutically active substance" as that term is used in the ' 230 Patent.

FN104. PSWTX 2757 is a demonstrative created by Plaintiffs which shows the degradation rate as a function of pH for both omeprazole and cefoxitin. It is reproduced on page 66 of Astra's Proposed Findings of Fact. Apotex asserts that Plaintiffs did not correctly transpose the omeprazole curve onto PSWTX 2757. Apotex does not take issue with the cefoxitin curve. The Court makes no finding as to whether there is, in fact, an error in PSWTX 2757. The Court bases its factual findings on the portions of Dr. Block's testimony that deal with the cefoxitin curve alone, not the portions that deal with a comparison between the cefoxitin and omeprazole curves.

Accordingly, the '980 Patent does not anticipate the claims of the '230 Patent.

E. *Obviousness Under* 35 U.S.C. s. 103

[51] Defendants Apotex, Impax, and Mylan/Esteve allege that the '505 and ' 230 Patents are invalid for obviousness under 35 U.S.C. s. 103. After considering the testimony and documents in evidence, as well as the parties' proposed findings of fact and conclusions of law, the Court finds that Defendants have failed to establish by clear and convincing evidence that the inventions of the '505 and '230 Patents would have been obvious to a person of ordinary skill in the art.

1. *Applicable Law*

[52] [53] A claimed invention is unpatentable due to obviousness if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. s. 103(a) (2000). Whether the invention was obvious under s. 103 is a legal conclusion based on certain factual inquiries, In re Huang, 100 F.3d 135, 138 (Fed.Cir.1996); *see also* Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1483 (Fed.Cir.1997), including: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claimed invention and the prior art; and (4) secondary, objective considerations of nonobviousness including long-felt need, commercial success, or the failure of others. Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966); *see also* Jones v. Hardy, 727 F.2d 1524, 1529 (Fed.Cir.1984). Where, as here, a patent challenger fails to present a prima facie showing of obviousness, the patent holder need not present rebuttal evidence of non-obviousness, since the challenger has not met its initial burden. *See* Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1350 (Fed.Cir.2000). For the reasons discussed below, Defendants have failed to establish a prima facie case for obviousness.

In KSR Int'l Co. v. Teleflex, Inc., No. 04-1350, 550 U.S. ----, 127 S.Ct. 1727 (2007), the Supreme Court emphasized that, when conducting the *Graham* obviousnessanalysis, a court should look to common sense and "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR Int'l, 127 S.Ct. at 1741. This hypothetical person of ordinary skill in the art is presumed to be aware of all prior art in the same or analogous fields, In re Gorman, 933 F.2d 982, 986 (Fed.Cir.1991), as well as elements of prior art that were designed to solve problems other than those faced by the patent inventor, KSR Int'l, 127 S.Ct. at 1742. ("Common sense teaches ... that familiar items may have obvious uses beyond their primary purposes ....").

The Supreme Court acknowledged that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does," because claimed inventions almost always rely on combinations of elements that are already known. *Id*. at 1741. However, the Court also noted that "[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." *Id*. A reason to combine known elements can be either express or implied. Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1291 (2006).

The Court must also look beyond the prior art references themselves for a reason to combine:

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patents at issue....

. . . . .

Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

KSR Int'l, 127 S.Ct. at 1740, 1742. A person of ordinary skill in the art can also find a reason to combine known elements in well-known principles or problem-solving strategies of the field. DyStar Textilfarben GmbH v. C.H. Patrick Co., 464 F.3d 1356, 1366 (Fed.Cir.2006). Courts look to these sources when conducting an obviousness analysis because "[i]n many fields it may be that there is little discussion of obvious techniques or combinations, and it is often the case that market demand, rather than scientific literature, will drive design trends." KSR Int'l, 127 S.Ct. at 1741.

[54] Ultimately, a court must ascertain what would have been objectively obvious to one of ordinary skill in the art at the time of the invention, not what was subjectively obvious to the inventor. *See Ryko Mfg. Co.*, 950 F.2d at 718; *accord* KSR Int'l, 127 S.Ct. at 1741-42. If the prior art teach away from combining known elements in the manner claimed by the invention at issue, discovering a successful way to combine them is less likely to be obvious. *See* KSR Int'l, 127 S.Ct. at 1740, 1745.

In conducting an obviousness analysis, "[a] factfinder should be aware ... of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *Id*. at 1742. This is because the genius of invention is often a combination of known elements that in hindsight seems preordained. *See* Raytheon Co. v. Roper Corp., 724 F.2d 951, 961 (Fed.Cir.1983) (stating that "virtuallyevery claimed invention is a combination of old elements"). However, avoiding hindsight bias does not preclude the application of common sense. KSR Int'l, 127 S.Ct. at 1742. A person of ordinary skill in the art will "pursue the known options" where there are a "finite number of identified, predictable solutions" to a particular problem because a person of ordinary skill is "a person of ordinary creativity, not an automaton." *Id*. at 1742.

2. *The Level of Ordinary Skill in the Art*

[55] The level of ordinary skill in the art may be found by inquiring into: (1) the type of problems encountered in the art; (2) prior art solutions to those problems; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the education level of active workers in the field. Custom Accessories, Inc., 807 F.2d at 962. All of those factors may not be present in every case, and one or more of them may predominate. Envtl. Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed.Cir.1983)

Based on the typical education level of active workers in the field of pharmaceutical formulation, as well as the high degree of sophistication required to solve problems encountered in the art, the Court finds that a person of ordinary skill in the art would have at least a college degree in a field of natural science such as pharmacy, pharmaceutical science, chemical engineering, or organic chemistry, and at least four years of work experience in the field of drug formulation. (Langer Tr. 6975:7-15; *see also* Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1293 (Fed.Cir.2006).)

3. *Asserted Prior Art*

a. *Plaintiffs' Objections to Certain Prior Art References*

Defendants assert numerous references as prior art. As an initial matter, Plaintiffs object to six of these references on the grounds that they do not qualify as prior art because they are not "printed publications" under 35 U.S.C. s. 102(b). The six contested references are: a Japanese-language publication entitled "Basic Course of Drug Development" edited by Kyosuke Tsuda and Hisashi Nogami ("Tsuda") (APO 702; APO 702A); a Japanese-language publication entitled "Up-to-Date Pharmaceutical Technology Series 'No. 1' " produced by the Japan Industrial Technology Federation ("Up-to-Date") (APO 703; APO 1269; ITX 400); a Japanese-language document entitled *Hydroxypropyl Methylcellulose TC-5* ("*TC-5*") (ITX 372); a brochure produced by the Shin-Etsu Chemical Company entitled *Hydroxypropyl Methyl Cellulose NF XII Pharmacoat* ("*Pharmacoat 1969*") (ITX 415); other Shin-Etsu brochures, including *Enteric Coating on Tablets Containing Alkaline Matter* ("*H-22*") (APO 401) and *Enteric Coating on Tablets Containing Alkaline Matter* ("*H-17*") (ITX 7); and brochures produced by Distillation Products Industries, a division of the Eastman Kodak Company (the "Eastman Brochures") (APO 275; APO 1257). Impax argues that all six references qualify as printed publications; Apotex argues only that Tsuda, Up-to-Date, and the Eastman Brochures qualify as printed publications. For the reasons set forth below, the Court concludes that Tsuda and Up-to-Date qualify as printed publications, but *TC-5, Pharmacoat 1969,* the other Shin-Etsu brochures, and the Eastman Brochures do not qualify as printed publications.

Whether a document is a printed publication is a legal determination based on underlying issues of fact and must be decided on a case-by-case basis. In re Klopfenstein, 380 F.3d 1345, 1350 (Fed.Cir.2004); Cooper Cameron Corp. v. Kvaerner Oilfield Prods., 291 F.3d 1317, 1321 (Fed.Cir.2002); In re Hall, 781 F.2d 897, 899 (Fed.Cir.1986). A document may be deemed a printed publication

upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation.

In re Wyer, 655 F.2d 221, 226 (Cust. & Pat.App.1981) (citation omitted); *see* Klopfenstein, 380 F.3d at 1349-51; Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135, 139 (Fed.Cir.1986); Massachusetts Inst. of Tech. v. AB Fortia, 774 F.2d 1104, 1109 (Fed.Cir.1985). "Cataloging a paper in a technical or scientific library makes the publication sufficiently accessible to those interested in the art to satisfy the

requirements of s. 102(b)." Friction Div. Prods., Inc. v. E.I. DuPont De Nemours & Co., 658 F.Supp. 998, 1008 (D.Del.1987) (citing In re Hall, 781 F.2d at 900).

i. The Tsuda Writing

Plaintiffs argue that Defendants have not shown that the National Library of Medicine ("NLM") actually had a copy of the Tsuda writing (ITX 16; APO 702) before the critical date of the '505 and '230 Patents (April 30, 1986).

