UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

WARNER CHILCOTT LABORATORIES IRELAND LIMITED, *et al.*, **Plaintiffs,** **v.** **IMPAX LABORATORIES, INC., *et al.*,** **Defendants.**	**Civ. No. 2:08-cv-06304 (WJM)**
WARNER CHILCOTT LABORATORIES IRELAND LIMITED, *et al.*, **Plaintiffs,** **v.** **MYLAN PHARMACEUTICALS INC., *et al.*,** **Defendants.**	**Civ. No. 2:09-cv-02073 (WJM)**
WARNER CHILCOTT LABORATORIES IRELAND LIMITED, *et al.*, **Plaintiffs,** **v.** **IMPAX LABORATORIES, INC.,** **Defendant.**	**Civ. No. 2:09-cv-01233 (WJM)**

OPINION

WILLIAM J. MARTINI, U.S.D.J.:

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Plaintiffs Warner Chilcott Company, LLC and Warner Chilcott (US), LLC (collectively, "Warner Chilcott") and Mayne Pharma International Pty. Ltd. ("Mayne") are pharmaceutical companies that develop or market brand name drug products. Mayne was formerly known as F. H. Faulding & Co., Ltd. ("Faulding"). Mayne is the owner of United States Patent No. 6,958,161 ("the '161 Patent"), entitled "Modified Release Coated Drug Preparation." The '161 Patent covers a modified release preparation of doxycycline hyclate that helps to maintain the drug's intended rate of release over time. Warner Chilcott has exclusive rights to market and sell products covered by the '161 Patent in the United States. Warner Chilcott sells such products under the brand name Doryx® Delayed Release Tablets ("Doryx Tablets").

Defendants Mylan Pharmaceuticals Inc. and Mylan Inc. (collectively "Mylan") and Impax Laboratories, Inc. ("Impax") are generic pharmaceutical companies. Mylan and Impax each filed Abbreviated New Drug Applications ("ANDAs") with the Food and Drug Administration ("FDA"), seeking approval to market generic versions of Doryx Tablets. In response to Defendants' ANDA filings, Plaintiffs filed these Hatch-Waxman actions, alleging that Mylan and Impax infringed the '161 Patent. Mylan and Impax assert that their generic products do not infringe the '161 Patent. Mylan and Impax also assert that the '161 Patent is invalid on the grounds of anticipation and obviousness.

The Court conducted a seven-day bench trial between February 1, 2012 and February 9, 2012. The parties submitted post-trial briefs and proposed findings of fact and conclusions of law on February 21, 2012. After carefully considering the record evidence and the parties' submissions, the Court makes the following findings.

First, the Court finds that Plaintiffs failed to prove, by a preponderance of the evidence, that Mylan's ANDA product infringes the '161 Patent. More specifically, the Court finds that Plaintiffs failed to prove that Mylan's ANDA product has a stabilizing coat, as required by the '161 Patent. Mylan does not apply a stabilizing coat to its ANDA product. And five widely-accepted scientific testing methods failed to show the presence of a stabilizing coat in Mylan's product. The one, novel "humidity test" relied on by Plaintiffs does not meet the *Daubert* standard for admissibility. Even if the "humidity test" met the *Daubert* standard, Plaintiffs still failed to prove that there was a stabilizing coat in Mylan's product. The Court also finds that Plaintiffs failed to prove that the alleged stabilizing coat in Mylan's product kept the migration of core materials to a minimum, such that the interaction of core materials with coating materials was reduced or prevented.

Second, the Court finds that Plaintiffs failed to prove, by a preponderance of the evidence, that Impax's ANDA product infringes the '161 Patent. The Court finds that Plaintiffs failed to prove that Impax's ANDA product has a stabilizing coat. Impax does

not apply a stabilizing coat to its ANDA product. And five widely-accepted scientific testing methods failed to show the presence of a stabilizing coat in the unaltered seeds in Impax's tablet. The one, novel "acetone wash test" relied on by Plaintiffs does not meet the *Daubert* standard for admissibility. Even if the "acetone wash test" met the *Daubert* standard, Plaintiffs still failed to prove that there was a stabilizing coat in Impax's product. The Court also finds that Plaintiffs failed to prove that the alleged stabilizing coat in Impax's product kept the migration of core materials to a minimum, such that the interaction of core materials with coating materials was reduced or prevented. The Court finds that Plaintiffs met their burden of proving that Impax's product provided the required level of dissolution storage stability. However, this does not change the Court's overall finding that Impax's ANDA product is non-infringing.

Third, the Court finds that Defendants failed to prove, by clear and convincing evidence, that the '161 Patent is invalid as anticipated by United States Patent No. 5,413,777 ("the '777 Patent"). The Court finds that the '777 Patent does not inherently disclose the dissolution storage stability limitations of the '161 Patent. The Court also finds that the '777 Patent does not anticipate the stabilizing coat limitation of the '161 Patent. Lastly, the Court finds that the '777 Patent does not anticipate the limitations that require that the active ingredient be an acid salt of doxycycline. The Court finds that the '777 Patent anticipates the tablet limitation of the '161 Patent. However, this does not change the Court's overall finding that the '161 Patent is not invalid as anticipated.

Fourth, the Court finds that Defendants failed to prove, by clear and convincing evidence, that the '161 Patent is obvious in light of prior art. The Court finds that the dissolution storage stability limitations of the '161 Patent are not rendered obvious by the prior art. The Court also finds that the stabilizing coat limitation of the '161 Patent is not rendered obvious by the prior art. Lastly, the Court finds that the limitations of the '161 Patent relating to the percentage of coated cores in the tablet are not rendered obvious by the prior art.

Finally, the Court finds that Defendants failed to establish their exceptional case claims by clear and convincing evidence. Accordingly, Mylan and Impax are not entitled to an award of attorneys' fees and expert fees under 35 U.S.C. § 285.

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). All proposed findings of fact and conclusions of law inconsistent with those set forth herein are rejected.

I. JURISDICTION, VENUE, AND APPLICABLE LAW

This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). This action arises under the Patent Laws of the United States, 35 U.S.C. § 1, *et seq.*; Defendants' counterclaims arise under the Declaratory Judgment Act,

28 U.S.C. §§ 2201 and 2202, and the Patent Laws of the United States, 35 U.S.C. § 1, *et seq*. Because this action arises under the Patent Laws, the Court must apply the precedents of the United States Court of Appeals for the Federal Circuit, which has jurisdiction over any appeal of this judgment. *See* 28 U.S.C. § 1295(a). The Court has personal jurisdiction over Defendants; no Defendant has contested personal jurisdiction in these actions. Venue is proper in this district under 28 U.S.C. § 1391(b) and (c), and 28 U.S.C. § 1400(b).

II. BACKGROUND[1]

Understanding the invention at issue requires a brief excursion into the history of the Doryx products.

A. THE DORYX® CAPSULE

Prior to the invention of the '161 Patent, Faulding developed a delayed release doxycycline hyclate capsule formulation, which was marketed under the brand name Doryx® Delayed Release Capsules ("Doryx Capsules" or the "Capsule"). Joint Appendix ("JA") 1470:2-5, ECF No. 288. Doxycycline hyclate is a broad-spectrum antibiotic that is used to treat bacterial infections such as severe acne. *See* JA 5469.

There are two issues associated with the rate at which doxycycline hyclate is released in the body (a drug's rate of release in the body is referred to as the drug's "dissolution profile"). If doxycycline hyclate is released immediately in the stomach, patients may experience gastric upset that could result in nausea and vomiting. JA 131:6-16; JA 1583 col. 2, ll. 55-64; JA 3289. If the drug is released too slowly, however, there will be an absorption (or "bioavailability") problem because less of the drug will be absorbed in the bloodstream. JA 1468:23-1470:1; JA 3299; JA 3385.

To address the competing problems of gastric upset and bioavailability, Faulding developed a modified release preparation[2] of doxycycline hyclate. JA 3289-90; JA 5653. Specifically, Faulding designed a drug formulation in which pellets containing doxycycline hyclate were coated in a special delayed release coating. JA 131:3-5. Multiple pellets would then be encased in a gelatin capsule. JA 1556:14-18; JA 5582. The special delayed release coating developed by Faulding maximized release of the

[1] The Court's findings of fact are not limited to those in this section, but also include any factual determinations that appear elsewhere in this Opinion. Many of the findings of fact are substantiated with citations to testimony or documentary evidence; however, such citations are not meant to be exhaustive authority for the finding. Some of the findings are based upon the record or inferences from the record that are not cited. Some of the citations may also include demonstratives. Any demonstratives included in the citations are cited for informational purposes only; such demonstratives do not constitute evidence.

[2] A "modified release preparation" is a drug formulation that prevents the active ingredient from being immediately released into the body. JA 1583. "Modified release preparations" encompass all formulations that do not have immediate rates of release, including delayed release formulations, extended release formulations, and sustained release formulations. *Id.*

active ingredient in the upper part of the small intestine. JA 3289-90. By creating a drug formulation that released the majority of the drug in the small intestine, Faulding solved the gastric upset problems associated with release in the stomach, and the bioavailability problems associated with release further down the gastrointestinal tract. JA 1470:2-10; JA 1471:23-1472:24; JA 3290.

An important aspect of the manufacture of pharmaceutical products is their stability over extended periods of time, which is commonly referred to as "shelf life." JA 1583. There are two general aspects to the stability or "shelf life" of a drug: (1) the chemical stability of the ingredients themselves ("chemical stability"), and (2) the maintenance over time of the drug's originally intended rate of release ("dissolution storage stability"). JA 1475-76; JA 1583; JA 3388.

The Doryx Capsule was marketed with a two year shelf life. JA 1311:13-14. The two-year shelf life in this case referred to the product's chemical stability: the active ingredient still functioned as an antibiotic after two years of storage. However, in 1990, scientists at Faulding observed that there was a problem with the drug's dissolution storage stability. JA 3286-91. They observed that the drug's rate of release would increase over time. JA 3290; JA 1470-72. Thus, if the drug were ingested immediately after being manufactured, the active ingredient would be released in the small intestine, as originally intended. But if the drug were ingested after sitting in storage for two years, more of the active ingredient would be released in the stomach, leading to an increase in the incidence of nausea. JA 3290; JA 1471:23-1472:20; JA 3386.

Faulding scientists were unable to determine the precise cause of the dissolution storage stability problem.[3] JA 3291; JA 1472:25-1473:7; JA 3387. In October 1993, the scientists compiled a long list of possible reasons for the dissolution instability. JA 3287-88; JA 1473:20-1475:3. The list contained 74 possible causes for the instability, and focused on factors related to the delayed release coating. *See* JA 3287-88. It was not until years later that Faulding unexpectedly discovered a solution to the dissolution storage stability problem. JA 1475:9-17; JA 1476:25-1477:15; JA 3389.

B. THE '161 PATENT AND THE DORYX® TABLET

The '161 Patent embodies Faulding's solution to the dissolution storage stability problem. Faulding scientists found that adding a "stabilizing coat"[4] between the doxycycline hyclate core and the delayed release coating of the pellets prolonged the shelf life of the Doryx Capsule's rate of release. JA 1583-89. The scientists postulated that this "stabilizing coat" improved dissolution stability by minimizing the interaction between the active ingredient and the delayed release coating. *See* JA 1585 col. 6, l. 67 – 1586 col. 7, l. 2. The central issue for infringement is whether Mylan and Impax's

[3] To this day, Mayne scientists do not know precisely why the Doryx Capsules did not retain a stable dissolution profile after storage. *See* JA 1418:17-21.

[4] The Court will refer to the intermediate coating described in the '161 Patent as the "stabilizing coat," even though, in the '161 Patent, "stabilising" is spelled with an "s."

ANDA products contain this "stabilizing coat." The '161 Patent also provides that the pellets can be contained in a tablet instead of a capsule. JA 1589. That is why products covered by the '161 Patent are sold under the brand name "Doryx Tablets."

Claims 1 and 21 of the '161 Patent describe the three-part structure for the pellets: (1) a core element containing the active ingredient; (2) a modified release coating; and (3) a "stabilizing coat" between each core element and its modified release coating. *See* JA 1588 col. 12, ll. 36-47. The '161 Patent explains that the stabilizing coat "is intended to keep migration of core materials to a minimum such that their interaction with coating materials is reduced or prevented." JA 1585 col. 6, l. 67 - 1586 col. 7, l. 2. The '161 Patent states that the stabilizing coat can be comprised of "any suitable material." JA 1586 col. 7, ll. 4-5.

Claims 1, 2, 3, and 21 of the '161 Patent (among others) describe the Patent's dissolution storage stability limitations. Immediately after manufacturing, the pellets have their originally intended rate of release (a drug's originally intended rate of release is referred to as the drug's "pre-storage dissolution profile"[5]). *See* JA 1583. After a certain amount of time in storage, the drug's rate of release can change (a drug's rate of release after storage is referred to as the drug's "post-storage dissolution profile"). *Id.* The dissolution storage stability limitations of the '161 Patent set forth the extent to which the drug's pre-storage rate of release can differ from its post-storage rate of release. For example, Claim 1 of the Patent states that "the amount of active ingredient released at any time on a post-storage dissolution profile [must be] within 40 percentage points of the amount of active ingredient released at any time on a pre-storage dissolution profile." JA 1588 col. 12, ll. 43-47. The '161 Patent provides that dissolution stability testing should be conducted according to FDA guidelines, which specify that the product should be tested "in its container and package" under "accelerated conditions." JA 1583 col. 2, ll. 29-37.

Claims 16 through 22 of the '161 Patent describe the Patent's tablet limitations. The claims provide that a plurality of pellets can be compressed to form a tablet. *See* JA 1589 col. 13, ll. 44-46. Several claims also set forth the percentage of the preparation that can be comprised of pellets. Claim 17, for example, describes a preparation "wherein the percentage of coated core elements in each tablet is in the range of 20 to 40 by weight of the total dosage weight." JA 1589 col. 14, ll. 1-3.

The patent application that led to the '161 Patent was filed April 12, 2002.[6] JA 1579. The '161 Patent was issued by the United States Patent and Trademark Office ("PTO") on October 25, 2005. Final Pretrial Order, Stipulation of Facts ("SF") ¶¶ 9-10, ECF No. 252; JA 1578. The '161 Patent is the sole patent-in-suit.

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[5] A "profile" means that measurements were taken at more than one time point. JA 140:24-141:13. A dissolution "profile," for example, would reflect how much of the active ingredient is released after 10 minutes, then after 20 minutes, then after 30 minutes, etc.

[6] The inventors of the '161 Patent are David Hayes, Angelo Lepore, Stefan Lukas, and Eugene Quinn. SF ¶ 11.

C. PROCEDURAL HISTORY

Mayne filed New Drug Application ("NDA") No. 50-795 with the FDA for 75 mg, 100 mg, and 150 mg Doryx Tablets. SF ¶ 14. On May 6, 2005, the FDA approved the use of 75 mg and 100 mg Doryx Tablets. SF ¶ 15. On June 20, 2008, the FDA approved the use of 150 mg Doryx Tablets. SF ¶ 26.

Mylan submitted to the FDA ANDA Nos. 90-431 and 91-052, seeking approval to market generic versions of 75 mg, 100 mg, and 150 mg Doryx Tablets. SF ¶¶ 19, 29. Mylan included with its ANDA filings certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certifications") asserting that the '161 Patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Mylan's proposed generic drugs. SF ¶¶ 20, 30. Mylan received final FDA approval of its 75 mg and 100 mg ANDA products in December 2010, and thereafter began selling its 75 mg and 100 mg ANDA products in the United States. SF ¶ 21. Mylan received tentative FDA approval for its 150 mg ANDA product on June 10, 2011. SF ¶ 31.

Impax submitted to the FDA ANDA Nos. 90-505 and 91-132, seeking approval to market generic versions of 75 mg, 100 mg, and 150 mg Doryx Tablets. SF ¶¶ 16, 27. Impax included with its ANDA filings Paragraph IV Certifications asserting that the '161 Patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Impax's proposed generic drugs. SF ¶ 17, 28. Impax received final FDA approval of its 75 mg and 100 mg ANDA products in December 2010. SF ¶ 18.

In response to Defendants' ANDA filings, Plaintiffs filed these Hatch-Waxman actions, alleging that Mylan and Impax infringed the '161 Patent. These actions have been consolidated for purposes of discovery and trial.

On July 11, 2011, the parties participated in a hearing pursuant to *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995) (en banc). On July 20, 2011, this Court issued an opinion and order reflecting the Court's construction of the five disputed claim terms of the '161 Patent. The Court construed the phrase "stabilising coat is provided between each core element and its modified release coating" in Claims 1 and 21 to mean:

> [A] layer of material(s) between each core element and its modified release coating, which keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented.

Warner Chilcott Labs. Ireland v. Impax Labs., Inc., No. 08-6304, 2011 WL 2971155, at *7 (D.N.J. Jul. 20, 2011).

On August 24, 2011, Plaintiffs moved for a preliminary injunction to enjoin Mylan from selling its 150 mg ANDA product. *See* Mot. for Prelim. Inj., ECF No. 33 (No. 09-2073). On September 22, 2011, this Court granted Plaintiffs' motion, and Mylan subsequently appealed. *See* ECF Nos. 53, 56 (No. 09-2073). On December 12, 2011, the Federal Circuit vacated the preliminary injunction and remanded the action for further

proceedings. *See Warner Chilcott Labs. Ireland v. Impax Labs., Inc.*, No. 11-1611, 2011 WL 6144301 (Fed. Cir. Dec. 12, 2011). In remanding the action, the Federal Circuit noted that "the district court may consider entering a temporary restraining order after this court's mandate issues, then consolidating the preliminary injunction hearing with the bench trial on the merits." *Id.* at *5.