A record of the Tsuda writing appears in the 1971-75 NLM catalog. (*See* APO 1318.) The Tsuda writing bears a stamp, referred to as the "NLM Bethesda 14" stamp. Martha Fishel, a librarian who has worked at NLM since 1976 (*see* APO 950), testified that the NLM Bethesda 14 stamp was a post office abbreviation, and that "there are no volumes in the NLM collection beyond about the late 1970s that bear that NLM Bethesda 14 stamp." (Fishel Dep. Tr. 11:15-17, May 24, 2006.) "[C]ompetent evidence of the general library practice may be relied upon to establish an approximate time when a [reference] became accessible." In re Hall, 781 F.2d at 899 (holding that a single copy of a thesis in a German university library indexed by subject matter was a publicly accessible printed publication); *see also* Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1569 (Fed.Cir.1988) ("Evidence of routine business practice can be sufficient to prove that a reference was made accessible before a critical date."). Therefore, because the Tsuda writing bears a stamp that was used only until the late 1970s, and the Tsuda writing appears in the 1971-75 NLM catalog, the Court finds that NLM had a copy of the Tsuda writing before April 30, 1986.

Plaintiffs also argue that a reasonably diligent search would not have located the Tsuda writing because the Tsuda writing was not cataloged individually. The Tsuda writing is one volume of a twenty-one volume set. The 1971-75 NLM catalog listed the entire twenty-one volume set in several places under an English transliteration of its Japanese title, with a translation of the Japanese title noted parenthetically. (*See* APO 1318.) The catalog did not list each volume individually. NLM also cataloged the twenty-one volume set under the subject heading "Chemistry, Pharmaceutical." (APO 1318 at 2504 col. 3.) "Cataloging a paper in a technical or scientific library makes the publication sufficiently accessible to those interested in the art to satisfy the requirements of s. 102(b)." Friction Div. Prods., Inc. v. E.I. DuPont De Nemours & Co., 658 F.Supp. 998, 1008 (D.Del.1987) (citing In re Hall, 781 F.2d at 900). Between 1977 and April 30, 1986, a member of the public would have been able to locate the Tsuda book in the NLM by searching "Basic Course on Drug Development," the editors' names, or the subject heading "Chemistry, Pharmaceutical." (Fishel Dep. Tr. 20:9-21:15; 25:6-12; APO 1318.) Furthermore, the NLM's copy of the Tsuda book was available for lending to participating libraries in the United States through the NLM interlibrary-loan network. (Fishel Dep. Tr. 7:17-8:17.)

The Court finds that Defendants have shown by clear and convincing evidence that a person of ordinary skill in the art could have located the Tsuda writing with reasonable diligence. Accordingly, the Tsuda writing qualifies as a printed publication.

ii. The Up-to-Date Writing

The Court previously declined to find that the Up-to-Date writing qualified as published prior art because the First Wave defendants failed to provide sufficient evidence that "Up-to-Date was a publication accessible to the public." Astra v. Andrx, 222 F.Supp.2d at 576. Here, Plaintiffs again argue that Defendants have failed to show that Up-to-Date was accessible to the public. The Court disagrees.

Defendants presented new evidence about Up-to-Date, including the deposition testimony of Ms. Mieko Takebe, taken by Eon (before the claims against Eon were dismissed). Ms. Takebe has been a librarian in the University of Tokyo Library system for more than twenty years and recently worked in the Graduate

School of Pharmaceutical Sciences library. (Takebe Dep. Tr. 5:6-6:2, Apr. 12, 2004).

According to the deposition testimony of Ms. Takebe, the Library of Pharmaceutical Sciences first received a copy of the Up-to-Date book on April 19, 1971. (Takebe Dep. Tr. 21:13-17, 24:19-25:5, 27:14-28:22, APO 871, APO 872.) The Up-to-Date book was cataloged, shelved, and accessible in the Library of Pharmaceutical Sciences not later than 1972. (Takebe Dep. Tr. 37:23-38:13, 41:16-43:17, 44:7-11, 45:1-47:14, APO 869, APO 874). It was checked out of the Library of Pharmaceutical Sciences at least five times prior to April 30, 1986. (Takebe Dep. Tr. 18:17-20:6; APO 869.)

The Court finds that Up-to-Date was sufficiently accessible that a person of ordinary skill in the art could have located it with reasonable diligence, and thus it qualifies as a printed publication.

iii. The *Pharmacoat 1969* Writing

Plaintiffs argue that Defendants have presented no evidence that the *Pharmacoat 1969* writing (ITX 415) was made publicly accessible prior to the critical date. Brochures must be made publicly accessible in order to qualify as printed publications. *See* Astra v. Andrx, 84 Fed.Appx. 76, 81 (Fed.Cir.2003); In re Wyer, 655 F.2d 221, 226 (Cust. Pat.App.1981). Impax presents no evidence that *Pharmacoat 1969* was disseminated or distributed to anyone prior to the critical date. Instead, Impax asserts that *Pharmacoat 1969* is "self-proving"-i.e., it must have been distributed to individuals in the field simply because it is a brochure. The Court finds this reasoning insufficient to show public availability. Given the absence of any evidence that *Pharmacoat 1969* was actually distributed to anybody prior to the critical date, the Court finds that Defendants have failed to show that the *Pharmacoat 1969* writing qualifies as a printed publication.

iv. The *TC-5* Writing

This Court previously declined to find that the *TC-5* writing (ITX 372) qualified as published prior art. Astra v. Andrx, 222 F.Supp.2d at 576. *TC-5* is a trade name used by Shin-Etsu, a Japanese manufacturer, to describe a low-viscosity HPMC. Late in the Second Wave trial, Impax attempted to have Mr. Harold Zeller, the United States distributor of Shin-Etsu's HPMC, testify regarding the *TC-5* writing. The Court precluded his testimony.(Trial Tr. at 5435:7-5436:12.) The Court found that at that late stage in the trial, the testimony "with respect to th[e] *TC-5* brochure would be severely prejudicial" to Plaintiffs because Astra had attempted to, but was unable to get discovery on the *TC-5* writing, and Defendants had not identified Mr. Zeller in response to interrogatories asking for the identification of witnesses and facts. (*Id*.)

Impax maintains that *TC-5* is a printed publication because the *TC-5* writing was cited in the European equivalent of the '505 Patent (Linderoth Dep. Ex. 36), even though the Court rejected precisely this argument during the First Wave proceedings. *See* Astra v. Andrx, 222 F.Supp.2d at 578 ("The fact that an applicant for a patent, in responding to an Office Action, elects to distinguish a cited reference on the merits does not constitute an admission that the document qualifies as prior art for this case."). Mere citation by the European Patent Office does not show that the *TC-5* writing is a printed publication under United States law. *See* id. at 577. Defendants have failed to satisfy their burden of showing that the *TC-5* writing qualifies as a printed publication.

v. The *H-22* and *H-17* Writings

Defendants have not shown that *H-22* (APO 973) or *H-17* (ITX 7) qualify as printed publications.FN105 While Impax argues that the *H-22* writing has a publication date of 1979, no party has presented any evidence that *H-22* or *H-17* were accessible to the public prior to the critical date. The scant testimony on the topic is insufficient to establish public accessibility. (*See, e.g.,* Chambliss Tr. 6189:23-6191:1) ("[H-17 is] an example of the kind of technical brochure you got from the companies."). Accordingly, the Court

finds that Defendants have failed to show that *H-22* and *H-17* are printed publications under s. 102(b).

FN105. Apotex does not contest this.

vi. The Eastman Brochures

The only evidence put forth by Defendants to show that the Eastman Brochures (APO 275; APO 1257) are printed publications comes from the deposition of James A. Michalski, who began working at Eastman Chemical in 1992. (Michalski Dep. Tr. 10:3, 5:4-22, Sept. 16, 2003). Although Mr. Michalski had no personal knowledge regarding the distribution or publication of the Eastman Brochures, as a Rule 30(b)(6) witness, he testified on behalf of the company as a whole. *See* L-3 Comm. Corp. v. OSI Sys., Inc., 2005 WL 712232, at (S.D.N.Y. Mar.28, 2005); *see also* Fed.R.Civ.P. 30(b)(6) ("[T]he organization so named shall designate one or more officers, directors, or managing agents, or other persons who consent to testify on its behalf .... [who] shall testify as to matters known or reasonably available to the organization."). However, Defendants have not shown that information about the circulation and availability of the Eastman Brochures in the 1960's and 1970's is currently "known or reasonably available to the organization." It appears that nobody presently at Eastman knows how the Eastman Brochures were distributed. (*See* Michalski Dep. Tr. 25:14-23; 27:14.) While Michalski can testify as to matters outside his own personal knowledge, he cannot testify as to matters about which the company itself lacks knowledge. *See* L-3 Comm. Corp., 2005 WL 712232, at *1. Absent some reason to think that the procedures in the 1960's and 1970's were similar to the time periods with which Michalski was familiar, his testimony is insufficient to show that the Eastman Brochures qualify as printed publications.

Likewise, Michalski's testimony does not establish a routine business practice encompassing the Eastman Brochures because he did not relay information about distribution practices at the time the Eastman Brochures were produced. *Cf.* Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1569 (Fed.Cir.1988) ("Evidence of routine business practice can be sufficient to prove that a reference was made accessible before a critical date."). There is no document at Eastman that describes the general practice for distributing brochures or other documents prior to 1986. (Michalski Dep. Tr. 108:7-10.) Michalski could not say whether the Eastman Brochures had been distributed at trade shows (Michalski Dep. Tr. 88:3-6, 107:21-25), nor did he know whether any of the brochures had been requested by clients or customers (Michalski Dep. Tr. 108:1-6).

Accordingly, the Court finds that Defendants have failed to show that the Eastman Brochures qualify as printed publications. Having determined what is prior art, the Court turns to a comparison of the prior art and the '505 and ' 230 Patents.

b. *The Remaining Asserted Prior Art References*

Apotex argues that various combinations of the '495 Patent (APO 5; APO 5A); an article entitled "Development of an Oral Formulation of Omeprazole" by Ake Pilbrant and C. Cederberg in the *Scandinavian Journal of Enterology* ("Pilbrant & Cederberg") (APO 345; APO 345A); Tsuda (APO 702; APO 702A); Up-to-Date (APO 703; APO 1269; ITX 400); the '226 Patent (APO 1254), the '815 Application (APO 281); the '980 Patent (APO 1268); and the so-called "cornucopia of prior art" render obvious claims 1, 6, 7, and 13 of the ' 230 Patent, and claims 1, 5, 6, and 10 of the '505 Patent.

The "cornucopia of prior art" includes Pilbrant & Cederberg (APO 345A); an article entitled "Tablet Coating ... Wet and Dry" by Jack Cooper and William Gunsel ("Cooper & Gunsel") (APO 270A); UK Patent No. 760,403 (the "'403 Patent") (APO 252), U.S. Patent No. 3,524,756 (the "'756 Patent") (APO 1263); two chapters from a pharmaceutical treatise entitled *Remington's Pharmaceutical Sciences* (the

"Remington's" references) (APO 1297; APO 351A); a chapter entitled "Tablet Coating" by John R. Ellis, Elliott B. Prillig, and Clarence J. Endicott in *The Theory and Practice of Industrial Pharmacy* ("Ellis") (APO 313A); a publication entitled *Hager's Handbook of Pharmaceutical Practice* by P.H. List and L. Horhammer ("*Hager's Handbook*") (APO 299); U.S. Patent No. 4,544,562 (the "'562 Patent") (APO 423); U.S Patent No. 3,789,117 (the "'117 Patent") (APO 411); U.S. Patent No. 4,540,685 (the "'685 Patent") (APO 424); Volume 17 of the *Kirk-Othmer Encyclopedia of Chemical Technology* ("*Kirk-Othmer*") (APO 306A); a publication entitled *Practical Course in Laquer Coating* by Klaus Lehmann ("*Lehmann*") (APO 316); and German Patent No. 1 204 363 (the "'363 Patent") (APO 294; APO 1310).FN106

FN106. The Cornucopia of Prior Art also includes the Eastman Brochures and *H-22*. These two references do not qualify as printed publications. *See supra* Parts III.E.3.a.v-vi.

Impax argues that various combinations of the '495 Patent; the ' 226 Patent; U.S. Patent No. 3,371,015 (the "'015 Patent") (ITX 312); Up-to-Date; *Hager's Handbook;* Tsuda; the '219 Patent; and Pilbrant & Cederberg render obvious claims 1, 6, 7, and 10 of the '230 Patent and claims 1, 5, 6, 8, 10 of the '505 Patent.FN107 Mylan/Esteve argues that the ' 226 Patent renders obvious claims 3, 4 and 11 of the ' 505 Patent and claims 8 and 15 of the ' 230 Patent, and that the '495 Patent renders obvious claim 7 of the ' 505 Patent and claim 8 of the ' 230 Patent. Mylan/Esteve also argues that the '495 Patent, the ' 226 Patent, and the ' 980 Patent render obvious the process claims-claim 14 of the ' 505 Patent and claim 12 of the ' 230 Patent. Defendants incorporate each other's obviousness arguments by reference throughout their submissions.

FN107. Impax also argues that *TC-5, Pharmacoat 1969,* and *H-17* render the enumerated claims obvious. These three references do not qualify as printed publications. *See supra* Parts III.E.3.a.iii-v.

4. *Comparison of the Prior Art and the '505 and* '230 Patents

In what follows, the Court compares the prior art to the claimed inventions and concludes that the prior art do not render the claimed inventions obvious. The Court has taken into account the "inferences and creative steps that a person of ordinary skill in the art would employ" and concluded that Defendants have failed to show that the interrelated teachings of the prior art references would provide a person of ordinary skill in the art with a reason to combine known elements to achieve the inventions claimed by the '505 and '230 Patents. KSR Int'l, 127 S.Ct. at 1741. In making this determination, the Court has also considered the background knowledge of a person of ordinary skill in the art; the nature of the problem to be solved and other problems in the field; and the effects of demands known to the pharmaceutical formulation community or present in the pharmaceutical formulation market. *Id*. at 1740, 1742. The innovations in the '505 and '230 Patents are "more than the predictable use of prior art elements according to their established functions." Id. at 1740.

Defendants rely on three primary varieties of prior art when asserting their obviousness arguments. First, Defendants cite references which they claim disclose a core containing an acid labile pharmaceutically active substance, a subcoating disposed on the core, and an enteric coating. (*See* Block Tr. 6536:4-24, 6560:24-6561:15; APO 281; APO 1268; ITX 335 8:62-9:20.) Such references include the '815 Application, the '980 Patent, and the '226 Patent. Examples of the pharmaceutically active substances in the cores of these references include the sodium salt of M-4 carboxylic acid, the sodium salt of cefoxitin, and potassium penicillin G. (*See* Block Tr. 6537:14-6538:7; APO 281; APO 1268 9:15-64; ITX 335.)

As discussed in greater detail below, references of this first variety do not disclose active ingredients which qualify as acid labile pharmaceutically active substances, because they do not have the same acid sensitivity as omeprazole. A person of ordinary skill in the art would know that compounds with different acid sensitivities behave differently in the gastrointestinal system. Because of this difference, a person of

ordinary skill in the art would not combine the enteric coating and subcoating from references of the first variety with omeprazole or other acid labile pharmaceutically active substances. (*See, e.g.,* Langer Tr. 7057:17-7060:13, 7060:14-7062:24, 7029:15-7030:20, 7005:18-1006:15.) Moreover, the '226 Patent teaches away from the drug delivery method claimed for omeprazole because one of the goals of the ' 226 Patent is to deliver a portion of its active ingredient in the stomach. *See* infra Parts III.E.4.c, III.E.4.g. The goal of the '505 and '230 Patents, on the other hand, is to permit the omeprazole drug molecule to pass unharmed through the stomach's acid environment, which quickly destroys it, and to deliver omeprazole only to the upper intestine. *See infra* Part III.E.4.c.

Second, Defendants cite references which disclose omeprazole but do not disclose a subcoating or an ARC in a solid formulation. Such references include the '495 Patent and Pilbrant & Cederberg. A person of ordinary skill in the art would not employ a subcoating along with the innovations in these references when formulating an omeprazole drug delivery system, because these references do not identify stability problems or a reaction between an acid labile pharmaceutically active substance and an enteric coating, which would suggest a need for a subcoating or an ARC. (*See, e.g.,* Langer Tr. 7041:13-17.)