Consistent with the Federal Circuit's recommendation, this Court consolidated the preliminary injunction hearing with a bench trial on the merits, which the Court conducted between February 1, 2012 and February 9, 2012. At trial, Mylan's counsel indicated that Mylan received final FDA approval for its 150 mg ANDA product. JA 1334:11-15. On February 8, 2012, pursuant to the recommendation of the Federal Circuit, this Court entered a temporary restraining order enjoining Mylan from launching its generic version of 150 mg Doryx Tablets. TRO, ECF No. 133 (No. 09-2073); TRO, ECF No. 269 (No. 08-6304). The temporary restraining order was entered with the consent of the parties, "in order to permit this Court time to complete the pending trial of this matter, consider the evidence and render a decision." *Id.*

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The Court will now address: (1) Plaintiffs' infringement cases against Mylan and Impax, (2) Defendants' invalidity defenses of anticipation and obviousness, and (3) Defendants' exceptional case claims.

III. INFRINGEMENT

To prove infringement, the patentee must show that it is more likely than not that the proposed ANDA product would, if commercially marketed, meet the claim limitations of the patent-in-suit. *See Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1287 (Fed. Cir. 2010); *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). Infringement must be proved by the patentee by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988); *Kegel Co., Inc. v. AMF Bowling, Inc.*, 127 F.3d 1420, 1425 (Fed. Cir. 1997).

A determination of infringement is a two-step analysis. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1466 (Fed. Cir. 1998). First, the Court construes the scope and meaning of the asserted patent claims as a matter of law. *Id.* In this case, the Court construed the claim terms at issue in its Opinion dated July 20, 2011. *See Warner Chilcott Labs. Ireland v. Impax Labs., Inc.*, No. 08-6304, 2011 WL 2971155, at *7 (D.N.J. Jul. 20, 2011). Second, the construed claims are compared to the allegedly infringing product to determine whether each and every claim limitation is present. *Cybor Corp.*, 138 F.3d at 1467. Literal infringement, a type of direct infringement, exists if any one of a patent's asserted claims covers the alleged infringer's product. *See Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 374 (1996). Literal infringement

is shown where each limitation of at least one asserted claim of the patent-in-suit is found in the alleged infringer's product. *See Panduit Corp. v. Dennison Mfg. Co., Inc.*, 836 F.2d 1329, 1330 n.1 (Fed. Cir. 1987).

Plaintiffs allege that Mylan and Impax's ANDA products both infringe the '161 Patent. The Court will first address Defendants' motions for judgment as a matter of law on the issue of infringement. The Court will then address Plaintiffs' infringement case against Mylan, followed by Plaintiffs' infringement case against Impax.

A. MOTIONS FOR JUDGMENT AS A MATTER OF LAW

During the bench trial, Defendants each made oral motions for judgment as a matter of law pursuant to Federal Rule of Civil Procedure 50. JA 184:1-1861. Because Rule 50 pertains only to jury trials, the Court will construe Defendants' motions as motions for judgment on partial findings under Federal Rule of Civil Procedure 52(c). *Compare* Fed. R. Civ. P. 50(a)(1) (Motion for judgment as a matter of law may be made after "a party has been fully heard on an issue during a jury trial"), *with* Fed. R. Civ. P. 52(c) (Motion for judgment on partial findings may be made after "a party has been fully heard on an issue during a nonjury trial").

Consistent with the terms of Rule 52(c), the Court exercised its discretion to reserve on the motions during the trial. JA 611:6-8; Fed. R. Civ. P. 52(c) ("The court may, however, decline to render any judgment until the close of the evidence."); *see also Payne ex el Estate of Payne v. Equicredit Cor. of America*, 71 F. App'x 131, 133 (3rd Cir. 2003) (The district court was "clearly within the strictures of Rule 52(c), and properly acted within its discretion to decline to render judgment until the close of all evidence."). The Court now concludes that the best course of action is to render a judgment based on due consideration of all of the evidence, testimony, and applicable law, and the parties' post-trial submissions. Accordingly, the Rule 52(c) motions are **DENIED**.

B. MYLAN'S ANDA PRODUCT DOES NOT INFRINGE THE '161 PATENT

Plaintiffs assert that Mylan's ANDA product infringes claims 1, 2, 5, 10, 16, 17, and 20-22 of the '161 Patent. SF ¶ 36.

Mylan's ANDA product, like the Doryx Tablet, is comprised of a series of beads that have been compressed into tablet. The parties agree that the beads have a doxycycline hyclate core and a delayed release coating. The only issue for infringement is whether Mylan's beads contain a "stabilizing coat." JA 145:11- 146:25. If the Court finds that Mylan's product contains a stabilizing coat, then Mylan's product infringes the '161 Patent. If the Court finds that Mylan's product does not contain a stabilizing coat, then Mylan's product does not infringe.

Consistent with this Court's claim construction, to prove that Mylan's ANDA product contains a "stabilizing coat," Plaintiffs must show that the product has:

> [A] layer of material(s) between each core element and its modified release coating, which keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented.

Warner Chilcott Labs. Ireland, 2011 WL 2971155, at *7.

For the reasons set forth below, the Court finds that Plaintiffs failed to prove, by a preponderance of the evidence, that Mylan's ANDA product infringes the '161 Patent. Specifically, the Court finds that Plaintiffs failed to prove that: (1) Mylan's ANDA product has "a layer of material(s) between each core element and its modified release coating"; and that (2) the alleged stabilizing coat "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

1. Plaintiffs Failed To Prove That Mylan's ANDA Products Has "A Layer Of Material(s) Between Each Core Element And Its Modified Release Coating"

Plaintiffs assert that Mylan's ANDA product has a "stabilizing coat." Specifically, Plaintiffs allege that each bead in Mylan's ANDA product has a 10 to 40 micron layer of povidone and crospovidone between its core elements and its delayed release coating. *See* JA 154:7-19; JA 201:23-202:2.

The Court finds that Plaintiffs failed to prove that Mylan's ANDA product has "a layer of material(s) between each core element and its modified release coating." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7. The Court makes this finding for three reasons. First, it is undisputed that Mylan does not apply a stabilizing coat to its ANDA product. Second, five widely-accepted scientific testing methods did not show the presence of a stabilizing coat in Mylan's product. Finally, the one novel test that Plaintiffs rely on failed to show that there is a stabilizing coat in Mylan's product. Each of these findings is explained in greater detail below.

a. Mylan Does Not Apply a Stabilizing Coat to its ANDA Product

It is undisputed that Mylan does not apply a stabilizing coat to its ANDA product during the manufacturing process.

The manufacture of Mylan's ANDA product takes place in three stages. In the first stage, Mylan manufactures the uncoated active ingredient core beads by thoroughly mixing dry ingredients doxycycline hyclate, lactose, and crospovidone with purified water, sodium lauryl sulfate, povidone, and sodium chloride. JA 597:11-598:11. The resulting material is fed into an extruder machine, and the extruded material is then spheronized, dried, and screened. JA 598:18-599:12; JA 944:11-945:2. In the second stage, the uncoated core beads are fed into a specialized coating unit referred to as a Wurster coater, where a single, uniform delayed release coating containing hypromellose phthalate ("HPMCP") is sprayed onto the beads. JA 599:14-24. In the final stage, the delayed release coated beads are blended with inactive ingredients and fed into a tablet-

compressing machine to produce 75 mg, 100 mg or 150 mg tablets. JA 600:3-12. Plaintiffs do not dispute that Mylan applies a single delayed release coating onto its beads and does not apply any other coating. JA 427:25-428:5.

b. Five Widely-Accepted Scientific Testing Methods Did Not Show the Presence of a Stabilizing Coat In Mylan's Product

Five widely-accepted scientific testing methods did not show the presence of a stabilizing coat in Mylan's product. These five testing methods are: (1) Confocal Raman spectroscopy ("Raman"); (2) Time of Flight Ion Mass Spectroscopy ("ToF-SIMS"); (3) Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy ("ATR-FTIR"); (4) Atomic Force Microscopy ("AFM"); and (5) Scanning Electron Microscopy ("SEM").

The Court finds that each of these five testing methods is scientifically reliable and that the test results as a whole demonstrate that there is no stabilizing coat in Mylan's product. The Court specifically finds that Raman and ToF-SIMS data affirmatively show that there is no stabilizing coat in Mylan's product. The Court finds that the ATR-FTIR, AFM, and SEM tests conducted by Plaintiffs' expert, Dr. Martyn Davies, confirm that there is no stabilizing coat.

i. Raman Spectroscopy

For over twenty years, Raman has been used to determine the identity and location of materials in pharmaceutical products. JA 622:25-623:6. Raman has been subjected to extensive and rigorous peer review and is widely accepted and used by the pharmaceutical industry, academia, and contract labs. JA 630:16-631:1. Raman is the primary testing method relied on by Mylan, and was one of the first testing methods conducted by Plaintiffs' expert, Dr. Davies.

Dr. Neil Everall, Mylan's expert witness on Raman spectroscopy, is a world-renowned expert in Raman and infrared technology. JA 617:24-618:3. He was the first scientist to publish an article regarding the fundamentals of Raman spectroscopy, and the proper acquisition and interpretation of Raman data. JA 617:1-13; JA 3644-54. He is the editor of a definitive five volume encyclopedia set regarding Raman and infrared spectroscopy, and has analyzed hundreds of pharmaceutical samples using these techniques. JA 617:14-18; JA 3644-54. The Court qualified Dr. Everall as an expert regarding the application of Raman infrared spectroscopy and the interpretation of Raman and infrared data. JA 619:19-620:2.

The Court finds that Raman data provides the strongest evidence that there is no stabilizing coat in Mylan's product. The Court will address: (1) the methodology for using Raman and analyzing Raman data; (2) the Raman testing of Mylan's ANDA product and the results of that testing; and (3) the conclusions of the Court.

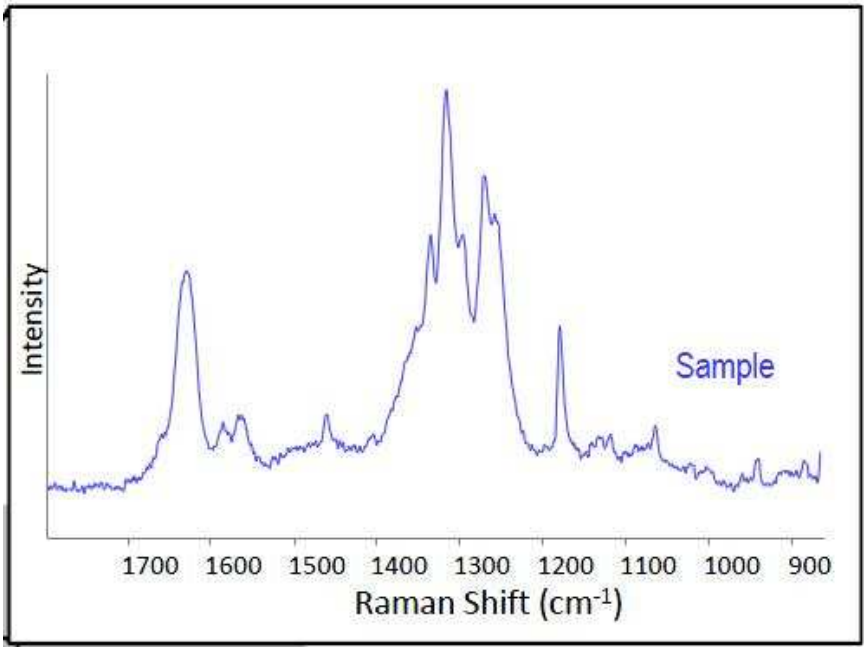
1) Methodology

Raman is a well-established method for determining the chemical composition and structure of pharmaceutical products. Raman does this by using chemical "fingerprints" to identify particular molecules.

Raman testing is conducted using a Raman machine, which has two parts: an optical microscope and a spectrometer. JA 623:14-22. The optical microscope is used to shine a laser beam onto a sample, which causes the material at the surface of the sample to scatter the laser light. JA 623:23-626:1. The Raman spectrometer measures wavelength patterns in the scattered light, and uses these wavelength patterns to generate Raman spectra. JA 624:14-626:1. The Raman spectra that are produced are referred to as "fingerprints" because each molecule produces a unique spectrum. JA 625:20-626:1.

Raman spectra are plotted on an X-Y graph. JA 625:12-19. The x-axis, called the "Raman Shift," shows the wavelengths of light that are being detected by the spectrometer. JA 625:15-17. The y-axis, called "intensity," shows the amount of light being detected at each wavelength. JA 625:12-19; JA 3908. An example of a Raman spectrum is shown in Figure 1.

Y-Axis



X-Axis

Figure 1. Raman Spectrum. JA 3908.

Within each spectrum, scientists look for bands or peaks that are particularly distinctive, and they use these "characteristic peaks" or "characteristic bands" to help identify the molecule in the sample. JA 625:12-626:1. In Figure 1, for example, there is a characteristic band pattern at 1200-1400 wavelengths and at 1180 wavelengths.

Raman can be used to determine both the chemical composition of a product and the structure of a product. JA 625:20-JA 626:1. To determine the chemical composition of an unknown sample, scientists first obtain or develop a list of materials that they know or suspect are in the sample. They then obtain "fingerprints" for each individual material. These fingerprints are referred to as "reference spectra." JA 626:2-19. Next, scientists obtain a "fingerprint" from the unknown sample that they are testing ("sample spectrum"). *Id.* Finally, the scientists compare the sample spectrum to all the reference spectra that were collected. If the sample spectrum matches one of the reference spectra, then the material in the sample is identified. JA 626:2-19.

To determine the structure of a product, scientists can use various types of Raman analysis. Three types of structural Raman analyses were discussed at trial: (1) two-dimensional mapping, (2) one-dimensional line scanning, and (3) single point measurements. JA 638:18-24. To obtain two-dimensional maps, Raman data are taken from an area of a sample surface. JA 639:6-20. A computer analyzes the Raman data and then generates a two-dimensional, color-coded map that identifies each component on the surface and where it is located. JA 639:4-20; JA 641:10-16. To obtain Raman line scans, the laser beam in the optical microscope is moved along a single line, and the spectrometer acquires spectra at fixed intervals along that line. *See* JA 655:13-16. To obtain Raman single point measurements, the laser beam is positioned at a point of interest on the sample, and the spectrometer acquires the Raman spectrum for that point. JA 680:19-25.

2) Testing and Results

Dr. Everall performed a series of Raman analyses on Mylan's delayed release coated beads. JA 638:18-24. Dr. Everall received samples of Mylan's beads and samples of each of the ingredients used to manufacture the beads. JA 631:5-8. Using the ingredient samples, Dr. Everall generated reference spectra (or "fingerprints") for each material in the bead, including doxycycline (the active ingredient in the core), HPMCP (the primary ingredient in the delayed release coating), povidone/crospovidone[7] (the materials that allegedly comprise a stabilizing coat), lactose, and the other excipients. *See* JA 631:14-634:11; JA 3683. In a stack plot[8] containing the reference spectra generated by Dr. Everall, one can plainly see that the reference spectrum for each material is unique and readily distinguishable from the other spectra. *See* JA 3683. It is also easy to identify the characteristic peaks for each material. *See id.*

Next, Dr. Everall tested the delayed release coated beads themselves. Sample beads, chosen at random, were cross-sectioned using two different methodologies: (1) gluing beads onto an SEM stub and cross-sectioning them with a diamond

[7] The spectrum for povidone is the same as the spectrum for crospovidone. JA 633:7-20.

[8] A "stack plot" is a conventional way of comparing Raman spectra by displaying the reference spectra one on top of the other. JA 632:11-19; JA 3683. The reference spectra in JA 3683 were scaled to approximately the same maximum intensity to facilitate comparison of key bands of interest. JA 632:14-19.

ultramicrotome blade; and (2) embedding the beads in an epoxy resin and cross-sectioning them with a diamond ultramicrotome blade.[9] JA 634:20-635:4; JA 635:25-636:21. After Dr. Everall confirmed the quality of the cross-sections, he selected a microscope objective that was optimized for detecting a layer of povidone and crospovidone, optimized the laser focus just beneath the delayed release coating, and recorded Raman spectra from the face of the cross-sections. JA 637:11-638:17.

Dr. Everall performed three types of Raman analyses: (a) two-dimensional mapping, (b) one-dimensional line scanning, and (c) single point measurements. JA 638:18-24. Each type of analysis affirmatively showed that there is no stabilizing coat in Mylan's beads.

a) Dr. Everall's Two-Dimensional Maps

Dr. Everall's two-dimensional mapping clearly demonstrated the absence of a stabilizing coat in Mylan's product.

Dr. Everall acquired Raman spectra from two 90 by 90 micron areas of Mylan's cross-sectioned beads. JA 3695; JA 3696; JA 642:25-643:10. Dr. Everall used a computer to identify the materials that were present in these areas, and created color-coded maps to show how the components were distributed in each area. JA 641:11-16. Each color in the maps corresponded with a distinct chemical species that was identified in the cross-section. JA 641:19-20.

As noted above, both parties agree that the innermost part of Mylan's bead is a core comprised of the active ingredient (doxycycline) and various excipients. Both parties also agree that Mylan's bead is covered in a 10 to 12 micron delayed release coating containing HPMCP. *See* JA 643:10-11; JA 974:1-7. Plaintiffs allege that, between the delayed release coating and the core, there is a 10 to 40 micron stabilizing coat. JA 154:7-19; JA 201:23-202:2.

If there were a stabilizing coat in Mylan's product, one would expect to see the following in the Raman maps: (1) a 10 to 12 micron layer of color corresponding with HPMCP (the delayed release coat); next to (2) a 10 to 40 micron layer of color corresponding with povidone (the stabilizing coat); next to (3) various sections of different colors corresponding with the active ingredient and other excipients (the core). This is not what Dr. Everall found.