Third, Defendants cite numerous references which describe subcoatings and subcoating techniques but do not disclose omeprazole, such as Tsuda and Up-to-Date. Defendants argue that various combinations of these references render all or part of the claimed inventions obvious. These references provide no reason-explicit or implicit-to apply the disclosed subcoatings to an omeprazole formulation. (*See, e.g.,* Langer Tr. 7029:15-7030:20, 7041:13-17.) Moreover, Tsuda teaches away from omeprazole because it warns against applying its subcoating to moisture-sensitive drugs, and omeprazole is highly sensitive to moisture. *See infra* Part III.E.4.b.

a. *The '495 Patent and Pilbrant & Cederberg*

Defendants argue that the '495 Patent and Pilbrant & Cederberg in combination with other prior art references render obvious claims 1, 5, 6, 8, and 10 of the '505 Patent and claims 1 and 6 of the '230 Patent. In the First Wave, the Court found that the '495 Patent and Pilbrant & Cederberg, alone or in combination with other prior art references, do not render obvious any claims in the '505 or '230 Patents. *See* Astra v. Andrx, 222 F.Supp.2d at 582-83. Upon consideration of the evidence presented in the Second Wave trial, the Court reaches the same conclusion.

First, the '495 Patent does not disclose or suggest any negative interaction between its core and enteric coating. (Signorino Tr. 6440:21-25, 6442:22-6443:10; Langer Tr. 7025:1-20; *see also* Astra v. Andrx, 222 F.Supp.2d at 581.) The '495 Patent is not a "formulation" patent; rather, it discloses new salts of omeprazole in a syrup, an injectable, and one directly enteric-coated solid dosage form. *See* Astra v. Andrx, 222 F.Supp.2d at 583. This directly enteric-coated solid dosage form teaches that omeprazole can be directly enteric-coated, but omeprazole loses stability when it is directly enteric-coated. (*See* Langer Tr. 6982:5-21.) Apotex argues that a person of ordinary skill in the art would recognize a potential stability problem because Example 12, the solid dosage form, discloses a magnesium omeprazole salt in direct contact with a cellulose acetate phthalate ("CAP") enteric coating. (*See* ITX 225 at 12 Ex. 12.) However, the '495 Patent does not specifically identify a stability problem in Example 12 or anywhere else. A person of ordinary skill in the art would not infer such a problem from the '495 Patent, even if he were aware that omeprazole is acid labile.

Second, the '495 Patent does not disclose an ARC, nor does it disclose or suggest using an ARC to solve the stability problems addressed by the '505 and '230 Patents. (Langer Tr. 7024:1-25.) Apotex argues that, based on the disclosure in Pilbrant & Cederberg that omeprazole is acid labile and is more stable at a higher pH, a person of ordinary skill in the art would have been motivated to combine an antacid, such as calcium carbonate, with the omeprazole core. A person of ordinary skill in the art would not suspect any need to add an ARC from looking at the disclosures in the '495 Patent, Pilbrant & Cederberg, or any other references,

because the '495 Patent does not disclose a stability problem. (Langer Tr. 7024:1-25; Signorino Tr. 6447:12-6448:7.) Nor would a person of ordinary skill in the art would infer a stability problem from looking at Pilbrant & Cederberg simply because omeprazole is acid labile. (*See* Langer Tr. 7024:1-25.)

Third, as the Court concluded as part of its anticipation analysis, the '495 Patent does not disclose a subcoating of any kind. (*See* Signorino Tr. 6447:9-11; Langer Tr. 7025:1-20; Anticipation, *supra* Part III.D; *see also* Astra v. Andrx, 222 F.Supp.2d at 572.) A person of ordinary skill in the art would find no reason to employ a subcoating from looking at the '495 Patent, even when viewed in light of the numerous prior art references that disclose subcoatings and subcoating techniques, *e.g.,* Tsuda and Up-to-Date. (APO 702; APO 703.) Defendants have not demonstrated any reason to combine the '495 Patent with any of the other cited prior art references to address the problems solved by the claimed inventions; thus, they have shown no reason why a formulator would add a subcoating to the '495 Patent.

Fourth, Pilbrant & Cederberg discloses enteric-coated granules containing omeprazole, but it does not disclose a subcoating, nor does it disclose the addition of an ARC to the granules. (Langer Tr. 7054:5-7055:6; APO 345.) Pilbrant & Cederberg also does not disclose or suggest a problem with the application of an enteric coating to an active core, nor does it disclose a reaction between the enteric coating and the underlying granules. While the article recommends that a desiccant be included with the drug packaging because omeprazole is sensitive to moisture, this falls far short of suggesting that omeprazole might negatively interact with an enteric coating and thereby cause loss of enteric protection and reduced gastric acid resistance. (*See* Langer Tr. 7052:9-7054:4; Signorino Tr. 6441:1-4, 6442:20-6443:10; *see also* Astra v. Andrx, 222 F. Supp 2d at 581-82.) Pilbrant & Cederberg teaches that omeprazole can be directly enteric-coated. (*See* Langer Tr. 6982:5-21.)

In addition, formulators employed the buffering compound in Pilbrant & Cederberg to neutralize stomach acid, not to stabilize omeprazole in formulation. (Langer Tr. 7054:5-7057:11.) Plaintiffs' formulators added the ARC to the core in the claimed inventions in order to stabilize the omeprazole in the formulation. This, in turn, created problems with gastric acid resistance, which Plaintiffs solved by employing a subcoating. (*See* Langer Tr. 7041:13-17.) While a person of ordinary skill in the art can look to prior art designed to solve problems other than those addressed by the claimed inventions, KSR Int'l, 127 S.Ct. at 1742, such a person would not employ an ARC based on the '495 Patent because the buffer in the '495 Patent was used for an entirely different purpose than the ARC in the claimed inventions.

Accordingly, the '495 Patent and Pilbrant & Cederberg, alone or in combination with other prior art references, and viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, do not render obvious any claims in the '505 or '230 Patents.

b. *Tsuda, Up-to-Date, and Other Subcoating References*

Apotex argues that the combination of Tsuda, Up-to-Date, and various other prior art references render obvious claims 1, 5, and 10 of the '505 Patent, and claims 1, 6, and 13 of the '230 Patent.FN108 Impax argues that these references render obvious claims 1(b) of the ' 505 Patent.

FN108. Other generic subcoating references include *Hager's Handbook, Kirk-Othmer,* the Remington's references, and *Lehmann*.

Tsuda, Up-to-Date, and the other subcoating references describe various drug coating and subcoating techniques. None of the subcoating references disclose omeprazole, an alkaline omeprazole salt, or an ARC. Defendants have failed to show that the subcoating references themselves, the nature of the problem to be solved or other problems in the field, or the background knowledge of a person of ordinary skill in the art

provide any reason to combine the disclosed subcoatings with other prior art references that disclose omeprazole, such as the '495 Patent. Absent such a reason to combine, Tsuda, Up-to-Date, the other subcoating references, alone or in combination with other prior art references, and viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, fail to render obvious any claims in the '505 or '230 Patents.

Tsuda identifies a reaction between a core and an enteric coating, and it describes a sugar subcoating used to separate the enteric coating from the core. (*See* APO 702 at 14.) Tsuda discloses several diagrams of core tablets, one which has a penicillin core and six coating layers, and another which has an unspecified core, a sugar subcoating layer, and an enteric coating. (APO 702 at 2 Fig. 2.4.5.) In a section entitled "Sugar coating for enteric preparations," Tsuda states: "the [enteric] base may often react with the drug in the core tablet; the enteric coating layer is therefore formed on the subcoating layer." (APO 702 at 14.) Tsuda lists penicillin as an applicable drug for an enteric sugar-coated tablet. (*See* APO 702 at 4.)

First, Defendants have not shown that Tsuda discloses a core containing omeprazole or an acid labile pharmaceutically active substance. As the Court previously found, penicillin, the active ingredient in Tsuda, is not an acid labile pharmaceutically active substance as that term is used in the ' 230 Patent. *See* Anticipation, *supra* Part III.D; Claim Construction, *supra* Part II.B.1. A person of ordinary skill in the art would not apply the teachings of Tsuda in formulating the substances claimed in the '505 and ' 230 Patents because Tsuda does not disclose an active ingredient that exhibits the same type of acid sensitivity as those substances. (*See* Langer Tr. 7029:15-7030:20.) A person of ordinary skill in the art would know that compounds with different acid sensitivity can behave differently in the varying pH environments of the gastrointestinal system. (*See* id.; Langer Tr. 7057:17-7060:13.) Accordingly, because of this difference in acid sensitivity, a person of ordinary skill in the art would not have applied Tsuda to the stability problems faced in developing formulations of omeprazole or other acid labile pharmaceutically active substances.