Dr. Everall's maps identified four distinct chemical species in the bead cross-sections: (1) HPMCP (shown in purple); (2) crystalline doxycycline (shown in green); (3) lactose (shown in red); and (4) amorphous doxycycline intimately mixed with povidone (shown in blue). JA 641:10-642:4; JA 651:14-22; JA 3695; JA 3696. In both Raman maps, HPMCP appears as a distinct, continuous layer running around the outermost part of the bead. JA 643:10-11; JA 646:2-4; JA 652:2-4; JA 3696; JA 3695.

[9] Dr. Everall hired Richard Lees to cross-section the sample beads. Richard Lees, an expert in optical and electron microscopy, had previously cross-sectioned thousands of samples for analysis. JA 635:13-16; JA 717:22-24.

The HPMCP coating appears to be approximately 6 to 12 microns wide. JA 646:11-13; JA 652:10-12; JA 3695; JA 3696. This is consistent with the presence of the delayed release coating.

Next to the HPMCP coating, however, there is no layer of color corresponding with povidone. JA 647:7-16; JA 652:13-653:2; JA 654:13-16; JA 3695; JA 3696. Instead, both Raman maps show a mixture of crystalline doxycycline (green), lactose (red), and amorphous doxycycline mixed with povidone (blue) randomly distributed beneath the delayed release coating. JA 646:14-647:6; JA 652:13-653:2; JA 654:17-19; JA 3695; JA 3696. There is no evidence of a layer of any single material within 40 microns of the delayed release coating. JA648:3-8; JA 653:9-11; JA 3695; JA 3696. The Raman maps do not show a higher concentration of povidone anywhere inside the bead. JA 754:1-15; JA 758:3-760:9; JA 3695; JA 3696. The fact that povidone does not appear as a separate chemical species, and instead appears as part of a mixture with amorphous doxycycline, is consistent with the thorough mixing of those ingredients that occurs during the first phase of Mylan's manufacturing process. JA 759:11-19; JA 3695; JA 3696.

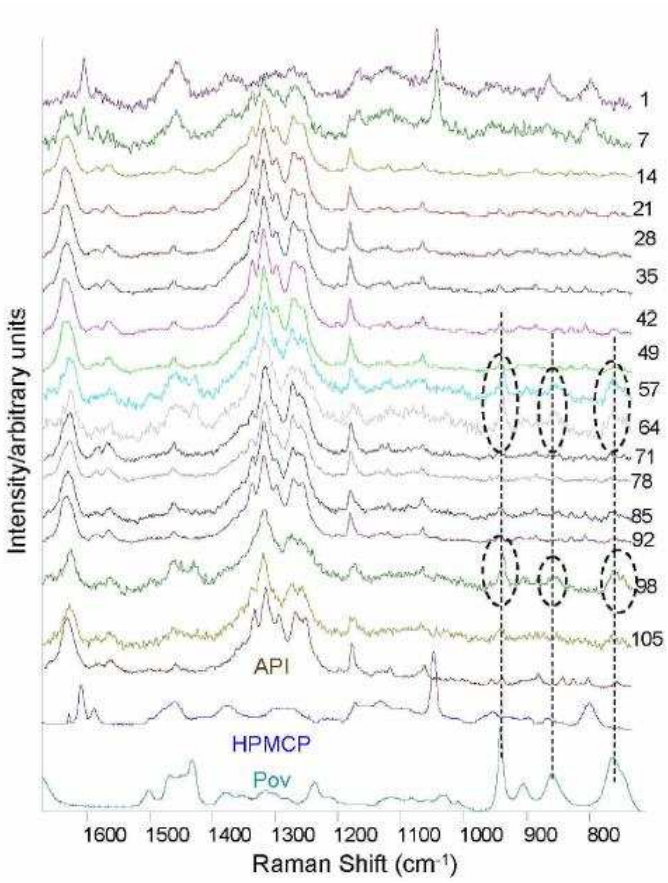
The Court finds that Dr. Everall's two-dimensional maps clearly demonstrate the absence of a stabilizing coat in Mylan's product.

b) Dr. Everall's One-Dimensional Line Scans

Dr. Everall's Raman line scans clearly demonstrate the absence of a stabilizing coat in Mylan's product.

Dr. Everall performed five Raman line scans on Mylan's cross-sectioned beads. JA 655:7-16. Dr. Everall's Raman line scans began on the outside edge of the delayed release coating and moved toward the interior of the bead. JA 655:10-21. Dr. Everall produced summaries of the Raman spectra acquired in each of the line scans. *See* JA 3692; JA 3686; JA 3688; JA 3690; JA 3694. Each summary is a graph (plotted on an X-Y axis), containing a vertical "line" of spectra that corresponds with the position of the molecules in the line scan. An example of one of Dr. Everall's Raman line scan graphs is shown in Figure 2.

Y-Axis



X-Axis

Figure 2. Raman Line Scan. JA 3692.

The numbers on the right-hand side of the y-axis identify the position along the line scan at which the data was acquired. JA 659:6-10. These numbers correspond to microns. Thus, position number 1 at the top of the y-axis indicates that the data was acquired 1 micron from the perimeter of the bead. JA 659:5-19; JA 661:10-662:17; JA 663:10-16; JA 3692. Position 105 at the bottom of the y-axis indicates that the data was acquired 105 microns from the perimeter of the bead. The reference spectra for the active pharmaceutical ingredient ("API"), HPMCP, and povidone were included on the bottom of the graph for the purpose of comparison. JA 659:20-660:6; JA 3692.

If there were a stabilizing coat in Mylan's product, one would expect to see: (1) a set of spectra matching the HPMCP reference spectrum in the top 10 to 12 microns of the graph (the delayed release coat); followed by (2) a set of spectra matching the povidone reference spectrum in the next 10 to 40 microns of the graph (the stabilizing coat); followed by (3) a mixture of spectra matching the reference spectra for API and the other excipients in the remainder of the graph (the core). This is not what Dr. Everall found.

The Raman line scan graph shown in Figure 2 provides clear evidence that there is no stabilizing coat in Mylan's bead. *See* JA 3692. At the top of the graph, at position 1 and position 7, there are two spectra that are nearly identical to the HPMCP reference spectrum. This is consistent with the presence of a 10 to 12 micron HPMCP delayed

release coating on the outside of the bead. However, the set of spectra in the next 40 microns of the graph, at positions 14 through 49, look nothing like the reference spectrum for povidone. Instead, they look nearly identical to the reference spectrum for API. The graph does not reflect the presence of a continuous layer of povidone. However, the graph does reflect the presence of povidone within the core of the bead: the characteristic peaks for povidone appear at the 57, 64, and 98 micron positions, mixed with the peaks for API. JA 661:10-663:3; JA 663:10-16; JA 667:4-17; JA 3692.

Dr. Everall's four other Raman line scans yielded the same results. For example, the line scan data presented in one graph showed that HPMCP was present at positions 4 through 20, and API was present at positions 25 through 55. JA 670:11-19; JA 3685; JA 3686. The characteristic peaks for povidone did not appear anywhere in the graph. The Raman line scan data in another graph showed that HPMCP was present at positions 6 through 28,[10] and that API was present at positions 38 through 128. JA 670:11-19; JA 3688. The characteristic peaks for povidone did not appear anywhere in the graph. JA 674:22-675:3. The Raman line scan data in yet another graph showed that HPMCP was present at positions 6 through 20, and that API was present at positions 17 through 81.[11] JA 676:7-25; JA 3689; JA 3690. The characteristic peaks for povidone did not appear anywhere in the graph. JA 677:12-20.

In short, the characteristic peaks for povidone do not appear as a layer between the spectra for HPMCP and the spectra for API in any of Dr. Everall's line scans. Accordingly, Dr. Everall's line scans clearly demonstrate the absence of a stabilizing coat in Mylan's product.

c) Single Point Measurements

Dr. Everall's single point measurements clearly demonstrate the absence of a stabilizing coat in Mylan's product.

Dr. Everall acquired nine single point measurements from Mylan's cross-sectioned beads. JA 680:15-17; JA 681:1-2. Two of the measurements were taken within the delayed release coating; the remaining seven measurements were taken at various positions just beneath the delayed release coating (*i.e.*, where the alleged povidone layer would be located). JA 681:3-8. The Raman single point measurements identified API and lactose directly beneath the delayed release coating. JA 681:9-12. The single point measurements did not detect a povidone layer beneath the delayed release coating. *Id.* The single point measurements support the conclusion that there is no layer of povidone adjacent to the delayed release coat. JA 681:13-17.

d) Dr. Davies's Raman Tests

[10] The Raman line scan corresponding with this graph was taken at an angle through the core rather than directly perpendicular, which is why HPMCP was detected at position 28 microns. JA 673:11-24; JA 3687; JA 3688.

[11] At position 0, there are characteristic peaks for the adhesive material used to hold the bead in place. JA 673:25-674:21.

On November 10, 2010, Dr. Davies performed Raman spectroscopy on Mylan's ANDA product. JA 412:5-10; JA3487; JA 252:5-7. Dr. Davies was not able to see the presence of a stabilizing coat using Raman. JA 252:11-12; JA 275:19-24. Dr. Davies did not rely on Raman in determining whether or not the Mylan ANDA product had a stabilizing coat. JA 412:23-25.

e) Plaintiffs' Critiques of Dr. Everall's Raman Testing

The Court found Plaintiffs' critiques of Dr. Everall's Raman data to be unpersuasive. Plaintiffs argued that Dr. Everall's Raman data failed to capture the alleged stabilizing coat because the Raman signals for povidone and crospovidone are so weak that they would either be undetectable or obscured by the much stronger signal for API. *See* Plaintiffs' Post-Trial Brief ("Pls.' Br.") at 19. This argument is belied by the fact that Dr. Everall successfully detected the signal for povidone in both his area maps and his line scans, even though povidone was mixed in with other ingredients. *See* JA 680:3-9; JA 3692.

Plaintiffs further argued that Dr. Everall's area maps and line scans were not representative of the bead surface. Plaintiffs accused Dr. Everall of cherry picking portions of the bead where the core materials had migrated all the way to the delayed release coat. Pls.' Br. at 20-21. Plaintiffs note that the stabilizing coat may "contain drug and have gaps" and that there were "many regions in Dr. Everall's area maps where povidone (the 'blue region') was in contact with the delayed release coating." Pls.' Br. at 20. Plaintiffs' arguments are unpersuasive. Dr. Everall's performed 16 Raman tests and Dr. Davies performed additional Raman tests, all of which failed to show a stabilizing coat in Mylan's product. Plaintiffs are essentially arguing, then, that more than 16 tests yielded atypical results, while not one test yielded typical results. The Court finds this unlikely. Furthermore, Plaintiffs misconstrue Dr. Everall's test results. The area maps did not show a continuous layer of povidone with some gaps in it for pieces of core material. The area maps showed that povidone was intimately mixed with amorphous API (the "blue region"), and that this mixture was randomly distributed throughout an 80 by 80 micron region of the bead, along with crystalline API, lactose, and other excipients.

Finally, Plaintiffs raise a host of other challenges to Dr. Everall's testing process, including, for example, that Dr. Everall's data was prone to focusing errors, and that the surfaces of his bead cross-sections were too rough. Pls.' Br. at 18. The Court finds the remainder of Plaintiffs' arguments to be unavailing. Plaintiffs' arguments raise a host of minor issues, none of which materially impacted the results of the Raman testing. *See* JA 626:20-627:19 (uneven sample surfaces are common in Raman testing); JA 657:22-658:6 (Raman does not depend upon perfect focus on the sample surface). Plaintiffs' arguments also ignore the fact that Dr. Davies's Raman testing (which presumably was conducted perfectly) yielded the exact same results.

3) Conclusions

The Court found Dr. Everall's testimony to be credible, consistent, and well-supported by the data. The Court found Dr. Everall's procedures to be reliable enough to produce accurate results.

The Court finds Raman to be an extremely reliable testing method for three reasons. First, Raman is widely-accepted by the scientific community and has been used by the pharmaceutical industry for over twenty years. *See* JA 630:16-631:1. Its importance as a form of chemical composition testing is underscored by the fact that it is one of the first methods of testing used by Dr. Davies. Second, Raman has the chemical specificity and sensitivity to detect specific materials with an impressive degree of precision. *See* JA 620:12-18. By using chemical "fingerprints" for each material, Raman can identify every material in a compound, even when those materials are mixed together. Third, Raman has the spatial resolution to show how each of these materials is distributed on nearly a micron-by-micron basis. *See* JA 623:7-11. The Court finds that, if there were a 10 to 40 micron stabilizing coat of povidone and crospovidone in Mylan's bead, Raman would have detected it.

The Raman data overwhelmingly reflect the absence of a stabilizing coat in Mylan's product. Dr. Everall performed 16 Raman tests: he generated 2 Raman maps, conducted 5 Raman line scans, and acquired 9 Raman single point measurements. Every single test showed that no stabilizing coat was present in Mylan's ANDA product. In fact, every single test showed that the structure of Mylan's bead was identical to the structure created during the manufacturing process: a single, delayed release coating surrounding a mixture of API, povidone, and other excipients. Dr. Davies performed his own Raman tests and saw no stabilizing coat in Mylan's product. The Court therefore finds that Raman data provides the strongest evidence that there is no stabilizing coat in Mylan's beads.

ii. ToF-SIMS Testing

The ToF-SIMS technique has been subjected to intense peer review for over one hundred years and is now widely accepted in the scientific community. JA 784:19-785:5. ToF-SIMS has been used to determine the chemical composition of drug products since the 1980s, and today it is regularly used for that purpose by pharmaceutical companies, contract laboratories, and academics. JA 785:6-12.

Dr. Nicholas Winograd, Mylan's expert on ToF-SIMS, was one of the first chemists to work in the field of secondary ion mass spectroscopy ("SIMS"), and is a pioneer in the field. JA 768:14-22; JA 3700-67. Prof. Winograd is the Chair of the International SIMS Committee and has authored more than 200 peer-reviewed publications pertaining to ToF-SIMS. JA 770:1-2; JA 3700-67; JA 770:24-771:9. The Court qualified Prof. Winograd as an expert in SIMS imaging and SIMS data interpretation. JA 771:18-772:3.

The Court finds that ToF-SIMS data provides strong supporting evidence that there is no stabilizing coat in Mylan's product. The Court will address: (1) the

methodology for using the ToF-SIMS technique and analyzing ToF-SIMS data; (2) the ToF-SIMS testing of Mylan's ANDA product and the results of that testing; and (3) the conclusions of the Court.

1) Methodology

ToF-SIMS is a surface analysis technique, which measures the top few molecular layers of a surface. JA 127:6-10. ToF-SIMS uses chemical "fingerprints" to identify specific molecules on a sample surface. ToF-SIMS is especially useful for analyzing compounds that contain a mixture of chemical species. JA 2385.

The ToF-SIMS technique uses a projectile that is fired to a specific point on the surface of an object. JA 775:5-776:7. When a sample is hit with the projectile, the resulting collision causes positively and negatively charged particles to come off of (or desorb from) the surface of the sample. JA 777:21-778:8. The molecules and fragments that desorbed from the surface form a plume above the surface. JA 778:9-24. These molecules and fragment particles are collected and brought to a mass spectrometer, where they are analyzed using a time of flight analyzer. JA 777:21-779:9. The time of flight analyzer measures the molecules and fragments based on their mass. JA 778:25-779:9. The mass data collected by the spectrometer is referred to as a "fingerprint" because mass information is unique for every molecule. JA 777:21-780:7. Every molecule contained in the plume is identified by comparing data obtained from a sample with reference data generated for each of the molecules. JA 777:21-781:20.

ToF-SIMS can be used to produce a map of chemical images of a surface. JA 224:2-19. To generate a map, data is obtained from multiple points along the surface of a sample by sweeping the projectile over multiple spots. JA 781:21-12; JA 782:3-25. The data is then compiled to create a mass spectral image. *Id.* The ToF-SIMS mass spectral image contains 65,536 individual mass spectra which are used to create a picture of the surface of the sample. JA 782:3-25. The ToF-SIMS mass spectral image can be separated into individual images with the chemical information for each molecule. JA 782:3-25; JA 783:5-21. ToF-SIMS is especially useful for looking at the distribution and structure of molecules in bead systems. JA 772:13-15. According to a publication authored by Dr. Davies, ToF-SIMS is a powerful method for characterizing cross-sections of drug dosage forms because it allows for imaging with high spatial resolution and spectroscopy for molecular chemical identification. JA 2379.

2) Testing and Results

Prof. Winograd performed a series of ToF-SIMS tests on Mylan's beads.[12] Prof. Winograd received the following samples from Mylan: (1) a set of control samples for each ingredient used to manufacture Mylan's beads; (2) Mylan beads that had a delayed

[12] Prof. Winograd was assisted by Alan Piwowar, is a post-doctoral candidate in Prof. Winograd's laboratory. JA 785:13-18. Dr. Piwowar received a Ph.D in SIMS, and has over 10 years of experience working with SIMS. JA 785:21-786:5 (RGM). Prof. Winograd performed the analysis of the ToF-SIMS data obtained from the Mylan beads. JA 786:18-19.

release coating on them; and (3) Mylan beads that did not have a delayed release coat on them. JA 786:20-25. For his ToF-SIMS analysis, Prof. Winograd used a projectile called "C-60" (also known as a "Buckyball"[13]), a projectile that completely transformed the SIMS field. JA 775:4-776:7; JA 777:10-17.