Second, Tsuda teaches away from applying its contents to drugs like omeprazole. Even if a formulator were to realize that Tsuda's subcoating is a means of addressing a negative interaction between an enteric coating and a core, Tsuda warns against employing the disclosed subcoating with a moisture-sensitive drug like omeprazole. (Langer Tr. 7029:15-7030:20.) The sections of Tsuda relied upon by defendants relate to enteric-coated tablets with sugar subcoatings. Omeprazole was known to be moisture-sensitive, and Tsuda warns against using sugar coating for moisture-sensitive drugs. (*See id.*) Tsuda states: "This dosage form [*i.e.,* enteric-coated tablets with a sugar subcoating] is adopted when there is *no possibility* of a reduction of drug stability in case of penetration of a small amount of water into the core tablet ...." (APO 702 at 4 (emphasis added).) A person of ordinary skill in the art would know that the penetration of a small amount of water into the core would reduce the stability of omeprazole. (Langer Tr. 7029:15-7030:20.)

Turning to the next reference, Up-to-Date contains two disclosures upon which Defendants rely for their obviousness arguments: "When tablets contain an alkaline substance, the Eudragit [enteric] coating shows decreased acid resistance; when they contain an acidic substance, the rate of Eudragit coating dissolution in alkaline conditions decreases. In such cases, it is necessary to provide a neutral subcoating under the Eudragit coating." (APO 703 at 0051844.) Up-to-Date states in a subsequent section that *TC-5,* which is Shin-Etsu's name for HPMC, "is also used as an undercoating agent in coating with AEA, Eudragit L, SE, CAP, MPM, etc., for the purpose of preventing them from reacting with the active component." (APO 703 at 0051848.)

While Up-to-Date more clearly identifies the negative consequences of the reaction between the enteric coating and the active ingredient than Tsuda does, Up-to-Date still fails to render obvious any claims of the '505 or '230 Patents. First, Defendants have not identified any prior art that shows a negative reaction between omeprazole and an enteric coat. Absent such a showing, a person of ordinary skill in the art looking at the '495 Patent, Pilbrant & Cederberg, or another prior art disclosing omeprazole would have no

reason to combine it with the teachings of Tsuda, Up-to-Date, or any other subcoating reference. Likewise, a person of ordinary skill in the art looking at Up-to-Date or any other subcoating reference would have no reason to combine it with the teachings of the '495 Patent or another prior art that discloses omeprazole. Absent some reason to pick out omeprazole or another acid labile pharmaceutically active substance, Up-to-Date, alone or in combination with other prior art references, cannot render obvious any of the asserted claims.

Second, the disclosure in Up-to-Date that subcoatings can address reactions between alkaline substances and their enteric coatings is not a sufficient reason to combine. The core in the '505 and '230 Patents reacts with the enteric coating because Plaintiffs' formulators added an ARC to the core in order to solve the problem of omeprazole discoloration and stabilize the drug during manufacture and long-term storage. (*See* Langer Tr. 7041:13-17.) This contributed to another problem-low gastric acid resistance-which the formulators solved by adding a subcoating. (*See id*.) The relationship between the initial problem and the subcoating solution are too attenuated to be obvious to a person of ordinary skill in the art. Likewise, the use of an ARC is not so well known in the field of pharmaceutical chemistry that it would be obvious to a person of ordinary skill in the art, nor would it be obvious based on disclosures in the prior art. As a consequence, no combination of prior art can render obvious the use of a subcoating to solve the problem of low gastric acid resistance.

The preceding arguments apply with equal force to the other subcoating references relied upon by Defendants, such as *Hager's Handbook, Kirk-Othmer,* the Remington's references, *Lehmann,* and Cooper & Gunsel. (*See* APO 299; APO 306A; APO 1297; APO 351A; APO 316; APO 270A.) The Court considered *Hager's Handbook* in the First Wave. *See* Astra v. Andrx, 222 F.Supp.2d at 590. *Hager's Handbook* does not specify the nature of the "non-reactive sublayers" or "protective layer" that it discloses, although it does identify an incompatibility between a core and materials used to coat the core. (*See* APO 299; APO 299D at 760, 776; APO 299D-1; APO 299D-3.) *Kirk-Othmer* teaches generally that, to resolve a negative reaction between incompatible materials, one should add a separating layer. (*See* APO 306A at 280.) However, *Kirk-Othmer* relates to tablet compression techniques and the stacking of layers within a tablet's core, not to a subcoating disposed between the core and an enteric coating. (*See id*.) The Remington's references also relate to separating two drugs in a tablet core, not a subcoating separating a drug in a core from its coating. (Langer Tr. 7047:9-7048:25.) *Lehmann* relates to an enteric-coated pharmaceutical and discloses that "[o]ther insulating coats may be necessary if there is any interaction on drugs coming into direct contact with the lacquer coating" (APO 316A at 105682; APO 316A), but provides no guidance as to the type of insulating coats to be employed. Cooper & Gunsel discloses a water- *insoluble* subcoating, unlike the subcoating in the '505 or ' 230 Patents. (APO 270A at 00110066.)

Defendants cite these references for the noncontroversial proposition that subcoating techniques were known in the art at the time of the '505 and '230 Patent applications. However, the primary purpose of the subcoating was different in the '505 and '230 Patents:

[T]his comes up repeatedly in a lot of these references-that Astra didn't stabilize or protect the active ingredient with a subcoating. They stabilized it with an alkaline reacting compound. That in turn led to other problems like gastric acid resistance.

(Langer Tr. 7041:13-17.) Plaintiffs then used a subcoating to address the gastric acid resistance problems. (*See* id.; Langer Tr. 6972:8-6973:20.) The nature of the problem to be solved calls for an inert, water-soluble, rapidly disintegrating subcoating. A person of ordinary skill in the art would not employ a subcoating with these characteristics based on disclosures in the prior art. (*See* Langer Tr. 6988:17-6989:9.) And even if these prior art references were to disclose an inert, water-soluble, rapidly disintegrating subcoating which resolved a negative interaction between an enteric coating and an alkaline core, a person of ordinary skill in the art would have no reason to combine the disclosed subcoating with omeprazole or

another acid labile pharmaceutically active substance because none of these references disclose an ARC. (*See* Langer Tr. 6976:14-6977:14.) It was the addition of the ARC that created the problems with gastric acid resistance that led Plaintiffs to employ a subcoating in the '505 and '230 Patents.

Accordingly, these subcoating references, alone or in combination with other prior art references, viewed from the perspective of a person of ordinary skill in the art, do not render obvious any claims in the '505 or '230 Patents.

c. *The* '226 Patent

Defendants argue that the '226 Patent, in combination with other prior art references, renders obvious claims 1, 5, 6, 8, and 10 of the '505 Patent and claims 6, 7, 10, 13, and 14 of the '230 Patent. The '226 Patent relates to tablets of penicillin and penicillin salts. (*See* ITX 335.) The ' 226 Patent discloses a core containing penicillin surrounded by a barrier layer, which is in turn surrounded by an enteric coating. (*See id*. 8:62-9:20.) The '226 Patent also discloses a second barrier layer disposed on the enteric coating, as well as an additional amount of penicillin disposed on the second barrier layer. (*See id*.) The Court previously found that the ' 226 Patent does not anticipate any claims in the '505 or '230 Patents. *See* Anticipation, *supra* Part III.D. The '226 Patent, alone or in combination with any other prior art reference, also does not render obvious any claims in the '505 or '230 Patents.

First, Defendants have not shown that the '226 Patent discloses omeprazole or an acid labile pharmaceutically active substance. A person of ordinary skill in the art would not apply the teachings of the '226 Patent in formulating the substances claimed in the '505 and '230 Patents because the '226 Patent does not disclose an active ingredient that exhibits the same type of acid sensitivity as those substances.

Second, the '226 Patent contains no reason to combine its barrier layer with any of the prior art references which disclose omeprazole or acid labile pharmaceutically active substances.FN109 The specification of the ' 226 Patent explicitly states that the purpose of the barrier layer is to separate the penicillin salt of the core from the enteric coating because the two are incompatible. (*See* ITX 335 at 2:3-5, 3:13-15, 3:34-35.) However, in order for the ' 226 Patent to provide a reason to combine its subcoating with omeprazole, a person of ordinary skill in the art would have to infer from the ' 226 Patent that any drug core could react with an enteric coating, so any enteric-coated drug would require a subcoating. This is too broad an inference for obviousness purposes, because the prior art disclose many directly enteric-coated pharmaceutical formulations. (*See, e.g.,* PSWTX 1108; ITX 358; APO 252; Langer Tr. 6982:7-21; *see also* Amgen, Inc. v. Hoechst Marion Roussel, 314 F.3d 1313, 1355 (Fed.Cir.2003) ("[W]e hold a presumption arises that ... disclosures in a prior art patent are enabled.").)