Prof. Winograd obtained reference spectra for each material in Mylan's bead, including doxycycline, sodium lauryl sulfate, lactose, and povidone/crospovidone.[14] JA 787:5-17; JA 788:1-6; JA 3770. Prof. Winograd generated a summary of the positive ion measurements and negative ion measurements for each control sample, either of which can be used to characterize a sample. JA 788:7-14; JA 3770. The reference spectra for each material was readily distinguishable from the reference spectra for the other materials. JA 788:15-790:4; JA 3770. For example, the characteristic mass peak for doxycycline was mass 445 in the positive and mass 443 in the negative, while the characteristic mass peak for HPMCP (phthalate) was mass 149 in the positive and mass 121 in the negative. JA 788:22-789:22; JA 3770.

Prof. Winograd's summary of reference spectra shows that ToF-SIMS can detect a distinct spectrum for povidone and crospovidone. JA 790:5-12; JA 3770. The characteristic mass peaks for povidone and crospovidone are mass 138 in the positive and mass 208 and mass 283 in the negative. JA 788:22-789:15; JA 3770. Prof. Winograd noted that the ToF-SIMS spectrum for providone and crospovidone has an intensity that is approximately one-third the intensity of doxycycline or sodium lauryl sulfate, but that does not prevent ToF-SIMS from detecting povidone. JA 790:13-791:9; JA 829:25-830:3; JA 3770. Prof. Winograd further noted that mass 138 (one of the characteristic mass peaks for povidone) has very little background noise caused by other fragment ions. JA 830:4-14.

Prof. Winograd analyzed two forms of Mylan beads using the ToF-SIMS technique. He analyzed: (1) a randomly selected uncoated bead (*i.e.*, a whole bead that did not have delayed release coating); and (2) cross-sections of randomly selected delayed release coated beads. JA 794:15-795:4; JA 804:6-14.

a) Prof. Winograd's Tests of Mylan's Uncoated Bead

Prof. Winograd's ToF-SIMS analysis of Mylan's uncoated bead clearly shows the absence of a stabilizing coat in Mylan's product.

Plaintiffs allege that there is a 10 to 40 micron stabilizing coat in Mylan's bead comprised of povidone and crospovidone, just beneath the delayed release coat. If there were a stabilizing coat in Mylan's product, one would expect Mylan's uncoated bead to have a 10 to 40 micron layer of povidone and crospovidone surrounding a mixture of API and other excipients. Because ToF-SIMS is a surface-specific technique, one would

[13] C-60 is called the "Buckyball" because it is shaped like a soccer ball and the person who discovered it was named Buckminsterfullerine. JA 776:8-777:1.

[14] Povidone and crospovidone have the same reference spectra. JA 791:10-14.

expect the ToF-SIMS image of an uncoated bead to show a high concentration of povidone and crospovidone, with perhaps a minimal amount of core materials showing in spots where the core materials had broken through the stabilizing coat. JA 816:12-817:2; JA 3771; JA 3776. That is not what Prof. Winograd found.

Prof. Winograd produced a high-quality mass spectral image of an uncoated Mylan bead, along with individual images that reflected the chemical information for each molecule. JA 796:16-797:3; JA 3776. The images show that doxycycline (m/z 445) and sodium lauryl sulfate (m/z 23) are physically present all over the surface of the uncoated Mylan bead, and are uniformly distributed throughout the surface. JA 798:18-19; JA 853:17-22; JA 3776; JA 800:17-20; JA 854:1-5. The images show that a patch of lactose (m/z 365) is present on the surface of the uncoated Mylan bead. JA 801:12-22; JA 3776. Finally, the images show that there is a small amount of povidone (m/z 138) randomly distributed across the surface of the uncoated bead. JA 801:23-802:15; JA 854:6-13; JA 3776.

Prof. Winograd's images show no evidence of a layer of any single material on the surface of the uncoated bead. JA 803:20-24; JA 3776. Instead, his images show that all the core materials — including doxycycline, sodium lauryl sulfate, lactose, and povidone — are present on the surface of the uncoated bead. JA 803:25-804:4; JA 3776. While Plaintiffs are correct that data showing some core materials at the surface of the bead is not inconsistent with the presence of a stabilizing coat, data showing a high concentration of core materials around the ***entire*** surface of the uncoated bead suggests that there is not "a layer of material(s) between each core elements and its modified release coating." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

b) Prof. Winograd's Tests of Mylan's Coated, Cross-Sectioned Beads

Prof. Winograd's ToF-SIMS analysis of cross-sections of Mylan's coated beads shows the absence of a stabilizing coat in Mylan's product.

The Mylan delayed release coated beads were cross-sectioned so that Prof. Winograd could obtain ToF-SIMS data from the inside of the beads. JA 804:19-25. Prof. Winograd generated two types of images: (1) two-dimensional SIMS images, and (2) and two-dimensional and three-dimensional color-coded images.

If Mylan's product had a stabilizing coat, one would expect to see the following in the two-dimensional SIMS images of Mylan's cross-sectioned beads: (1) an image showing HPMCP as a distinct layer around the circumference of the bead; (2) a series of images showing core materials randomly distributed throughout the center of the bead; and (3) an image showing povidone as a distinct layer between the core and the delayed release coating. JA 985:21-986:18. That is not what Prof. Winograd found.

Prof. Winograd generated a series of two-dimensional positive ion and negative ion SIMS images for a cross-sectioned bead that was embedded in resin. *See* JA 3774; JA 3775. The images (particularly the positive ion SIMS image) show that HPMCP (m/z

149) forms a distinct, visible layer around the circumference of the bead. *Id.* The images show that doxycycline (m/z 445) and sodium lauryl sulfate (m/z 23) are randomly distributed throughout the center of the bead, and that there are patches of lactose throughout the core. *Id.* Finally, the images (particularly the negative ion SIMS image) show that small amounts of povidone and crospovidone are distributed fairly evenly throughout the center of the bead. *Id.* The images do not show a concentration of povidone or crospovidone anywhere in the bead. *Id.* Prof. Winograd's two-dimensional SIMS images thus provide strong evidence that there is no stabilizing coat in Mylan's beads.

Prof. Winograd's color-coded images also provide some, limited support for the proposition that there is no stabilizing coat in Mylan's bead. Prof. Winograd generated two-dimensional and three-dimensional color-coded images of cross-sectioned beads. JA 3771; JA 3772. The field of view of the two-dimensional image is approximately 500 by 500 microns; the field of view of the three-dimensional image is 1000 by 1000 microns. *Id.* Prof. Winograd arbitrarily assigned the following colors to various ingredients: blue represents HPMCP (the delayed release coat), green represents doxycycline (API), red represents sodium lauryl sulfate (an excipient). JA 808:13-25. Prof. Winograd chose not to include the signal for povidone (m/z 138) in either of the color-coded images because, as he explained, povidone "doesn't show up very well in this kind of a format." JA 809:20.

If there were a layer of povidone adjacent to the delayed release coating, one would expect to see a dark gap in the images between the delayed release coating and the core materials. JA 814:20-815:2; JA 3772. The Court could discern no dark gap between the delayed release coating and the core materials in either of the color-coded images. Both images showed a distinct blue HPMCP layer around the outside of the bead, and a mixture of green doxycycline and red sodium lauryl sulfate adjacent to the HPMCP coating and throughout the center of the bead.

That said, the Court finds that these images have limited probative value, as this image format does not show the location of povidone in the bead. The Court is also skeptical that it would be able to discern a dark 10 micron gap in a 500 by 500 micron or 1000 by 1000 micron image. As such, the Court accorded these images very little weight.[15]

[15] During the trial, Prof. Winograd described a three-dimensional color-coded image of Mylan's cross-sectioned bead as one of his "favorite images of all time." JA 808:9. While the Court agrees that the three-dimensional color-coded images were impressive, the Court found it extremely puzzling that Prof. Winograd chose to use an image format that did not display the one ingredient that was actually at issue in this case. The Court found Mylan's heavy reliance on these images during the preliminary injunction hearing to be especially confusing. The Court now understands that the failure of the color-coded image format to display povidone is not an indication that ToF-SIMS, as a whole, is unable to detect povidone. It is just that the positive and negative ion SIMS images are able to show povidone much more clearly.

c) Dr. Davies's ToF-SIMS Tests

On October 20, 2010, Dr. Davies performed a ToF-SIMS analysis on the Mylan ANDA product. JA 224:20-24; JA 3481. Dr. Davies did not rely on his ToF-SIMS analysis in determining whether or not Mylan's ANDA product had a stabilizing coat. JA 409:22-25.

d) Plaintiffs' Critiques of Prof. Winograd's ToF-SIMS Testing

Plaintiffs argue that ToF-SIMS is not a suitable technique for determining whether there is a stabilizing coat because it is extremely difficult to detect povidone using ToF-SIMS. In support of this argument, Plaintiffs point to a paper that Dr. Davies published in Analytical Chemistry in 2000, discussing the difficulty of detecting povidone using ToF-SIMS. The Court finds that, while the ToF-SIMS signal for povidone is weaker than the signals for other materials, ToF-SIMS is nonetheless capable of detecting povidone. The reference spectra for povidone show that povidone has easily identifiable characteristic peaks that differ significantly from the peaks for the other materials in Mylan's beads. Moreover, in the positive and negative ion SIMS images for Mylan's coated and uncoated beads, one can clearly see the spatial distribution of povidone. Finally, the Court agrees with Mylan that Dr. Davies's Analytical Chemistry publication is outdated, as his testing for that article pre-dated the availability of the C-60 ("Buckyball") projectile that transformed the field. JA 775:4-776:7; JA 777:10-17; JA 408:14-409:2; JA 2378-91.

Plaintiffs make a series of additional arguments that ToF-SIMS is not reliable. To the extent that Plaintiffs take issue with Prof. Winograd's color-coded images, that Court agrees that these images are not particularly probative. To the extent that Plaintiffs take issue with Prof. Winograd's other images, however, the Court disagrees with Plaintiffs' assessments.

Plaintiffs argue that Prof. Winograd's images do not reflect the amount of each material in the beads. However, the fact that the images do not reflect the ***amount*** of each material in the bead is not as important as the fact that the images accurately reflect the ***location*** of each material in the bead, as that is the key issue here. Plaintiffs also argue that Prof. Winograd's images showed gaps in the delayed release coating, and that the delayed release coating appears to be too thick in some of the images. However, these issues are not as important as the fact that the images clearly show a very distinct layer of HPMCP running around the circumference of the bead. Finally, Plaintiffs argue that Prof. Winograd's samples may have been covered with dust from other beads. Plaintiffs provide no evidence that the samples were covered in dust, and, in any event, this should not have affected the cross-sectioned beads. The Court therefore finds Plaintiffs' remaining arguments to be unpersuasive.

3) Conclusions

The Court found Prof. Winograd's testimony to be helpful, credible, and supported by the data. The Court found Prof. Winograd's procedures to be reliable enough to produce accurate results.

The Court finds ToF-SIMS to be a reliable testing method for three reasons. First, ToF-SIMS is widely-accepted by the scientific community and has been used to determine the chemical composition of drug products for decades. Its importance as a form of chemical composition testing is underscored by the fact that it is one of the first methods of testing used by Dr. Davies. Second, by using unique chemical "fingerprints" associated with different molecules, ToF-SIMS is able to identify specific materials and mixtures of materials with an impressive degree of precision. Third, ToF-SIMS can detect the spatial distribution of a number of different materials. The Court finds that, if there were a 10 to 40 micron layer of povidone or crospovidone in Mylan's bead, ToF-SIMS would have detected it.

The ToF-SIMS data overwhelmingly reflect the absence of a stabilizing coat in Mylan's product. Prof. Winograd performed ToF-SIMS analysis on coated and uncoated Mylan beads. Every test showed that no stabilizing coat was present in Mylan's ANDA product. In fact, every test showed that the structure of Mylan's bead was identical to the structure created during the manufacturing process: a single, delayed release coat surrounding a mixture of API, povidone, and other excipients.

iii. ATR-FTIR Testing

ATR-FTIR uses light to determine the chemical composition of the material that the light is hitting. JA 682:6-9. ATR-FTIR works by shining an infrared beam of light onto a sample at an angle so that the light reflects back. *Id.* The difference between the projected light and the reflected light provides an infrared spectrum that is unique for every molecule. JA 126:15-20.

On March 2 and 9, 2011, Dr. Davies performed an ATR-FTIR analysis of Mylan's ANDA product. JA 413:1-4; JA 3491-95. Dr. Davies used ATR-FTIR to analyze one delayed release coated bead and six uncoated beads (*i.e.*, beads without delayed release coating). JA 173:6-15. One would expect the coated Mylan beads to be covered in a layer of HPMCP, reflecting the presence of the delayed release coating. That is exactly what Dr. Davies found. JA 175:24-176:1; JA 684:14-685:7; JA 3698. If there were a stabilizing coat in Mylan's beads, one would expect the uncoated beads to produce an ATR-FTIR spectrum for povidone and crospovidone. JA 685:8-18; JA 3698. That is not what Dr. Davies found. Instead, Dr. Davies's ATR-FTIR data for ***all six*** uncoated beads showed that there was a mixture of core materials (including doxycycline, lactose, and povidone) directly underneath the delayed release coating. JA 3698; JA 3699; JA 682:12-15; JA 176:13-15; JA 176:25-177:1.

Dr. Davies did not rely on his ATR-FTIR testing results in determining whether or not Mylan's ANDA product had a stabilizing coat. JA 413:12-14.

iv. AFM Testing

AFM is a high resolution imaging technique. JA 126:4-12. AFM uses a sharp stylus probe that is suspended from a cantilever, and as the stylus moves up and down over the sample, a high resolution image is obtained. JA 168:9-169:1; JA 3317. AFM is a standard technique for determining the structure of a pharmaceutical composition. JA 410:13-15. On November 10, 2010, Dr. Davies performed an AFM analysis on Mylan's ANDA product. JA 410:7-12; JA 3485. With AFM, Dr. Davies was "not able to distinguish [a] separating layer" between the delayed release coat and the core. JA 411:19-20. Mylan's expert, Dr. Buckton, agreed that Dr. Davies's AFM data does not show or suggest that a stabilizing coat exists. JA 951:15-21.

Dr. Davies did not rely on his AFM testing results in determining whether or not Mylan's ANDA product had a stabilizing coat. JA 169:4-7; JA 3485; JA 410:20-23; JA 951:15-21.

v. SEM Testing

SEM is a high resolution imaging technique, which scans a beam of electrons over a sample surface to produce a high resolution image. JA 125:25-126:3. On October 20, 2010, Dr. Davies performed an SEM analysis on Mylan's ANDA product. JA 403:12-16; JA 404:7-9; JA 3479-80. Dr. Davies's SEM analysis of Mylan's product did not show a stabilizing coat. JA 403:12-16; JA 404:7-9; JA 3479-80.

vi. Conclusion

Dr. Everall's Raman tests showed that there was no stabilizing coat in Mylan's ANDA product. Prof. Winograd's ToF-SIMS analysis showed that there was no stabilizing coat in Mylan's ANDA product. Dr. Davies's Raman, ToF-SIMS, ATR-FTIR, AFM, and SEM tests showed that there was no stabilizing coat in the Mylan's ANDA product. All of these sophisticated testing methods produced results that were consistent with the structure of the bead that was created during Mylan's manufacturing process: a single, delayed release coating surrounding a mixture of doxycycline, povidone, and other excipients. The Court therefore finds that the evidence overwhelmingly indicates that there is no stabilizing coat in Mylan's ANDA product.

c. Dr. Davies's Humidity Test Does Not Support a Finding that there Is a Stabilizing Coat in Mylan's Product

Instead of relying on any of the five widely-accepted testing methods described above, Plaintiffs' expert, Dr. Davies, relies on a novel "humidity test" to show that there is a layer of povidone and crospovidone in Mylan's ANDA product. Before trial, Mylan moved to preclude Dr. Davies from testifying about the humidity test on the basis of *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993) ("*Daubert*"). The Court reserved on the *Daubert* motion. For the reasons set forth below, the Court now finds that Dr. Davies's humidity test does not meet the *Daubert* standard. The Court also finds that, even if the humidity test met the *Daubert* standard, the test does not support a finding that there is a stabilizing coat in Mylan's product.

The Court will address: (1) the methodology for and results of Dr. Davies's humidity test; (2) the reasons that the humidity test does not meet the *Daubert* standard; and (3) the reasons that the humidity test would not support a finding that there is a stabilizing coat in Mylan's product, even if it met the *Daubert* standard.

i. Dr. Davies's Humidity Test: Methodology, Testing, and Results

Dr. Davies began his investigation of Mylan's product in October 2010, when he performed optical microscopy on Mylan's delayed release coated beads. JA 403:2-16. Optical microscopy is an imaging technique that essentially takes a high resolution picture of a sample, but does not provide any chemical information about the sample. JA 125:14-22; JA 147:4-8. Dr. Davies generated several optical images of cross-sectioned Mylan beads. JA 153:10-21; JA 2019. Dr. Davies stated that he observed a dark layer in his images, just beneath the delayed release coating, which he believed was a layer of crospovidone and povidone. JA 152:21-155:3; JA 554:24-556:6; JA 2019-20.

According to Dr. Davies, after he observed the dark layer in his optical microscopy images, he developed a humidity treatment test to highlight the povidone and crospovidone layer. JA 153:10-155:3. Dr. Davies's humidity treatment was based on his understanding that povidone and crospovidone are hygroscopic (*i.e.*, they absorb and attract water) and would absorb moisture more quickly than other components in Mylan's bead. JA 154:22-156:12; JA 889:8-890:14; JA 2399, JA 2404; JA 3313. Dr. Davies stated that exposure to humidity causes these two molecules to swell and darken. JA 160:5-18; JA 2021.

To perform his humidity test, Dr. Davies used the humidity chamber in one of his microscopes. JA 159:6-15. Dr. Davies took cross-sectioned Mylan beads and exposed them to 90% relative humidity ("RH"). JA 159:16-160:2; JA 3314. Dr. Davies first tried a 2 second exposure to humidity and then tried a 5 second exposure. JA 222:14-15. Dr. Davies eventually decided that a 5 second exposure was best. When asked by the Court why he selected a 5 second exposure for the test, Dr. Davies said, "I was interest[ed] in discerning this crospovidone/povidone layer, and I felt that just 5 seconds would be appropriate for that." JA 222:17-19. He noted that if samples were exposed to longer periods of humidity, too much water vapor would be absorbed by the bead. JA 159:16-160:2; JA 221:39-222:9; JA 417:10-23. After the beads were exposed to humidity, Dr. Davies re-imaged them under the optical microscope. JA 160:3-18; JA 2021.

Dr. Davies found that the dark region in the bead cross-sections that he had identified in his optical images became distinctly darker after the humidity treatment. JA 160:3-18; JA 2021. Dr. Davies stated that this layer became darker because of the swelling of crospovidone and povidone as a result of the humidity exposure. *Id.* Dr. Davies performed imaging before and after humidity treatment on eight different beads on several different days, and stated that, in all cases, he observed the darkened layer after exposure to humidity. JA 161:18-25.

Dr. Davies conducted an image analysis on his optical images to confirm that certain areas of the bead had darkened. JA 164:9-165:7; JA 2031-34; JA 3316. He used an image analysis computer program that measured the brightness of each pixel in the image. JA 165:8-25. According to Dr. Davies, the image analysis confirmed the presence of a dark layer of povidone and crospovidone between the core element and delayed release coating. JA 167:10-13; JA 558:19-161:10.

Dr. Davies also performed a control experiment. JA 162:1-13. Dr. Davies made two tablets, one containing a dry mixture of doxycycline hyclate and crospovidone, and another containing a dry mixture of the major components of Mylan's beads (including doxycycline hyclate, lactose, and crospovidone). JA 162:5-11; JA 593:6-7; JA 595:16-18; JA 596:6-9. The control tablets were cross-sectioned, imaged by optical microscopy, exposed to the humidity treatment, and then re-imaged by optical microscopy. JA 162:5-13; JA 162:5-13. Dr. Davies observed a darkening of the crospovidone in the tablets, and no change in any of the other ingredients. JA 162:14-163:13; JA 2029-30.

Based on these observations, Dr. Davies concluded that there was a 10 to 40 micron stabilizing coat of povidone and crospovidone in Mylan's beads. JA 154:15-19; JA 201:23-202:2; JA 555:14-21.

ii. Dr. Davies's Humidity Test Does Not Meet the Daubert Standard

Federal Rule of Evidence 702 permits expert testimony only if, *inter alia*, "the testimony is based on sufficient facts or data" and "the testimony is the product of reliable principles and methods." Fed, R. Evid. 702. "The burden for demonstrating admissibility lies with the proponent of the expert testimony, by a preponderance of the evidence." *United States v. Schiff*, 538 F. Supp. 2d 818, 833-34 (D.N.J. 2008), *aff'd* 602 F.3d 152 (3d Cir. 2010). The linchpin requirements of Rule 702 are the "reliability" of the testimony offered and its relevance, otherwise referred to as its "fit." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. at 589-92.

District courts ensure that these requirements are met by acting as a "gatekeeper" between expert evidence and the trier of fact. *United States v. Schiff*, 602 F.3d 152, 172 (3d. Cir. 2010); *Daubert*, 509 U.S. at 589. As many federal courts have noted, however, the gatekeeping function of the court is relaxed in the context of a bench trial because a court is better equipped than a jury to weigh the probative value of expert evidence. *See United States v. Brown*, 415 F.3d 1257, 1269 (11th Cir. 2005) ("There is less need for the gatekeeper to keep the gate when the gatekeeper is keeping the gate only for himself."). Thus, a district court conducting a bench trial may admit evidence during the trial, subject to the understanding that the court may later exclude it or disregard it if it turns out not to meet the standards for reliability and relevancy established by Rule 702. *See In re Salem*, 465 F.3d 767, 777 (7th Cir. 2006) ("[W]here the factfinder and the gatekeeper are the same, the court does not err in admitting the evidence subject to the ability later to exclude it or disregard it if it turns out not to meet the standard of reliability established by Rule 702."). "[T]he court in a bench trial need not make reliability determinations

before evidence is presented, [however], the determinations must still be made at some point." *Metavante Corp. v. Emigrant Sav. Bank*, 619 F.3d 748, 760 (7th Cir. 2010); *see also Seaboard Lumber Co. v. U.S.*, 308 F.3d 1283, 1302 (Fed. Cir. 2002).

In this case, Mylan made a pre-trial *Daubert* motion to preclude Dr. Davies from testifying regarding his humidity treatment test. The Court reserved its decision on the *Daubert* motion, and admitted the evidence during the trial with the understanding that the Court could later disregard the testimony. After careful review of the evidence and the motion papers submitted by the parties, the Court now finds that Dr. Davies's humidity test does not meet the *Daubert* requirements of reliability and fit.

1) Reliability

In order to be reliable, expert testimony must have "a grounding in the methods and procedures of science." *Daubert*, 509 U.S. at 590. In other words, determining whether expert evidence is reliable "requires a determination as to its scientific validity." *In re Paoli R.R. Yard PCB Litig.* ("*In re Paoli*"), 35 F.3d 717, 742 (3d. Cir. 1994) (citation omitted). Relying on both *Daubert* and its own precedent, the Third Circuit has articulated eight non-exclusive factors to consider when deciding whether to admit evidence as "reliable" under Rule 702 and *Daubert*:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

United States v. Mitchell, 365 F.3d 215, 235 (3d. Cir. 2004) (citation omitted). "[A] district court should take into account all of the factors . . . as well as any others that are relevant." *In re Paoli*, 35 F.3d at 742.

For the reasons set forth below, the eight factors articulated by the Third Circuit weigh in favor of excluding Dr. Davies's testimony regarding his humidity treatment.[16]

[1] Whether a Method Consists of a Testable Hypothesis. The first factor, "testability," asks whether the proposition at issue is "capable of being proved false." *Mitchell*, 365 F.3d at 235. The Court in this case must consider whether the premises on which the humidity test relies are testable or actually tested. The relevant premise in this is case is whether one can determine the location of povidone and crospovidone in Mylan's bead by subjecting the bead to a 5 second exposure of 90% RH. This premise

[16] The Court's finding pertains solely to the use of Dr. Davies's self-created humidity treatment for the purpose of identifying povidone and crospovidone in Mylan's ANDA product. The Court's analysis does not extend to the use of humidity exposure testing in other contexts and for other purposes.

could be falsified if the same test were run on a bead where the location of the povidone and crospovidone was known, and the test failed to identify the povidone and crospovidone. Mylan notes that Dr. Davies could have tested Plaintiffs' product, where the location of the stabilizing coat was known, to determine whether the humidity test worked. The Court agrees that this would have been a helpful control test, had Dr. Davies performed it.[17] Dr. Davies did run "control tests" on dry tablets containing some of the ingredients in Mylan's beads. However, the dry mixed compacts he used were quite different from Mylan's beads, which were manufactured using wet granulation and spheronization. Thus, these "control tests" are of limited utility. The Court therefore concludes that it is theoretically possible to test Dr. Davies's hypothesis, but no such testing has been done.

[2] Whether the Method Has Been Subject to Peer Review. Dr. Davies's humidity treatment test has never been peer reviewed or published. Dr. Davies could not point to a single peer-reviewed, academic paper in which short exposure to humidity was used to determine whether a pharmaceutical product had a layer or coat. JA 416:11-15. Indeed, the scientific literature is devoid of any reference to humidity experiments as a method to determine the chemical composition of a pharmaceutical product. JA 864:2-5.

[3] The Known or Potential Rate of Error. Dr. Davies made no effort to quantify the rate of error associated with his humidity treatment test. He did not provide any data that would allow anybody else to quantify the rate of error inherent to his test.

[4] The Existence and Maintenance of Standards Controlling the Technique's Operation. Dr. Davies provides nebulous standards for controlling the operation of his humidity test. Dr. Davies exposed Mylan's beads to an arbitrary amount of humidity, 90% RH, for an arbitrary amount of time, approximately 5 seconds. The 90% humidity figure selected by Dr. Davies was not substantiated by any sort of scientific explanation. JA 865:19-23. Dr. Davies did not describe why 90% RH was superior to 20% RH or 95% RH, for example. Similarly, Dr. Davies provided no scientific explanation for why five seconds was the appropriate exposure time. When asked, he merely stated that "I felt that just 5 seconds would be appropriate." JA 222:17-19; *see also* JA 864:13-865:23. The fact that Dr. Davies provided almost no explanation for the parameters he used for his humidity treatment supports excluding evidence of the testing. *See Elcockv. Kmart Corp.*, 233 F.3d 734, 747-48 (3d Cir. 2000) (rejecting expert methodology that was "never explained . . . in rigorous detail").

[5] Whether the Method Is Generally Accepted. Dr. Davies's humidity test is not generally accepted by the scientific community. There is no scientific community that generally accepts the use of humidity treatments for the purpose of identifying specific chemical components and their spatial arrangement in pharmaceutical

[17] Mylan argued that Dr. Davies's decision not to run the humidity test on Plaintiffs' product was telling as to the test's validity. The Court declines to make such an inference with respect to Plaintiffs, as none of the parties in this case chose to perform any of their tests on Plaintiffs' product.

compositions. JA 952:19-22. In fact, Dr. Davies was not aware of any other scientist having used a humidity test to determine whether a pharmaceutical product had a layer or a coat. JA 415:5-9. Dr. Davies did point to one publication that discussed the use of humidity exposure in exploring "the effect of excipients on the kinetics of dehydration and hydration." JA 2392; JA 414:9-415:4. However, the fact that another scientist exposed pharmaceutical ingredients to humidity to explore completely unrelated properties does not save Dr. Davies's application of his humidity treatment in this case. *See Reliance Ins. Co. v. Keystone Shipping Co.*, 102 F. Supp. 2d 181, 190 (S.D.N.Y. 2000) (rejecting "unorthodox and unproven" application of standard technique). Finally, Plaintiffs argue that the humidity treatment test is based on well-known scientific principles, like the fact that different materials react differently to water. Pls.' Br. at 2. While it is undoubtedly true that different molecules can ***have*** different reactions to water, Dr. Davies provided no support for the proposition that one can identify molecules ***based on*** their different reactions to water. Thus, the Court cannot conclude that humidity tests are generally accepted for that purpose.

[6] The Relationship of the Technique to Methods Which Have Been Established to Be Reliable. Methods which have been established to be reliable do not support the reliability of Dr. Davies's humidity treatment test. The premise underlying Dr. Davies's humidity treatment is that components in a pharmaceutical composition can be identified based on their differing reactions to humidity. Well-established chemical composition tests such as Raman, ToF-SIMS, and ATR-FTIR are premised on entirely different scientific principles, and thus lend no support to Dr. Davies's method. Existing humidity exposure tests have never been used to identify components in a pharmaceutical composition. *See* JA 414:9-416:7. Thus, this factor weighs in favor of exclusion.

[7] The Qualifications of the Expert Witness Testifying Based on the Methodology. None of the parties dispute Dr. Davies's qualifications.

[8] The Non-Judicial Uses to Which the Method Has Been Put. The humidity treatment test has not been put to any non-judicial uses. In fact, the test has never been used outside the context of this case. *See* JA 415:23-416:7. This factor therefore weighs in favor of exclusion. *See Mike's Train House, Inc. v. Lionel, L.L.C.*, 472 F.3d 398, 408 (6th Cir, 2006) (noting that the fact that the "methodology was created for purposes of litigation further supports our conclusion that [the testimony] was not reliable under *Daubert*").

Overall, the eight factors set forth by the Third Circuit weigh in favor of exclusion. Dr. Davies's humidity test is not used by the scientific community. It is neither peer-reviewed nor published. There is no known rate of error. It is not controlled by rigorous scientific standards and it is not grounded in well-established methods. All the evidence before the Court suggests that Dr. Davies created the test purely for this case. And the proponents of the expert testimony are the only ones who vouch for its reliability. In short, upholding the reliability of Dr. Davies's humidity test would allow the very abuse that *Daubert* and its progeny aimed to remedy. "That abuse is the hiring of reputable

scientists, impressively credentialed, to testify for a fee to propositions that they have not arrived at through the methods that they use when they are doing their regular professional work [and instead, merely paying such scientists] to give an opinion helpful to one side in a lawsuit." *Braun v. Lorillard Inc.*, 84 F.3d 230, 235 (7th Cir. 1996).

2) Fit

If an expert's methodologies satisfy the *Daubert* standard for reliability, the Court must still determine whether that evidence actually supports, or "fits," the expert's conclusions. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997); *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644, 657 (D.N.J. 2008). *Daubert* explains that "'fit' is not always obvious, and scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes." *Daubert*, 509 U.S. at 591. Thus, "even if an expert's proposed testimony constitutes scientific knowledge, his or her testimony will be excluded if it is not scientific knowledge for the purposes of the case." *In re Paoli*, 35 F.3d at 743.

The Court finds that Dr. Davies's humidity test does not "fit" with the factual issues in this case. While humidity tests may be scientifically valid for some purposes, such as exploring "the effect of excipients on the kinetics of dehydration and hydration," JA 2392, that does not make the tests valid for other, unrelated purposes, such as identifying specific chemical components in a compound. At most, the humidity treatment test shows that portions of Mylan's bead absorb water when exposed to a certain level of humidity. The ability of Mylan's bead to absorb water, however, is not in dispute. Rather, the issue in dispute is whether there is a layer of materials in Mylan's beads between the core element and the delayed release coating. Dr. Davies's humidity treatment test is not a scientifically valid method for making that determination.

3) Conclusion

For the forgoing reasons, the Court concludes that Dr. Davies's testimony regarding his humidity treatment test of Mylan's ANDA product does not meet the *Daubert* standard and the requirements of Rule 702. Accordingly, Mylan's *Daubert* motion is **GRANTED**.

iii. Even if Dr. Davies's Humidity Test Met the Daubert Standard, the Test Would Not Support a Finding that there Is a Stabilizing Coat in Mylan's Product

1) The Humidity Test, Standing Alone, Does Not Show that There Is a Stabilizing Coat in Mylan's Product

Plaintiffs introduced evidence that portions of Mylan's bead darken after being exposed to humidity. Based on that evidence, Plaintiffs ask the Court to conclude that there is a stabilizing coat in Mylan's beads, in between each bead's core element and its

delayed release coating, comprised of povidone and crospovidone. The Court declines to take such a large logical leap.

Dr. Davies posits that portions of Mylan's beads darkened after humidity exposure because those portions are comprised of povidone and crospovidone. However, reaching this conclusion requires accepting a string of other premises, including that (1) povidone and crospovidone are the most hygroscopic materials in Mylan's bead, (2) when exposed to 90% RH for 5 seconds, povidone and crospovidone absorb more water than any other ingredient in Mylan's bead, (3) because povidone and crospovidone absorb more water than any other ingredient in Mylan's bead, povidone and crospovidone will swell more than any other ingredient in Mylan's bead, (4) because povidone and crospovidone swell more than any other ingredient in Mylan's bead, the povidone and crospovidone portions of the bead will darken more than any other ingredient in Mylan's bead.

Dr. Davies's theory is attenuated, but there is some support for it. First, the Salameh article cited by Dr. Davies notes that povidone and crospovidone tend to darken in response to humidity. Second, in the "compacts" that Dr. Davies used in his control experiment, the povidone and crospovidone portions darkened more than the other ingredients when exposed to 90% RH for 5 seconds. While this is somewhat compelling, Dr. Davies's compacts were not made the same way as the Mylan beads, so they may not function as a good control. For example, Dr. Davies used dry mixes of powders instead of granulating and spheronizing the materials, so the active ingredient and the povidone did not have a chance to intimately mix. JA 451:15-24. In addition, the compacts did not include all of the excipients found in the Mylan's bead core (such as sodium chloride), which could impact water absorption. JA 991:18-20.

Although Dr. Davies's theory provides one possible explanation for the selective darkening in Mylan's bead, there are other possible reasons for this darkening. Mylan proffered two alternative theories. First, Mylan suggested that the localized darkening could be a consequence of variations in density in different areas of the bead. According to Mylan, the materials inside the beads are not likely to have a uniform density because the materials were spheronized during the manufacturing process. The darkening in the beads could be a result of the fact that less dense areas of the bead absorbed more water than the denser areas. Second, Mylan suggested that the difference in water absorption could be a result of the fact that the core contains amorphous API. Amorphous materials are more hygroscopic than crystalline materials, so this could explain why certain portions of the bead absorbed more water than others.

The amount of the samples that darkened in most of the images is more consistent with Mylan's theories than with Dr. Davies's theory. Povidone and crospovidone together comprise 17% of the materials in Mylan's ANDA product. JA 958:10-12; JA 959:10-13. However, more than 17% of the samples darkened in the majority of the images. JA 971:14-17. In fact, some of Dr. Davies's "after" images of a Mylan bead show darkening across the entire bead, or in different areas of the bead, rather than just the outer region around the surface. Darkening across the entire bead, or darkening in

different areas of the bead, are both consistent with the notions that the portions of the bead that are darkening are less dense and/or contain amorphous API. JA 964:11-21; JA 3521-22; JA 3525-26; JA 965:10-14; JA 3529-30; JA 3531-32.

On balance, the Court finds Mylan's theories to be more plausible than Dr. Davies's theory. Accordingly, the Court finds that the humidity test, standing alone, does not show that there is a stabilizing coat in Mylan's product.