FN109. In addition, the Court previously found that Defendants have failed to present clear and convincing evidence that potassium penicillin G in the '226 Patent has an alkaline pH such that the '226 Patent discloses an "alkaline salt" as that phrase is used in the '230 Patent. *See* Anticipation, *supra* Part III.D.

Third, a person of ordinary skill in the art would not have applied the teachings of the '226 Patent to omeprazole, or another acid labile pharmaceutically active substance, because penicillin is not as moisture-sensitive as omeprazole. (Langer Tr. 7013:8-20.) Tsuda states that penicillin can be sugar coated (APO 702 at 4)-a coating that is not appropriate for highly moisture-sensitive drugs like omeprazole. (Langer Tr. 7012:21-7013:20; PSWTX 1108 at 113; Chambliss Tr. 6256:15-20.)

Finally, the '226 Patent actually teaches away from the claimed drug delivery mechanism because the object of the '226 Patent is to deliver a portion of the penicillin to the stomach, and then to deliver the rest of the penicillin further down the gastrointestinal tract. (*See* APO 2129 8:62-9:20.) To achieve this goal, part of

the penicillin in the '226 Patent is disposed outside the enteric coating and part is disposed in the core. (*See* id.; Langer Tr. 7174:3-20.) In contrast to penicillin, omeprazole is destroyed immediately upon release in the stomach. (*See* Langer Tr. 7001:13-20.) The goal of the '505 and '230 Patents is to deliver their active ingredients only in the upper intestine, not in the stomach. (*See* APO 1; APO 3.) Because the goals of the '226 Patent and claimed inventions diverge with respect to such a crucial aspect of drug delivery, the '226 Patent teaches away from omeprazole, and a person of ordinary skill in the art would not have considered the '226 Patent pertinent to an omeprazole formulation. (Langer Tr. 7005:18-7006:15.)

Accordingly, the '226 Patent, alone or in combination with any other prior art references, and viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, does not render obvious any claims in the '505 or '230 Patents.

d. *The '815 Application*

Apotex argues that the '815 Application renders claim 1 of the '230 Patent obvious because it discloses all the elements of claim 1 of the '230 Patent- *i.e.,* an alkaline salt of an acid labile pharmaceutically active substance, namely M-4 carboxylic acid, in a core with a water-soluble, HPMC subcoating, and an enteric coating layer. Apotex also argues that a person of ordinary skill in the art would substitute the subcoat in the '815 Application for the barrier layer from Example I of the '226 Patent and insert it between the core and enteric coating of Example 12 of the '495 Patent, thereby rendering obvious claim 1 of the '505 Patent.

Neither the prior art itself, nor the nature of the problem to be solved or other problems in the field, nor background knowledge would lead a person of ordinary skill in the art to perform this sort of mental gymnastics. First, this Court previously found that M-4 carboxylic acid is not an acid labile pharmaceutically active substance or an alkaline salt as those terms are used the '230 Patent. *See* Anticipation, *supra* Part III.D. Defendants have not shown that the disclosures in the '815 Application relate to an active ingredient that exhibits the same type of acid sensitivity as the substances claimed in the '230 and '505 Patents. A person of ordinary skill in the art would not look to the '815 Application to prepare a solid dosage form of the claimed active ingredients in the '230 Patent or omeprazole in the '505 Patent. (*See* Langer Tr. 7058:5-7060:13.)

Second, a person of ordinary skill in the art would not consider using the subcoats claimed in the '230 and '505 Patents based on the '815 Application, because the '815 Application seeks delivery of its active ingredient in the stomach (*See* APO 281), which is acidic, rather than in more alkaline regions in the upper intestine. A person of ordinary skill in the art seeking to formulate omeprazole would have sought release in the upper intestine in order to enhance the bioavailability of omeprazole.

Third, a person of ordinary skill in the art would not combine the ' 815 Application with the other references in the manner described, because Example 2 of the '815 Application shows that M-4 carboxylic acid can be directly enteric-coated without deleterious effects. (*See* Langer Tr. 7057:12-7058:4.) Omeprazole cannot be directly enteric-coated and remain stable, which is one of the primary reasons for the subcoating innovations of the '505 and ' 230 Patents. A person of ordinary skill would have no reason to combine the '815 Application with other references such as the '226 Patent, the '495 Patent, or the generic subcoating references in the manner described in the claimed inventions, because he would think that omeprazole could be directly enteric-coated and remain stable.

Accordingly, the '815 Application, alone or in combination with any other references, and viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, does not render obvious any claims of the '505 and '230 Patents.

e. *The* '980 Patent

Apotex argues that the '980 Patent renders obvious claim 1 of the '505 Patent. Apotex argues that the '980 Patent teaches that the sodium salt of cefoxitin in the core of its Example 54 is incompatible with the hydroxypropyl methylcellulose phthalate ("HPMCP") enteric coating, because the '980 Patent uses an HPMC pre-coat to separate the core and the enteric coat. Apotex also argues that a person of ordinary skill in the art would substitute the pre-coat in the '980 Patent for the barrier layer from Example I of the '226 Patent and insert it between the core and enteric coating of Example 12 of the '495 Patent, thereby rendering obvious claim 1 of the '505 Patent.

A person of ordinary skill in the art would not view the pre-coat in the ' 980 Patent as a layer meant to separate the core and enteric coat due to incompatibility, which is the primary purpose of the subcoating in the '505 and '230 Patents. Even if the '980 Patent did teach that its core and enteric coat were incompatible and required separation with a pre-coat layer, Apotex has not shown any reason to combine the elements of the prior art references in the manner described. The Court has found that the '980 Patent does not disclose an alkaline salt as that term is used in the '230 Patent, and so it does not anticipate the '230 Patent. *See* Anticipation, *supra* Part III.D. Cefoxitin is more stable in acidic environments than in alkaline environments. *See* Anticipation, *supra* Part III.D. Because the '980 Patent relates to an active ingredient that does not exhibit the same type of acid sensitivity as the substances claimed in the '230 and '505 Patents, a person of ordinary skill in the art would not add the barrier layer from the ' 226 Patent to the omeprazole formulation in the '495 Patent based on the ' 980 Patent. (*See* Langer Tr. 7060:14-7062:20.)

The Court finds that the '980 Patent, alone or in combination with any other references, and viewed through the eyes of a person of ordinary skill in the art, does not render obvious any claims of the '505 and '230 Patents.

f. *The "Cornucopia of Prior Art" and Other Prior Art References*

Defendants also argue that various other prior art references-many of which were not discussed in meaningful detail at trial-render obvious claim 1 of the '505 Patent and claims 1, 6, and 10 of the '230 Patent. These include the '219 Patent, the '015 Patent, the '363 Patent, the '756 Patent, the '685 Patent, the '562 Patent, the '117 Patent, the '403 Patent, Ellis, *Hager's Handbook, Kirk-Othmer,* The Remington's references, *Lehmann,* and Cooper & Gunsel. The Court has already considered the following generic subcoating references: *Hager's Handbook, Kirk-Othmer,* the Remington's references, *Lehmann,* and Cooper & Gunsel. *See supra* Part III.E.4.b. The aforementioned prior art references, alone or in combination with any other prior art references, when viewed from the perspective of a person of ordinary skill in the art, do not render obvious any claims in the '505 or '230 Patents.

The Court previously concluded that the '219 Patent does not anticipate any claims in the '505 or '230 Patents. *See* Anticipation, *supra* Part III.D. The Court also previously discussed how the '219 Patent teaches away from the claimed inventions because it discloses the addition of stearic acid. *See* infra Part III.E.4.g note 113. The '219 Patent, alone or in combination with any other references, and viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, does not render obvious any claims in the '505 or '230 Patents because the subcoatings that it discloses contain fatty acids (*see* Chambliss Tr. 6235:16-6237:6), which would degrade omeprazole.

The '363 Patent is disclosed in the '505 and '230 Patents and was considered by the Patent Examiner. (*See* APO 1; APO 3.) A person of ordinary skill in the art would not combine the disclosures in the '363 Patent with any other prior art references in formulating the claimed substances because the ' 363 Patent attempts to deliver the claimed substance in the lower part of the small intestine and colon, not in the upper intestine. (*See* PSWTX 1A 2:30-57.) Similarly, the '015 Patent attempts to deliver the claimed substance in the stomach rather than the upper intestine.(*See* ITX 312.) Because the goals of these patents and the claimed

inventions diverge, they teach away from omeprazole, and a person of ordinary skill in the art would not have considered the '015 Patent or '363 Patent pertinent to an omeprazole formulation. *See supra* Part III.E.4.c.