2) The Humidity Test, When Evaluated in Light of the Other Tests Conducted, Does Not Show that There Is a Stabilizing Coat in Mylan's Product

The results of the humidity test, standing alone, are extremely questionable. However, there is no reason to rely on the results of the humidity test when Raman, ToF-SIMS, and ATR-FTIR data are available. The Court finds these tests to be eminently more reliable for two reasons.

First, these three tests are all widely-accepted by the scientific community. Raman and ToF-SIMS, for example, have been used for decades and have been extensively peer-reviewed. JA 622:25-623:6; JA 630:16-631:1; JA 784:19-785:12. Similarly, ATR-FTIR is "widely used in the industry," even according to Dr. Davies. JA 126:20.

Second, the Raman, ToF-SIMS, and ATR-FTIR tests are far more sophisticated and far more precise than Dr. Davies's humidity test. Each of these three techniques uses state of the art "fingerprint" technology that is capable of identifying every molecule in a composition and where that molecule is located in relation to the others. Even Dr. Davies acknowledges that these are appropriate tests for determining the chemical composition and spatial distribution of molecules in a pharmaceutical composition. JA 126:13-127:10. Dr. Davies's humidity test, in contrast, does not provide chemical information regarding the components in the bead. JA 962:18-24; JA 965:15-21; JA 954:19-955:5. Instead, Dr. Davies relies on a series of assumptions to reach the conclusion that the images he generated showed povidone. Even if the Court assumes that the humidity test can accurately identify povidone, there is no allegation that the humidity test is capable of identifying any other molecules in a pharmaceutical composition.

Accordingly, it makes little sense to rely on the results of the humidity test when Raman, ToF-SIMS, and ATR-FTIR test results are available. Frankly, it would be a bit like trying to tell the time of day by estimating the position of the sun when you could just look down at your watch.

3) Dr. Davies's Testimony that Mylan's Product Has a Stabilizing Coat Was Not Credible

There are two reasons that the Court did not find Dr. Davies's testimony that Mylan's product has a stabilizing coat to be credible.

First, Dr. Davies performed his humidity test shortly before his expert report was due, and only after a litany of other testing methods had failed to demonstrate the presence of a stabilizing coat in Mylan's product.[18] Dr. Davies was asked by the Court why he waited until March 2011 to conduct the humidity test, when he knew, in the October and November 2010 time frame, that he was looking for a layer of povidone and he knew that none of the traditional testing methods could detect povidone. JA 255:11-260:13. In response to the Court's questions, Dr. Davies stated that he was running up against discovery deadlines, report deadlines, and production deadlines, which prevented him from running the test earlier. JA 259:23-260:13. However, none of these deadlines prevented Dr. Davies from running the other six tests first, and Dr. Davies later acknowledged that the humidity tests could be done in a day. JA 257:22-25; JA 261:6-9. The Court did not find Dr. Davies's testimony regarding the timing of the humidity test to be credible. The Court finds that it is more likely than not that Dr. Davies only created the humidity test because the litany of other tests that he performed failed to yield the desired result.

Second, the Court did not find Dr. Davies's testimony that Mylan's product has a stabilizing coat to be credible because Dr. Davies himself testified that he did not expect any of the components in Mylan's beads to interact to form an *in situ* layer. In this case, all of the ingredients in Mylan's tablets are known. Dr. Davies reviewed the list of ingredients used in Mylan's product and could not explain how those ingredients might interact to form a layer. JA 394:11-20. In fact, Dr. Davies signed a declaration stating that he did not expect that any of the components in the Mylan's beads to interact *in situ* to form a stabilizing coat. JA 394:22-25. Although Plaintiffs are not required to provide any explanation for how the alleged layer might form *in situ*, Dr. Davies's complete inability to provide any explanation for how these components might interact makes his finding that there is a layer less believable.

2. Plaintiffs Failed to Prove that the Alleged Stabilizing Coat "Keeps Migration of Core Materials to a Minimum Such That the Interaction of Core Materials With Coating Materials Is Reduced or Prevented"

In addition to proving that Mylan's ANDA product has "a layer of material(s) between each core element and its modified release coating," Plaintiffs must show that this layer is what "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented" (the "migration limitation"). *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

[18] On October 20, 2010, Dr. Davies performed optical microscopy, SEM analysis, and ToF-SIMS on the Mylan ANDA product. JA 403:12-16; JA 404:7-9. On November 10, 2010, Dr. Davies performed Raman spectroscopy and AFM analysis on Mylan's product. JA 410:7-12. On March 2 and 9, 2011, Dr. Davies performed ATR-FTIR analysis of the Mylan ANDA product. JA 413:1-4. It was not until March 10, 2011 that Dr. Davies first performed the humidity test. JA 413:15-21.

Dr. Davies conducted dissolution studies on Mylan's ANDA product and found that it meets the dissolution storage stability limitations set forth in the '161 Patent. Mylan does not dispute these results. Plaintiffs argue that a stabilizing coat would minimize the migration of core materials by virtue of its presence, and that the dissolution studies are sufficient to prove that Mylan's product meets the migration limitation. JA 327:4-12; JA 178:19-179:10. The Court disagrees.

The Court finds that Plaintiffs must offer evidence that the stabilizing coat is causing Mylan's product to have the required dissolution stability. The migration limitation itself requires that Plaintiffs prove causation. According to the Court's claim construction, Plaintiffs must prove that Mylan's product contains "a layer . . . which keeps the migration of core materials to a minimum . . . so that" the dissolution stability limitations are met. *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7. In other words, it is not enough that Plaintiffs show that the product has a layer and meets the dissolution stability limitations. Plaintiffs must also show that the layer is the reason that the product is stable. A stabilizing coat is just one possible way of creating dissolution storage stability. One could imagine a situation in which the required dissolution stability was achieved by other means (for example, by changing the composition of the delayed release coating, by changing the composition of the core, by changing the desiccants used, etc.). In that situation, dissolution studies would not be a good proxy for the migration of core materials, because the core materials might not be migrating at all.

Plaintiffs did offer some evidence that the stabilizing coat minimizes the migration of core materials (thus causing Mylan's product to have the required dissolution storage stability): Plaintiffs pointed to images of Mylan's bead that showed that there were core materials abutting the delayed release coating. JA 224:23-225:23; JA 560:17-20; JA 2020. But these images could mean one of two things. They could mean, as Plaintiffs suggest, that the core materials were initially in the middle of the bead, but slowly started to migrate out. Or they could mean, as Mylan suggests, that there were core materials adjacent to the delayed release coating since the moment the beads were manufactured.

There is no support for Plaintiffs' theory. Dr. Davies provided no evidence to support his opinion that large particles of drug, lactose, or other excipients abutting the delayed release coating migrated through the stabilizing coat. JA 560:1-5. There is some support for Mylan's theory. First, Mylan's theory is consistent with the bead manufacturing process. Second, Mylan's Raman and ToF-SIMS data show that the particles of core materials are quite large, and Mylan's experts testified that the particles would be too big to diffuse through a coat. JA 956:12-958:5; JA 970:22-971:6; JA 1007:17-1008:3.

The Court finds that, on balance, Mylan's explanation is the more plausible of the two. Therefore, the Court finds that Plaintiffs failed to prove that any alleged stabilizing coat "keeps migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

3. Conclusion

For the reasons set forth above, the Court finds that: (1) Plaintiffs failed to prove that Mylan's ANDA product has "a layer of material(s) between each core element and its modified release coating"; and that (2) Plaintiffs failed to prove that the alleged stabilizing coat "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

Accordingly, the Court concludes that Plaintiffs failed to prove, by a preponderance of the evidence, that Mylan's ANDA product infringes the '161 Patent.

C. IMPAX'S ANDA PRODUCT DOES NOT INFRINGE THE '161 PATENT

Plaintiffs assert that Impax's ANDA product infringes claims 1-3, 5, 10, and 16-22 of the '161 Patent. SF ¶ 35.

Impax's ANDA product, like the Doryx Tablet, is comprised of a series of seeds that have been compressed into tablet. The parties agree that the seeds have a doxycycline hyclate core and a delayed release coating. The primary issue for infringement is whether Impax's ANDA product contains a "stabilizing coat." If the Court finds that Impax's product contains a "stabilizing coat," then Impax's product infringes the '161 Patent. Consistent with this Court's claim construction, to prove that Impax's product contains a "stabilizing coat," Plaintiffs must show that the product has:

> [A] layer of material(s) between each core element and its modified release coating, which keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented.

Warner Chilcott Labs. Ireland, 2011 WL 2971155, at *7. The parties also dispute whether Impax's ANDA product provides the required dissolution stability.

For the reasons set forth below, the Court finds that Plaintiffs failed to prove, by a preponderance of the evidence, that Impax's ANDA product infringes the '161 Patent. Specifically, the Court finds that Plaintiffs failed to prove that: (1) Impax's ANDA product has "a layer of material(s) between each core element and its modified release coating"; and that (2) the alleged stabilizing coat "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7. The Court finds that Plaintiffs met their burden of proving that Impax's product provides the required level of dissolution storage stability. However, this does not change the Court's overall finding that Impax's ANDA product is non-infringing.

1. Plaintiffs Failed To Prove That Impax's ANDA Products Has "A Layer Of Material(s) Between Each Core Element And Its Modified Release Coating"

Plaintiffs assert that Impax's ANDA product has a "stabilizing coat." Specifically, Plaintiffs allege that each seed in Impax's ANDA product has a 4 to 6 micron layer of materials between its core element and its modified release coating, comprised of an "HPMCP (HP-50)-derived material"[19] and an enrichment of talc. *See* JA 498:20-23; JA 314:11-325:5.

The Court finds that Plaintiffs failed to prove that Impax's ANDA product has "a layer of material(s) between each core element and its modified release coating." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7. The Court makes this finding for three reasons. First, it is undisputed that Impax does not apply a stabilizing coat to its ANDA product. Second, five widely-accepted scientific testing methods failed to show the presence of a stabilizing coat in Impax's unaltered seeds. Finally, the one, novel acetone wash test that Plaintiffs rely on does not prove that there is a stabilizing coat in Impax's product. Each of these findings is explained in greater detail below.

a. Impax Does Not Apply a Stabilizing Coat to its ANDA Product

It is undisputed that Impax does not apply a stabilizing coat to its ANDA product during the manufacturing process. JA 346:19-25, JA 347:5-6.

The manufacture of Impax's product takes place in three stages. In the first stage, Impax makes core seeds by mixing, extruding, and spheronizing a mixture of the active ingredient (doxycycline hyclate) and other excipients. JA 1185:18-1186:9; JA 5103.

In the second stage, a delayed release coating mixture is created and sprayed onto the active core seeds. JA 1186:11-1187:10. The process for creating and applying the delayed release coating was designed to ensure that the coating is a substantially uniform mixture of the following four ingredients: (1) HP-50; (2) hydroxypropyl methylcellulose ("HPMC"); (3) triethyl citrate; and (4) talc. JA 1188:9-1189:13, JA 1196:16-1197:20; JA 1186:11-1187:10; JA 5103. To achieve this uniformity, Impax first makes a mixture that is 70% acetone and 30% water. JA 1186:15-18; JA 1187:12-1188:3; JA 5103; JA 4749. Impax then adds dry powders of HP-50, HPMC, and triethyl citrate to the liquid. JA 1186:19-22. This new mixture is vigorously stirred for at least ten minutes, until all three powders are successfully dissolved in the liquid (the mixture is stirred so aggressively that the stirring creates a vortex). JA 4751; JA 1186:11-1187:10; JA 1196:16-1197:20; JA 4751. Impax then adds talc to the mixture, while maintaining the vigorous mechanical stirring for at least another ten minutes. JA 1196:16-1197:20; JA 4751. Talc is insoluble in acetone and water, so the stirring disburses the talc particles, but does not dissolve them. JA 4751-52; JA 1196:16-1197:20. Once the talc particles have been evenly distributed throughout the mixture, the entire mixture is sprayed onto the core seeds. *Id.* After the mixture is applied, the acetone and water evaporate, leaving behind an even layer of delayed release coating surrounding the seeds. JA 1187:20-1188:3.

In the final stage, the delayed release seeds are blended with a mixture of inactive ingredients, and that mixture is compressed into 75 mg, 100 mg or 150 mg tablets. JA

[19] HP-50 is a type of HPMCP. Hereinafter, HPMCP (HP-50) will be referred to as "HP-50."

1189:15-1190:4; JA 5103. Once Impax's tablets are made, they are packaged in a sealed container with a desiccant. JA 1192:17-19.

b. Five Widely-Accepted Scientific Testing Methods Did Not Show the Presence of a Stabilizing Coat in Impax's Unaltered Seeds

Five widely-accepted scientific testing methods did not show the presence of a stabilizing coat in Impax's product. These five testing methods are: (1) ATR-FTIR; (2) ToF-SIMS; (3) SEM/EDS; (4) optical microscopy; and (5) AFM.

The Court finds that each of these five testing methods is scientifically reliable, and that the test results as a whole demonstrate that there is no stabilizing coat in Impax's product. The Court specifically finds that ATR-FTIR, ToF-SIMS, and SEM/EDS data affirmatively show that there is no stabilizing coat in Impax's product. The ToF-SIMS, SEM, optical microscopy, and AFM tests conducted by Dr. Davies on Impax's unaltered seeds further confirm that there is no stabilizing coat.

i. ATR-FTIR Testing

The ATR-FTIR technique uses light to determine the chemical composition of the material that the light is hitting. JA 171:24-173:3; JA 299:20-300:1. An ATR-FTIR spectrum contains characteristic peaks that are unique to the chemical being analyzed, similar to a fingerprint. *Id.* The ATR-FTIR technique is peer-reviewed, scientifically accepted, and routinely used in the industry for determining the structure of pharmaceutical compositions. JA 413:8-11; JA 4902-27.

Dr. Andre J. Sommer, Impax's ATR-FTIR expert, is the co-developer of the ATR-FTIR imaging technique and has been working with the technique since 1985. JA 1087:20-1088:2. Dr. Sommer is the Director of the Molecular Microspectroscopy Laboratory, where his research focuses on materials characterization and the development and application of molecular microspectroscopies for surface analysis. JA 1086:5-15. The Court qualified Dr. Sommer as an expert in ATR-FTIR spectroscopy and ATR-FTIR imaging. JA 1091:2-7.

Dr. Sommer performed ATR-FTIR analysis on Impax's seeds. JA 1099:17-1100:15. To prepare the samples of Impax's seeds for ATR-FTIR imaging, Dr. Sommer supervised the removal of the delayed release seeds from Impax's tablets, the selection of sample seeds for analysis, and the cross-sectioning of the seeds using a microtome. JA 1104:5-1105:4. Dr. Sommer performed ATR-FTIR analysis on two locations on five different seeds. JA 1106:3-5. Dr. Sommer's technique collected more than 16,000 individual infrared scans over an area of approximately 200 by 200 microns of a cross-sectioned seed. JA 1099:17-1100:15. Dr. Sommer used a technique that has the resolution to detect features that are less than one micron thick. JA 1115:1-12.

Dr. Sommer's data clearly shows that there is no stabilizing coat in Impax's product. All of Dr. Sommer's images show that Impax's seeds have a single, well-

defined delayed release layer. *See, e.g.*, JA 4829; JA 4831; JA 4834; JA 4836. The talc-specific images show that talc is randomly distributed throughout the delayed release layer. *See, e.g.*, JA 1107:15-1109:5; JA 4836; JA 4834; JA 4829; JA 4831. None of the images show a concentration of talc near the core. *Id.* Similarly, the HP-50 specific images show that HP-50 is distributed in a fairly uniform manner throughout the delayed release coat. *Id.* There is no evidence in any of the images of a separate layer of "HP-50 derived material" inside or outside of the delayed release coat. JA 1091:18-1092:4.

The Court found Dr. Sommer's testimony regarding ATR-FTIR to be credible and well-supported. The Court found Dr. Sommer's procedures to be reliable enough to produce accurate results. The Court found Dr. Sommer's ATR-FTIR data to be extremely reliable, as the technique he used had high selectivity, sensitivity, and spatial resolution. The Court finds that an ATR-FTIR imaging technique that can detect features of less than one micron has the necessary resolution to detect the existence of a 4 to 6 micron layer of talc and other materials.[20] Dr. Sommer's ATR-FTIR data consistently and overwhelmingly reflect the absence of such a layer in Impax's product. In fact, Dr. Sommer's data showed that the structure of Impax's seed is identical to the structure created during the manufacturing process: a core seed surrounded by a single, delayed release coating.

ii. ToF-SIMS Testing

As explained in more detail above, ToF-SIMS is a surface analysis technique that measures the top few molecular layers of a surface and provides information about the chemistry of that surface. JA 1028:15-20; *see also* section III(B)(1)(b)(ii). ToF-SIMS has been used for decades and is widely accepted by the scientific community. *Id.*

Dr. Rana Sodhi, Impax's expert on ToF-SIMS, runs a surface analysis research facility at the University of Toronto. JA 1022:25-1023:10; JA 1025:5-7. Dr. Sodhi has published approximately 30 scientific papers in peer-reviewed journals focusing on the use of ToF-SIMS. JA 1025:8-13. He has prepared or supervised the preparation of samples for ToF-SIMS testing hundreds of times and has analyzed such samples thousands of times. JA 1023:23-1024:11. The Court qualified Dr. Sodhi as an expert in surface analysis, specifically ToF-SIMS. JA 1026:12-17.