The '117 Patent addresses attack by esterases, which is a very different problem than the reduced gastric acid resistance problem solved by Plaintiffs' scientists.FN110 (*See* APO 4111:55-64; Langer Tr. 7071:1-7073:1.) The ' 117 Patent also discloses medicaments such as pancreatin and bromelin, which Defendants have not shown to be acid labile pharmaceutically active substances. (*See* APO 4111:55-64; Langer Tr. 7071:1-7073:1.)

FN110. An esterase is an enzyme that splits esters into an acid and an alcohol.

The '756 Patent discloses a process for coating tablets with alternate tacky and non-tacky layers. (*See* APO 1263.) The '756 Patent teaches very generally that pharmaceutical formulators try to prepare dosage forms which are stable. The '756 Patent has no discernable relevance to Defendants' obviousness arguments. Defendants fail to meaningfully discuss the Ellis reference anywhere in their post-trial submissions.

The '685 Patent discloses 5-asa, which Defendants have not shown is an acid labile pharmaceutically active substance. 5-asa is acidic, not alkaline. (*See* PSWTX 2822; PSWTX 2823.) The '685 Patent also does not explain why there is a subcoating in its Example 2. (*See* APO 424.)

The '562 Patent discloses an HPMCP enteric coating disposed on an HPMC undercoating disposed on a pharmaceutical core. (*See* APO 423.) The '562 Patent does not offer any reason that a person of ordinary skill in the art would have considered trying HPMC as a subcoating for an omeprazole formulation. Even if a person of ordinary skill in the art were interested in using an HPMC undercoat, Scherer and other references would have taught that such an undercoat would require the addition of a strong acid such as stearic acid, which is incompatible with omeprazole. (*See* PSWTX 1621 at 6-7.)

The '403 Patent relates to ways of improving cellulose acetate phthalate enteric coating material by including inert mineral solids. The '403 Patent teaches away from the inventions claimed in the '505 and '230 Patents because it discloses formulations of erythromycin which are directly enteric-coated. (*See* PSWTX 1623A Ex. II, V, VI.)

For all of these reasons, the prior art references encompassed by the asserted "cornucopia of prior art," individually or in combination with any other references, when viewed from the perspective of a person of ordinary skill in the art, do not render obvious any claims in the '505 or '230 Patents.

g. *The Multiple Paths Facing a Person of Ordinary Skill in the Art*

In addition to the prior art references themselves, Plaintiffs' Dr. Langer testified to the multitude of possible paths and dead-ends that a person of ordinary skill in the art could have taken in attempting to formulate a stable omeprazole pharmaceutical formulation, none of which lead to the claimed inventions. (Langer Tr. 6973:11-25; 6975:5-6977:14.) FN111 As explained below,it would require more than ordinary skill to even identify the causes of many of the problems that would arise in formulating an effective oral drug delivery mechanism for omeprazole. Instead of conducting their analysis from the perspective of a person of ordinary skill in the art at the time the inventions were made, Defendants' experts started with the '505 and ' 230 Patents, picked and chose from the already-narrowed list of references that Defendants' lawyers provided, and worked backwards using improper hindsight. (*See* Langer Tr. 6968:7-14; 7079:13-15.)

FN111. Apotex argues that the portions of Dr. Langer's testimony which are based on the report of Dr.

Barry Marshall, an expert retained in the First Wave by Defendant Genpharm, Inc., are not admissible under Fed.R.Evid. 703. (*See* Langer Tr. 6979:16-6982:6.) Rule 703 permits experts to rely on otherwise inadmissible evidence in forming their opinions. Apotex argues that Dr. Marshall's report is not evidence "of a type reasonably relied upon by experts in the particular field" of pharmaceutical chemistry, because it was created for the purposes of patent litigation in Australia about the Australian equivalent of the '505 Patent. Pharmaceutical chemists do not typically rely on reports created for the purpose of patent litigation in performing their regular tasks and duties. In light of Dr. Langer's entire testimony, the Court finds that Dr. Langer formed his own opinion as to whether a person of ordinary skill in the art would be led to the inventions claimed in the '505 and '230 Patents, based in part on the prior art flagged by Dr. Marshall in his report. Those prior art include patents and publications, which are the sorts of references relied upon by working pharmaceutical chemists. Therefore, Dr. Langer's testimony, to which Apotex objects, is admissible.

An effective drug delivery mechanism for omeprazole is very difficult to formulate. (Langer Tr. 6970:18-25). Omeprazole is exceptionally acid labile; sensitive to heat, moisture, solvents, and light; and is most effective when released in the lower intestine. (*Id.*) Overcoming omeprazole's multiple sensitivities in order to reach its prime delivery location was a substantial challenge, and Plaintiffs went through many different approaches before creating a successful formulation. (Langer Tr. 6971:1-5.)

Plaintiffs' solutions to these challenges would have been far from obvious to a person of ordinary skill in the art. The problem-solving strategies necessary to reach the claimed inventions are specifically tailored to the formulation of the claimed inventions. With the possible exception of general drug coating techniques, Defendants have presented no evidence that the many techniques necessary to formulate the claimed compounds are so well-known, or widely used in the field of pharmaceutical formulation or drug delivery system design, that they would fall within the background knowledge of a person of ordinary skill in the art. *See* KSR Int"l, 127 S.Ct. at 1740-41. The Court addresses why general drug coating techniques do not provide a sufficient reason to combine *supra* in Part III.E.4.b.

A person of ordinary skill in the art would not necessarily have chosen to use an enteric coating to protect omeprazole. (Langer Tr. 6977:18-6979:4; PSWTX 2821-15.) For example, a formulator may first have tried a syrup containing an alkaline omeprazole salt, as disclosed in the '495 Patent (ITX 35811:9-37), or a liquid suspension of omeprazole with sodium bicarbonate, as disclosed in Pilbrant & Cederberg (PSWTX 1108 at 118-20). (Langer Tr. 6977:18-6979:4.) Santarus, Inc., a pharmaceutical company, took the latter approach in formulating an omeprazole product called Zegerid.FN112 (Langer Tr. 6977:18-6979:4; PSWTX 972.) A person of ordinary skill in the art considering Pilbrant & Cederberg might have administered an omeprazole granulate with antacids, *e.g.,* in an Alka-Seltzer(R) solution. (Langer Tr. 6978:11-6979:15; PSWTX 2808 at 718.)

FN112. While the Santarus product is not prior art, it demonstrates the viability of the latter approach.

Even if a person of ordinary skill in the art tried an enteric coating, that person would not expect the enteric coating to cause the omeprazole core to become unstable. (Langer Tr. 6976:9-13.) Acid-sensitive compounds are generally compatible with enteric coating materials. (Langer Tr. 6979:16-6980:15.) The Pilbrant & Cederberg article describes a directly enteric-coated omeprazole formulation. (Langer Tr. 6982:11-12; PSWTX 1108 at 116.) The '495 Patent discloses an alkaline omeprazole salt granulate in tablet form that is also directly enteric-coated. (ITX 358 12:1-30; Langer Tr. 6982:7-6983:14.) The '403 Patent contains an example of other acid labile substances that are directly enteric-coated. (Langer Tr. 6982:15-6982:6.) By teaching that omeprazole and other acid labile substances can be directly enteric-coated, these prior art teach away from the claimed inventions. *See* Astra v. Andrx, 222 F.Supp.2d at 586.

A person of ordinary skill in the art who tried an enteric coating and discovered a problem with omeprazole stability that he attributed to the enteric coating would attempt many different approaches other than a subcoating to resolve the instability. (Langer Tr. 6976:14-18.) Such a person would try to avoid using a subcoating. (*See* Block Tr. 6831:7-16; Langer Tr. 6983:15-6985:5.) One common-sense approach to resolve instability between an enteric coating and the core would be to alter the enteric coating by removing monomers and small acidic pieces from the enteric coating in order to render the enteric coating inert, or by picking an inert enteric coating material to begin with, as at least one formulator did. (Langer Tr. 6984:1-6985:12; PSWTX 1624 at 2:40-44, 3:60, 5:15-22.)

Even if a formulator chose not to alter the enteric coating, it would be more sensible to resolve the instability by altering the core rather than adding a subcoating. (Langer Tr. 6986:10-11.) To do so, a person of ordinary skill in the art would probably have added an antioxidant to the core, such as cysteine, sodium ascorbate, or sodium sulfite, rather than adding an ARC. (*See id.;* PSWTX 2592.) A person of ordinary skill in the art would have selected cysteine because it has been shown to prevent omeprazole discoloration. (*See* PSWTX 2594 at 482.) A person of ordinary skill in the art would not have added an ARC. (*See* Langer Tr. 6986:10-11.)

If a formulator were to add an ARC to the core rather than an antioxidant, neither the prior art, the nature of the problem to be solved, other problems in the field, nor his background knowledge would reveal that adding the ARC would cause increased solubility and decreased gastric acid resistance. Furthermore, a person or ordinary skill in the art would probably pursue a number of approaches other than employing a subcoating to solve these problems, including: (1) controlling the permeability of the enteric coat by increasing the thickness of the enteric coat; (2) adding components to the enteric coat such as pigments or plasticizers; or (3) using relatively insoluble ARCs rather than using a subcoating. (Langer Tr. 6987:8-6988:14.) This third option is the approach taken by Takeda Chemical Industries, Ltd. ("Takeda") in EPO 237 200 (the "'200 Application"), which relates to omeprazole and proton pump inhibitor formulations. (Langer Tr. 6988:1-7; PSWTX 787 at 8:36-41, 13:26-55, 14:34-15:29.) None of the examples in the '200 Application contain a subcoating, and it warns that polyvinyl pyrrolidine ("PVP") and polyethylene glycol ("PEG")-two of the materials the '505 and '230 Patents suggested as subcoating materials-would be incompatible with benzimidazole compounds like omeprazole. (Langer Tr. 6987:24-6988:16.) Thus, the '200 Application teaches away from the use of a subcoating. (Langer Tr. 6988:12-14.)

Additionally, if a person of ordinary skill in the art were to try a subcoating, that person would not select a subcoating that was water-soluble or rapidly disintegrating. (Langer Tr. 6988:17-6989:9.) A person of ordinary skill in the art would want to protect the omeprazole for as long as possible to ensure its release in the large intestine, where it would be most effective. (Langer Tr. 6989:1-6991:1; PSWTX 785 at 64, 69; PSWTX 1612 at 138.) Employing a water-soluble, rapidly disintegrating subcoating is ingenious because it is counter-intuitive. This is an excellent example of a drug formulation technique that falls beyond the background knowledge of a person of ordinary skill in the art and requires more than ordinary skill.

Finally, if a person of ordinary skill in the art were to employ a water-soluble, rapidly-disintegrating subcoat and an ARC in the core, that person would probably add a higher fatty acid, such as stearic acid, to the subcoating based on teachings in the prior art.FN113 (Langer Tr. 6993:8-14; 6997:1-6998:25.) Because omeprazole is so acid labile, adding an acid to the subcoat would degrade the omeprazole in the core and render the drug ineffective. (Langer Tr. 6993:6-7.) Thus, the prior art teaches away from the claimed invention.

FN113. Two prior art references support this conclusion by teaching the addition of a higher fatty acid such as stearic acid: the '219 Patent and the Scherer Patent. (*See* ITX 53; PSWTX 1621.) The '219 Patent addresses a similar problem to the instant case, namely, an enteric-coated alkaline core losing its gastric

fluid resistance properties over time during storage. (ITX 53 at 134.) The Scherer Patent specifically discusses the problem of interactions between an alkaline core and an enteric coating and resolves the problem with an acidic subcoating. (PSWTX 1621 at 6-7.) Nothing in either of these references suggests that a water soluble subcoat would work without having an acid present.

As shown in the preceding analysis, a person of ordinary skill in the art would not be able to identify the causes of many of the problems that would arise at each stage of the omeprazole formulation process. Both identifying the causes of these problems and solving them in the manner disclosed in the ' 505 and '230 Patents would not be obvious to a person of ordinary skill in the art.

h. *Market Pressures*

Defendants have not identified a design need or market pressure in the pharmaceutical formulation industry at the time of invention that provides a reason for combining known elements in the manner claimed. *See* KSR Int"l, 127 S.Ct. at 1740-41. In *KSR,* the Supreme Court considered a situation where there were a "finite number of identified, predictable solutions" to the problem at issue such that a person of ordinary skill in the art would be led by design needs or market pressures to try each possible solution in turn. *Id*. at 1742, 1744. The patent at issue claimed an adjustable automobile pedal with an electronic sensor attached to its pivot point. *Id*. at 1734-35. The ordinarily skilled automotive engineer in *KSR* faced a "marketplace that created a strong incentive to convert mechanical pedals to electronic pedals." *Id*. at 1744. The claimed innovation in *KSR* would have happened naturally in light of market pressures because there were only a few possible solutions to the brake pedal design problem at issue. *See id*. at 1742, 1744-45. Here, by contrast, there were "thousands and thousands of permutations and paths" facing a person of ordinary skill trying to formulate omeprazole. (Langer Tr. 6977:5-7.) The Patents are genuine innovations, not predictable upgrades. *See* KSR, 127 S.Ct. at 1739-40, 1745.

i. *Dependent and Process Claims*

Because the Court finds that Defendants have failed to show that any combination of prior art render obvious claims 1 of the '505 and '230 Patents, Defendants cannot demonstrate that any combination of prior art render obvious any of the asserted claims which are dependent on claims 1. The asserted dependent claims include claims 3, 4, 5, 6, 7, 8, 10, and 11 of the ' 505 Patent and claims 6, 7, 8, 10, 13, and 15 of the '230 Patent.

Mylan/Esteve argues that the '495 Patent, the '980 Patent, and the '226 Patent render obvious the process claims: claim 14 of the '505 Patent and claim 12 of the '230 Patent. Mylan/Esteve did not present any evidence at trial regarding obviousness or anticipation; rather, it chose to rely on the evidence submitted by Impax and Apotex. No expert witnesses addressed the validity of the process claims because these claims are asserted only against Mylan/Esteve, not against Impax or Apotex. Where a patent challenger fails to set forth persuasive evidence of invalidity, the very existence of the patent satisfies the burden on the validity issue. *See* Canon Computer Sys., Inc. v. Nu-Kote Int'l, Inc., 134 F.3d 1085, 1088 (Fed.Cir.1998). Accordingly, the existence of the '505 and '230 Patents satisfies Plaintiffs' burden as to the validity of the process claims.

Moreover, the '495 Patent, the '980 Patent, and the '226 Patent do not render obvious the process claims for the same reasons that they do not render obvious claims 1 of the '505 and '230 Patent. *See supra* Part III.E.4. Both process claims disclose a process for the preparation of an oral pharmaceutical containing a core, a subcoating, and an enteric coating which mirrors the composition of the pharmaceuticals disclosed in claims 1 of the ' 505 and '230 Patents. The asserted prior art references do not render obvious the claimed processes for all the reasons that they do not render obvious the claimed pharmaceutical formulations themselves. *See*

supra Part III.E.4.

5. *Secondary Considerations of Non-Obviousness*

Lastly, objective indicia of non-obviousness may include commercial success, failure of others, long felt but unsolved need, movement of the skilled in a different direction, copying, or other objective events which indicate non-obviousness. *See* Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299 (Fed.Cir.2006); Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1569 (Fed.Cir.1987). Where, as here, a patent challenger fails to present a prima facie showing of obviousness, the patent holder need not present rebuttal evidence of non-obviousness, since the challenger has not met its initial burden. *See* Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1350 (Fed.Cir.2000). For the reasons discussed above, Defendants have failed to establish a prima facie case for obviousness, and the Court has no need to evaluate the parties' arguments regarding secondary considerations of non-obviousness.

F. *Conclusion*

Defendants have failed to show by clear and convincing evidence that any claims in the '505 or '230 Patents are rendered invalid for: (1) failing to satisfy the best mode, enablement, or written description requirements of 35 U.S.C. s. 112, para. 1; (2) being in the public use or described in a printed publication more than one year prior to the date of the application for patent in the United States under 35 U.S.C. 102(b); or (3) obviousness under 35 U.S.C. s. 103(a).

CONCLUSION

For the reasons stated above, the Court finds the following: Defendants Mylan and Esteve do not infringe the asserted claims of the '505 and '230 patents. Defendant Lek does not infringe the asserted claims of the '505 and ' 230 patents. Defendant Apotex literally infringes claims 1, 5, 6, and 10 of the '505 Patent, and claims 1, 6, 7, and 13 of the '230 patent. Defendant Impax literally infringes claims 1, 5, 6, 8, and 10 of the '505 Patent, and claims 1, 6, 7, 10, and 13 of the '230 Patent. The asserted claims of the '505 and '230 Patents are valid.

Astra is ordered to submit a proposed judgment incorporating the rulings contained in this Opinion and Order to the Court on or before June 6, 20007. Defendants shall file any objections on or before June 11, 2007.

SO ORDERED.

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