Dr. Sodhi conducted a ToF-SIMS analysis of Impax's seeds. First, he obtained ToF-SIMS reference spectra and identified characteristic peaks for each of the ingredients in Impax's seeds. JA 1028:11-14; JA 1032:20-23; JA 1035:17-1036:6; JA 5038-56. Next, Dr. Sodhi prepared sample seeds for testing by extracting the seeds from an Impax tablet, mounting the seeds in resin, and cutting the seeds to expose a cross-section close to the equator. JA 1033:19-24; JA 1033:25-1034:6; JA 1034:7-17. Dr. Sodhi followed this same procedure with three separate seeds. JA 1034:14-23. Dr. Sodhi

[20] The Court rejects Plaintiffs' argument that Dr. Sommer could not distinguish talc from HP-50. *See* JA 362:24-364:8. As Dr. Sommer explained at trial, the absorption strength for talc is over 7 times the absorption strength for HP-50, making talc readily distinguishable. JA 1111:9-1113:1.

then conducted a ToF-SIMS analysis on a total of seven different areas on the three cross-sectioned seeds. JA 1034:14-23. The size of the areas was a minimum of 150 by 150 microns, and spanned the surface from the core all the way to the outer surface of the delayed release coating. JA 1043:25-1044:4, JA 1044:13-16; JA 4807; JA 4810. Dr. Sodhi used a high spatial resolution, which allowed him to image features as small as 0.2 microns. JA 1036:11-19. Dr. Sodhi generated images that isolated various materials in the seed, including talc and HP-50. JA 1038:15-21.

Dr. Sodhi's data clearly shows that there is no stabilizing coat in Impax's product. All of Dr. Sodhi's images show that Impax's seeds have a single, well-defined delayed release layer. *See* JA 4806-10; JA 5059-67. The talc-specific images (associated with the magnesium peak) show that talc is distributed throughout the entire delayed release layer. JA 4806-07; JA 1037:17-25; JA 1039:16-1040:4, JA 1041:5-9. There is no evidence of a talc-enriched layer around the core. *Id.* Similarly, the HP-50 specific images (associated with the phthalate peak) show that there was a uniform distribution of HP-50 across the delayed release layer. JA 1041:10-17. There is no evidence of any layer of "HP-50 derived material" anywhere in Impax's seeds. JA 1041:10-17; JA 4807. In fact, there is no evidence of any layer, regardless of composition, inside or outside of Impax's delayed release coating. JA 1046:4-18, JA 1052:17-1053:3.

The Court found Dr. Sodhi's testimony regarding ToF-SIMS to be credible and well-supported. The Court found Dr. Sodhi's procedures to be reliable enough to produce accurate results. The Court found Dr. Sodhi's ToF-SIMS data to be reliable, as Dr. Sodhi analyzed multiple areas on multiple seeds and was able to generate precise, chemically-specific images for each area.[21] The Court finds that, if there were a 4 to 6 micron layer of talc and other materials in Impax's seeds, ToF-SIMS would have detected it.[22] *See* JA 1053:1-3. Instead, Dr. Sodhi's ToF-SIMS data consistently and overwhelmingly reflects the absence of such a layer in Impax's product. All of Dr. Sodhi's data showed that the structure of Impax's seed was identical to the structure created during the manufacturing process: a core seed surrounded by a single, delayed release coating. JA 1027:4-25; JA 1027:4-22.

Dr. Davies also tested cross-sectioned Impax seeds using ToF-SIMS. JA 350:6-25. Dr. Davies's ToF-SIMS data did not show the presence of a stabilizing coat in Impax's seeds. JA 457:4-15; JA 463:21-24; JA 1032:10-19.

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[21] Plaintiffs argue that no conclusions about the absence of a stabilizing coat can be drawn from Dr. Sodhi's analyses because ToF-SIMS is a non-quantitative method (*i.e.*, it provides no information about the relative amounts of different ingredients, only their presence or absence). JA 242:25-243:13. However, there is no dispute that ToF-SIMS can detect the spatial distribution of materials, which is at issue here.

[22] Dr. Davies's criticisms that talc is poorly detected using ToF-SIMS is contradicted by his own scientific publication, in which he reported the detection of talc in a layer using ToF-SIMS, relying on the same mass peak that Dr. Sodhi used. JA 1040:5-1041:4; JA 4898 (reporting imaging of talc in clusters ranging in size from 1 to 10 microns).

iii. SEM/EDS Testing

SEM coupled with Energy Dispersive Spectroscopy ("EDS") and imaging analysis ("SEM/EDS imaging") is a well-known, widely accepted analytical test methodology. SEM is a high resolution imaging technique, which scans a beam of electrons over a sample surface to produce a high-resolution image. JA 125:25-126:3; JA 301:21-302:8; JA 3357. EDS analyzes electrons that are emitted from a sample when it is hit with an electron beam. JA 1122:10-1123:3. EDS analysis allows for the identification of the molecules in a sample. *Id.* Like ATR-FTIR imaging, SEM/EDS allows for the construction of maps that illustrate the spatial distribution of molecules in a compound. *Id.* The Court qualified Impax's expert, Dr. Sommer, as an expert in SEM techniques. JA 1091:2-7.

Dr. Sommer conducted SEM/EDS imaging on three samples of Impax's delayed release seeds. JA 1106:9-18. To prepare the samples, Dr. Sommer removed the seeds from Impax's tablets and had them cross-sectioned. JA 1104:12-1105:4. SEM/EDS analysis and imaging was then used to map the location and relative concentration of talc in the cross-sectioned samples. JA 1106:15-18; JA 1123:18-1124:1. All of the EDS maps show that talc is randomly distributed throughout the entire delayed release coating, not enriched near the core. JA 5011-19.

The Court found Dr. Sommer's testimony regarding SEM/EDS to be credible. The Court finds Dr. Sommer's SEM/EDS data to be reliable. The Court finds that, if there were a 4 to 6 micron layer of talc and other materials between the delayed release coat and the core in Impax's seeds, SEM/EDS would have detected it. Instead, Dr. Sommer's data showed that the structure of Impax's seed was identical to the structure created during the manufacturing process.

Dr. Davies also conducted an SEM analysis of cross-sectioned Impax seeds. JA 302:9-14. Dr. Davies's SEM analysis showed that Impax's seeds had two parts: (1) a core element, and (2) a single, outer delayed release coating. JA 464:17- 22. Dr. Davies was not able to detect the presence of a stabilizing coat based on his SEM images. JA 304:7-9.

iv. Optical Microscopy

Dr. Davies conducted an optical microscopy analysis of cross-sectioned Impax seeds. JA 299:1-11. Dr. Davies's optical microscopy images showed that Impax's seeds had two parts: (1) a core element, and (2) a single, outer delayed release coating. JA 460:21-461:18; JA 299:1-16; JA 2862-63. Dr. Davies was not able to detect the presence of a stabilizing coat based on his optical microscopy images. JA 461:12-18.

v. AFM Testing

Dr. Davies conducted an AFM analysis on cross-sectioned Impax seeds. JA 461:23-462:1. Dr. Davies was not able to detect the presence of a stabilizing coat based on his AFM analysis. JA 462:14-20.

c. Dr. Davies's Acetone Wash Test Does Not Support a Finding that There Is a Stabilizing Coat in Impax's Product

Instead of relying on any of the five widely-accepted testing methods described above, Plaintiffs rely on a novel acetone washing method to show that there is a stabilizing coat in Impax's ANDA product. Before trial, Impax filed a *Daubert* motion seeking to preclude Dr. Davies from testifying about the acetone washing method. The Court reserved on the *Daubert* motion. For the reasons set forth below, the Court now finds that Dr. Davies's acetone washing method does not meet the *Daubert* standard. The Court also finds that, even if the acetone washing method met the *Daubert* standard, the test would not support a finding that there is a stabilizing coat in Impax's product.

The Court will address: (1) the methodology for and results of Dr. Davies's acetone washing method; (2) the reasons that the acetone washing method does not meet the *Daubert* standard; and (3) the reasons that the acetone washing method would not support a finding that there is a stabilizing coat in Impax's product, even if it met the *Daubert* test.

i. Dr. Davies's Acetone Wash Test: Methodology, Testing, and Results

In addition to testing Impax's delayed release coated seeds using the testing methods described above, Dr. Davies sought to analyze uncoated Impax seeds. Impax did not have uncoated seeds available, so Dr. Davies set out to remove the delayed release coating from the seeds himself. JA 307:1-10; JA 312:22-313:3; JA 468:13-469:1; JA 3360-61. Dr. Davies determined that the best way to remove the delayed release coating was to wash the seeds in a solvent that was 99% acetone and 1% water. JA 313:4-17. Dr. Davies placed five delayed release coated seeds in a vial with 20 mL of the solvent and had a technician "swirl" the vial by hand for 5 minutes. JA 307:1-10; JA 312:22-313:3; JA 468:13-469:1; JA 3360-61. Additional tests were done in which vials were swirled for 10 minutes and 20 minutes. The seeds were then rinsed twice using an additional 20 mL of the solvent. JA 313:18-23; JA 3360-61.[23]

After performing the Acetone Wash, Dr. Davies analyzed the washed seeds using ATR-FTIR and SEM.[24] JA 314:11-13; JA 316:2-6. Dr. Davies performed ATR-FTIR on both unwashed and washed seeds. Dr. Davies first conducted an ATR-FTIR analysis of the outside surface of unwashed Impax seeds. JA 299:17-22. As expected, the ATR-FTIR spectra of the unwashed seeds contained peaks associated with HP-50 and talc, components in Impax's delayed release coating. JA 300:24-301:15; JA 2869. Dr. Davies later conducted an ATR-FTIR analysis of the outside surface of 18 washed Impax seeds. JA 314:11-13; JA 316:2-6. Because Dr. Davies designed the acetone/water solvent to remove the delayed release coating, he expected that all of the components from the

[23] The Court will refer to this process as Dr. Davies's "Acetone Wash."

[24] The Court will refer to the analysis of Impax's washed seeds as Dr. Davies's "Acetone Wash Test."

delayed release coating would be removed after the wash, leaving only the exposed core seed. JA 314:11-21; JA 341:9-25. However, the ATR-FTIR spectra of the washed seeds were not consistent with Impax's core. JA 314:11-21; JA 341:9-25; JA 2869; JA 3365. Instead, the spectra had one peak associated with HP-50 and two peaks associated with talc. JA 314:22-315:17; JA 2869; JA 3365. Although these peaks also appeared in the spectra of Impax's unwashed seeds, the ratio of the HP-50 peak to the talc peaks was slightly different in Impax's washed seeds: the talc peak for the washed seed was higher relative to the HP-50 peak. *Id.* Based on these results, Dr. Davies concluded that Impax's seeds had a hidden stabilizing coat that was "enriched in talc." JA 314:22-315:11.

Dr. Davies also used SEM to analyze 6 Impax seeds that had been washed and cross-sectioned. JA 314:11-13; JA 316:2-6; JA 322:2-11; JA 2869-81. Dr. Davies's SEM data showed that, after a 5-minute Acetone Wash, about two-thirds of Impax's outer coating had been removed. JA 316:16-317:7. The remaining layer was insoluble in the acetone/water solvent, even after the washing procedure was conducted for 10 minutes and 20 minutes. JA 318:14-22; JA 320:24-321:5; JA 2869; JA 318:25-320:1; JA 321:6-322:1; JA 2878. Because the remaining layer produced spectra with an HP-50 peak, but did not dissolve as Dr. Davies expected, Dr. Davies concluded that Impax's seeds had a stabilizing coat containing an "HP-50 derived material." JA 323:24-325:5.

Based on this testing, Dr. Davies concluded that Impax's seeds have a layer of "HP-50-derived material" and an enrichment of talc between each core element and its delayed release coating, thus meeting the stabilizing coat limitation of the '161 Patent.

ii. Dr. Davies's Acetone Wash Test Does Not Meet the Daubert Standard

Impax filed a pre-trial *Daubert* motion to preclude Dr. Davies from testifying regarding his use of a 99:1 acetone:water solvent to remove the delayed release coating on Impax's seeds. The Court reserved its decision on the *Daubert* motion, and admitted the evidence during the trial with the understanding that the Court could later disregard the testimony. After careful review of the evidence and the motion papers submitted by the parties, the Court now finds that Dr. Davies's Acetone Wash Test does not meet the *Daubert* standard. Specifically, the Court finds that the eight factors set forth by the Third Circuit for evaluating the reliability of evidence weigh in favor of excluding Dr. Davies's Acetone Wash Test. *See United States v. Mitchell*, 365 F.3d 215, 235 (3d. Cir. 2004).[25]

[1] Whether a Method Consists of a Testable Hypothesis. Dr. Davies's Acetone Wash Test does consist of a testable hypothesis, but Dr. Davies made no effort to test it: Dr. Davies did not run a single control test for his washing method.

[25] The Court's finding is limited to Dr. Davies's use of a 99:1 acetone:water solvent to remove the delayed release coating on Impax's seeds. The Court expresses no opinion about the use of solvents to remove coatings, generally.

[2] Whether the Method Has Been Subject to Peer Review. Dr. Davies's Acetone Wash Test has never been published or subject to peer review. JA 478:22-479:17 (no peer-reviewed reference to support 99:1 acetone-water solution). Dr. Davies did reference a peer reviewed article where acetone was used to remove a coating, but it was not an HP-50 coating. JA 310:13-311:14; JA 3086 § 2.4.3.

[3] The Known or Potential Rate of Error. Dr. Davies made no effort to quantify the rate of error associated with his washing method. He did not provide any data that would allow anybody else to quantify the rate of error inherent to his method.

[4] The Existence and Maintenance of Standards Controlling the Technique's Operation. The standards controlling Dr. Davies's Acetone Wash Test appear to be arbitrarily chosen or imprecisely executed. There appears to be no support from any scientific sources for Dr. Davies's decision use a solvent comprised of 99% acetone and 1% water. In fact, Dr. Davies's decision to use a 99:1 ratio runs contrary to the recommendations in the HP-50 manufacturer's brochure. The manufacturer's brochure for HP-50 explicitly states that HP-50 will not completely dissolve in 100% acetone. *See* JA 5146. The manufacturer's brochure recommends using a solvent that is 95% acetone and 5% water, but Dr. Davies chose not to use this ratio. *See id.* Similarly, Dr. Davies did not use a mechanical stirring device or any other method of uniform agitation. Instead, the technicians who performed the experiments simply "swirled" the samples by hand for 5, 10 or 20 minutes. JA 1226:5-10. These are not the types of rigorous standards that one would expect to control a precise scientific experiment.

[5] Whether the Method Is Generally Accepted. Dr. Davies's Acetone Wash Test is not generally accepted in the scientific community. JA 467:8-11; JA0467:12-468:12; JA 1205:17-20. In fact, it appears that this method has never been used by the scientific community at all.

[6] The Relationship of the Technique to Methods Which Have Been Established to Be Reliable. Methods which have been established to be reliable do not support the reliability of Dr. Davies's Acetone Wash Test. In fact, Dr. Davies's decision to use a 99:1 ratio runs contrary to the recommendations in the HP-50 manufacturer's brochure. *See* JA 5146.

[7] The Qualifications of the Expert Witness Testifying Based On the Methodology. None of the parties dispute Dr. Davies's qualifications, and the Court finds that he is qualified to be an expert on the characterization of pharmaceutical systems.

[8] The Non-Judicial Uses to Which the Method Has Been Put. Dr. Davies's method has never been used outside the context of litigation.[26]

Overall, the eight factors set forth by the Third Circuit clearly weigh in favor of exclusion. Accordingly, Impax's *Daubert* motion is **GRANTED**.

[26] Dr. Davies has used this method in prior litigations. *See* JA 479:18-480:20.

iii. Even if Dr. Davies's Acetone Wash Test Met the Daubert Standard, the Test Would Not Support a Finding that there Is a Stabilizing Coat in Impax's Product

1) The Acetone Wash Test Does Not Show that There Is a Stabilizing Coat in Impax's Product

Dr. Davies's testing showed that something around Impax's core seeds did not dissolve when the seeds were washed in his acetone/water solvent. According to Plaintiffs, these test results show that there is a hidden stabilizing coat in Impax's seeds. According to Impax, these test results show that the Acetone Wash failed to remove all the remnants of the delayed release coating. The Court finds Impax's explanation of Dr. Davies's test results to be far more plausible.

There is almost no support for Plaintiffs' assertion that the Acetone Wash Test revealed a hidden layer. All that Plaintiffs have shown is that there are some materials on Impax's seeds that did not dissolve in his acetone solvent. Based solely on this failure to dissolve, Plaintiffs concluded that chemicals in Impax's seeds reacted to form an *in situ* layer that performs a stabilizing function. The Court finds that Plaintiffs failed to proffer enough evidence to support this enormous logical leap.

First, Plaintiffs completely failed to demonstrate that the alleged layer that Dr. Davies "discovered" exists in an actual, intact Impax seed. JA 477:24-478:21. All of the testing on Impax's intact seeds, including all the testing conducted by Dr. Davies, showed that there is no intermediate layer in Impax's product. Impax's ATR-FTIR, ToF-SIMS, and SEM/EDS data showed that there was no additional layer inside or outside of the delayed release coat. In addition, Dr. Davies's own SEM, ToF-SIMS, optical microscopy, and AFM analyses showed that there was no additional layer in Impax's unwashed seeds. JA 304:7-9; JA 466:25-467:3. The Court finds these tests to be far more reliable, as they did not chemically or physically alter Impax's product before analysis. *See* JA 1051:8-23; JA 1093:10-20; JA 1213:18-1214:5; JA 4560-62.

The fact that Dr. Davies's SEM analysis of an unwashed seed did not show the presence of a layer is especially compelling. Dr. Davies's SEM analysis was just an imaging technique; Dr. Davies made determinations about the composition of the samples based purely on a visual inspection of his SEM images. In high resolution images of washed seeds, for example, Dr. Davies said that he could "clearly see the flat plate-like crystals of talc," which is how he determined the dimensions of the alleged stabilizing coat. JA 317:16-17. But, if there were a stabilizing coat in Impax's seeds, these "flat plate-like crystals of talc" should have been just as visible in images of the unwashed seeds. JA 304:7-9; JA 464:17- 22. The fact that Dr. Davies did not "clearly see" this concentration of talc before conducting his Acetone Wash strongly suggests that there ***was*** no concentration of talc before he conducted his Acetone Wash.[27] JA 317:16.

[27] When Dr. Davies first conducted SEM on Impax's unwashed seeds, he was unable to identify

Second, the evidence overwhelmingly suggests that the materials in the delayed release coating did not fully dissolve during the Acetone Wash. The materials in Impax's delayed release coating have varying degrees of solubility in acetone and water. JA 1214:6-22; JA 1226:2-4; JA 324:19-21. Triethyl citrate, for example, is freely soluble in acetone. JA 1208:23-25. Talc, on the other hand, is insoluble in acetone, insoluble in water, and insoluble in any mixture of the two. JA 477:9-11; JA 1208:22. HP-50 swells or is partially soluble in 100% acetone, but can be dissolved in a mixture of 95% acetone and 5% water. JA 5146. There are no references that explain how HP-50 will behave in a mixture that is 99% acetone and 1% water. JA 479:9-17.

Dr. Davies's ATR-FTIR test results are exactly what one would expect to see, given the varying degrees of solubility of the materials in the delayed release coating. As expected, there were no signs of triethyl citrate in the ATR-FTIR data for Impax's washed seeds, likely because all of it dissolved. Also as expected, the data showed that there was a slight shift in the peaks for HP-50, likely because the HP-50 swelled and/or partially dissolved in the solvent.[28] Finally, the data showed that there was a much higher ratio of talc to HP-50, likely because some of the HP-50 dissolved, while none of the talc dissolved. Thus, the Court finds that it is more likely than not that whatever remained on the washed Impax seeds was comprised of the remnants of the delayed release coating that failed to dissolve during Dr. Davies's Acetone Wash.

Similarly, Dr. Davies's SEM images are exactly what one would expect to see if some of the materials in the delayed release coating did not completely dissolve. One can plainly see in the SEM images that the alleged "stabilizing coat" looks completely different in the washed and unwashed seeds. *See* JA 2882-85. The images of unwashed seeds consistently show a few large particles of talc, randomly distributed throughout the delayed release coating. The images of washed seeds, by contrast, consistently show a high concentration of small talc particles next to the core. *See* JA 2882-85. If Plaintiffs were correct that the alleged layer existed in intact seeds, then the layer would look roughly the same in the before-wash and after-wash images. Instead, these images are more consistent with Impax's theory that the talc particles broke up during the Acetone Wash and then remnants of the talc reattached to the surface of the seed.

Finally, it is likely that Dr. Davies's method of "swirling" the seeds in the solvent was insufficient to remove Impax's delayed release coating. Dissolution of a complex

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a stabilizing coat. *See* JA 304:7-12. After Dr. Davies conducted SEM on Impax's washed seeds, however, he went back to his original SEM images and superimposed colors on them to show where he thought the stabilizing coat would be. *See* JA 2872; JA 2882; JA 529:1-14.

[28] The Court finds that there was no separate "HP-50 derived material." Dr. Davies identified the "HP-50 derived material" using the same peak that he used to identify HP-50. JA 1230:14-1231:2. Dr. Davies's only evidence that HP-50 was different from the "HP-50-derived material" was that the "HP-50-derived material" did not wash away. JA 323:24-324:17. Dr. Davies asserts that it did not wash away because it had somehow transformed into a chemically distinct, insoluble material. The Court finds it far more likely that it did not wash away because HP-50 is only partially soluble in 99% acetone.

polymer is a very slow process that requires vigorous agitation. JA 1226:2-4. Impax, for example, established that dissolving the ingredients of the delayed release coating required vigorous stirring for at least 20 minutes, even when using a 70:30 acetone:water solvent. JA 4751. Impax also uses a mechanical stirrer that creates a vortex to dissolve the ingredients. *Id.* By comparison, Dr. Davies's method of "swirling" the seeds by hand seems insufficient. *See* JA 1216:15-1218:2. The Court therefore finds it highly likely that Dr. Davies's washing method left behind residual components that did not dissolve in the time allotted and under the conditions used.

In conclusion, the Court finds that the Acetone Wash Test does not support a finding that there is a stabilizing coat in Impax's product.[29]

2) Dr. Davies's Testimony that Impax's Product Has a Stabilizing Coat Is Not Credible

The Court did not find Dr. Davies's testimony that Impax's product has a stabilizing coat to be credible for four reasons.

First, Dr. Davies performed his Acetone Wash Test shortly before his expert report was due, and only after a litany of other testing methods had failed to show a stabilizing coat in Impax's product. In October and November 2010, Dr. Davies performed optical microscopy, SEM, AFM, and ToF-SIMS. JA 304:7-9; JA 350:17-25; JA 466:25-467:3. Dr. Davies commented that he thought these were the "best suited" tests to analyze the question of infringement. JA 291:20-292:1; JA 350:6-25; JA 455:16-456:14. Dr. Davies did not opt to conduct his acetone washing test until March 2011, only weeks before his infringement expert report was due. JA 453:15-20. The Court finds that it is likely that Dr. Davies only conducted the Acetone Wash Test because the slew of other tests that he performed failed to yield the desired result.

Second, Dr. Davies discovered the stabilizing coat in his SEM image of an unwashed seed five months after he determined that there was no stabilizing coat in the exact same image. Dr. Davies superimposed colors on an SEM image of one of Impax's unwashed seeds to highlight the location of the alleged stabilizing coat. *See* JA 2882-85. Dr. Davies heavily relied on this one color image to show that the stabilizing coat was present in Impax's seed before the wash test. However, five months before adding colors to this image, Dr. Davies had determined that the same image showed only a core and a delayed release layer. *Compare* JA 2872 *with* JA 2882.

Third, Dr. Davies could not identify the composition of the alleged stabilizing coat in Impax's product. Dr. Davies never characterized or isolated the "HP-50 derived material" in the alleged layer, and he could not identify the chemical structure or formula of the alleged material. JA 481:17-483:1, JA 483:13-18. The fact that Dr. Davies could

[29] The Court considered Impax's remaining arguments, but found that they lacked merit. Accordingly, the Court does not rely on Impax's other arguments in concluding that Plaintiffs failed to prove that there is a stabilizing coat in Impax's product.

not identify the mystery material in Impax's alleged stabilizing coat raises questions about Dr. Davies's conclusion that there is a hidden stabilizing coat in Impax's product.

Finally, Dr. Davies could not proffer any explanation as to how the ingredients in Impax's product might interact to form an *in situ* layer. Dr. Davies had no explanation for how the alleged "stabilizing coat" could have formed during Impax's manufacturing process. JA 484:3-7. In fact, Dr. Davies admitted that he had no reason to believe that any of the materials in Impax's product would interact to form an *in situ* layer. JA 348:22-349:3. This is especially puzzling given that Dr. Davies had no trouble providing such an explanation in other cases. *See* JA 479:18- 481:16 (in the "other litigation," Dr. Davies was able to identify the chemical structure of the material created *in situ* and was able to explain how the components in the product reacted to form an *in situ* layer). The fact that an expert as qualified as Dr. Davies could not proffer any explanation as to how these materials might react to create a layer further undercuts his conclusion that there is a stabilizing coat in Impax's product.[30]

2. Plaintiffs Failed to Prove that the Alleged Stabilizing Coat "Keeps Migration of Core Materials to a Minimum Such That the Interaction of Core Materials With Coating Materials Is Reduced or Prevented"

In addition to proving that Impax's ANDA product has "a layer of material(s) between each core element and its modified release coating," Plaintiffs must show that this layer is what "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented" (the "migration limitation").[31] *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7. The Court finds that Plaintiffs failed to prove that Impax's product meets the migration limitation.

Plaintiffs argue that a stabilizing coat would minimize the migration of core materials by virtue of its presence. JA 326:6-13; JA 327:4-12. Plaintiffs assert that, in the '161 Patent, dissolution stability testing is used as a "surrogate" for the migration of core materials. JA 326:5-327:15; JA 503:15-19; JA 506:7-14; JA 548:8-22; JA 1015:9-21; JA 3368. However, the dissolution stability testing in the '161 Patent is only a "surrogate" for minimizing migration because the Patentees performed a direct comparison of a product with a stabilizing coat and an identical product without a stabilizing coat. Thus, if the product with the stabilizing coat had better stability than the product without that stabilizing coat, the Patentees could infer that the stabilizing coat was contributing to stability by keeping migration to a minimum. JA 1236:6-1238:5;

[30] The Court notes that Plaintiffs were not required to identify the composition of the stabilizing coat, nor explain how it was formed. Thus, these issues go only to credibility.

[31] The migration limitation contains a causation requirement. Plaintiffs must prove that Impax's product contains "a layer . . . which keeps the migration of core materials to a minimum . . . so that" the dissolution stability limitations are met. *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

JA1588. In this case, however, Plaintiffs did not conduct a comparative study of Impax's product in which the only variable to change was the presence or absence of a stabilizing coat. As such, Plaintiffs were still required to offer some proof that the alleged stabilizing coat minimized the migration of core materials such that the dissolution stability limitations were met.

There are numerous factors that can affect dissolution stability other than the presence of a "stabilizing coat." JA 1238:12-20. In this case, Impax asserts that it achieved the required stability by switching from a silica gel desiccant to a molecular sieve desiccant. JA 1244:11- JA1245:18; JA5180. The Court need not determine whether desiccants are responsible for creating stability in Impax's product because Plaintiffs presented no evidence at all that a stabilizing coat is responsible for creating that stability. JA1238:6-11. Thus, the Court finds that Plaintiffs failed to prove, by a preponderance of the evidence, that the alleged layer in Impax's product "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

3. Plaintiffs Met Their Burden of Proving that Impax's Product Provides the Required Dissolution Storage Stability

Plaintiffs were required to show that Impax's ANDA product met the dissolution storage stability limitations of the '161 Patent. *See, e.g.*, JA 1583 col. 1, l. 66-col. 2, l. 13 ("upon *in vitro* dissolution testing, the amount of active ingredient released at any time on a post-storage dissolution profile is within 40 percentage points of the amount of active ingredient released at any time on a pre-storage dissolution profile"). The Court finds that Plaintiffs met this burden.

Dr. Davies performed post-storage dissolution testing on Impax's ANDA product, and determined that the product met the dissolution stability requirements of the '161 Patent. JA 296:8-298:9; JA 297:21-298:9; JA 3349-51; JA 3353. Dr. Davies tested the samples in their packaging, which, in Impax's case, included a foil sealed bottle containing a desiccant. JA 295:15-296:3; JA 1583 col. 2, ll. 29-41. Plaintiffs argue that the '161 Patent requires that samples be tested in their packaging. Impax argues that the '161 Patent requires that samples be tested without their packaging. Impax reasons that the "modified release preparation" is the tablet itself, and thus that the tablet itself must provide the required level of stability. JA 1170:18-21. The crux of Impax's argument is that, if its product is only stable because of the way it is packaged, then its product does not infringe the '161 Patent.

In one sense, Impax is correct. If Impax's product is only stable because of the way it is packaged, then Impax's product does not infringe the '161 Patent. However, this is a failure to meet the migration limitation, not the dissolution stability limitations. The dissolution stability limitations require that Impax's product have a certain level of stability. The dissolution stability limitations do not require that this stability be achieved in a particular way. The migration limitation, in contrast, does require that stability be

achieved in a particular way; namely, through the use of a stabilizing coat. As such, Plaintiffs inability to prove that a stabilizing coat is the source of the stability in Impax's product is a failure to meet the migration limitation, not a failure to meet the dissolution stability limitations.

To determine whether Impax's product meets the dissolution stability limitations, Plaintiffs were required to conduct testing in accordance with the procedures set forth in the '161 Patent. The plain language of the '161 Patent requires that Impax's product be tested "in its container and package." *See* JA 1583 col. 2, ll. 29-37 (stating that stability testing is to be conducted according to the FDA guidelines, which "define accelerated conditions as the storage of a pharmaceutical product (namely, in its container and package) . . . ."). Thus, Plaintiffs were correct to test the samples in their packaging and they are correct that Impax's product meets the dissolution storage stability limitations. However, this does not change the Court's overall finding that Impax's ANDA product is non-infringing.

4. Conclusion

For the reasons set forth above, the Court finds that: (1) Plaintiffs failed to prove that Impax's ANDA product has "a layer of material(s) between each core element and its modified release coating"; and that (2) Plaintiffs failed to prove that the alleged stabilizing coat "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented." *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

Accordingly, the Court concludes that Plaintiffs failed to prove, by a preponderance of the evidence, that Impax's ANDA product infringes the '161 Patent.

IV. VALIDITY

A patent duly issued by the United States Patent and Trademark Office ("PTO") is accorded a statutory presumption of validity. 35 U.S.C. § 282. Defendants, as challengers of the '161 Patent, must prove invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. Partnership*, 131 S.Ct. 2238, 2242 (2011); *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004). To be clear and convincing, evidence must "place[] in the factfinder 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" *Procter & Gamble Co. v. Teva Pharma. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Colo. v. N.M.*, 467 U.S. 310, 316 (1984)).

Defendants contend that the '161 Patent is invalid on two grounds: (1) anticipation, and (2) obviousness. The Court will address each argument in turn.

A. ANTICIPATION

Defendants assert that claims 1-3, 5, 10, 16, and 20-22 of the '161 Patent are anticipated by United States Patent No. 5,413,777 ("the '777 Patent"). JA 4297-326.

The Court finds that Defendants have not shown, by clear and convincing evidence, that the '161 Patent claims are anticipated by the '777 Patent.

In order to evidence anticipation of a claimed invention under 35 U.S.C. § 102, a single prior art reference must disclose every element of that invention, arranged as in the claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (to anticipate, a reference must disclose within its four corners all claim limitations "arranged or combined in the same way as recited in the claim."). "There must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (overruled on other grounds by *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009)).

The prior art reference can disclose each element of the invention either expressly or inherently. *Finisar Corp. v. DirectTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). To expressly anticipate, a "reference must clearly and unequivocally disclose the claimed invention or direct those skilled in the art to the invention without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083 (Fed. Cir. 2008) (internal quotation marks omitted). "A prior art reference may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference." *Allergan, Inc. v. Barr Labs., Inc.*, No. 09-333, 2011 WL 4000820, at *11 (D. Del. Sept. 8, 2011). However, a reference that only "probably" or "possibly" meets the claims cannot inherently anticipate as a matter of law. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.") (citations omitted); *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) ("[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation") (emphasis in original).

Defendants argue that all of the asserted claims of the '161 Patent are anticipated, either expressly or inherently, by the '777 Patent. Plaintiffs argue that: (1) the '777 Patent does not inherently disclose the dissolution storage stability limitation; (2) the '777 Patent does not anticipate the stabilizing coat limitation; (3) the '777 Patent does not anticipate the limitations that require that the active ingredient be an acid salt of doxycycline; and that (4) the '777 Patent does anticipate the tablet limitation. Each of the parties' arguments is addressed below.

1. The '777 Patent Does Not Inherently Disclose the Dissolution Storage Stability Limitations

Each claim of the '161 Patent includes a dissolution storage stability limitation, *i.e.*, a limit on the degree to which the pre-storage dissolution profile can differ from the post-storage dissolution profile. *See, e.g.*, JA 1588-89 ("upon *in vitro* dissolution testing,

the amount of active ingredient released at any time on a post-storage dissolution profile is within 40 percentage points of the amount of active ingredient released at any time on a pre-storage dissolution profile"). The '777 Patent does not provide any dissolution storage stability data for any preparations, so it is not clear, from the express terms of the '777 Patent, whether the '777 Patent formulation meets the limitations set forth in the '161 Patent. JA 1404:18-21. Defendants argue that the dissolution storage stability limitations included in the '161 Patent are inherently disclosed by the '777 Patent. The Court disagrees.

a. The Parties' Arguments

Defendants argue that Example 4 of the '777 Patent ("Example 4") expressly discloses the three structural elements that are described in Example 1 of the '161 Patent ("Example 1"): both preparations have (1) an active core consisting of an acid salt of a tetracycline, (2) a stabilizing coat containing HPMC, and (3) a modified release coating containing HPMCP. Although Defendants acknowledge that the other ingredients in the formulations are different, they argue that these three "functional" ingredients are the only ones that impact dissolution storage stability. Defendants reason that preparations with the same three-part structure and the same functional ingredients in each part must, as a matter of logic, meet the same dissolution storage stability limitations. Thus, Defendants conclude, the dissolution storage stability limitations included in the '161 Patent are inherent in the '777 Patent.

In support of this conclusion, Defendants offered two forms of evidence. First, Defendants introduced evidence that the PTO Patent Examiner (the "Examiner") who evaluated the '161 Patent assumed that other prior art references would inherently have the same dissolution stability if they had the same three-part structure and the same functional ingredients.[32] *See, e.g.*, JA 4412-13; JA 4435-36; JA 4440-41. Second, Defendants introduced the testimony of Dr. Kibbe, who testified that "[t]he modified release preparation of example 4 has the same functional elements [as claimed in the '161 patent], and therefore will behave functionally the same way. And so therefore, it must have the same stability profile." JA 1345:11-14; *see also* JA 1344:19-1345:19. Defendants did not conduct any tests, introduce any data, or cite to any literature references in support of their inherency argument. JA 1409:25-1410:13.

Plaintiffs argue that the fact that two preparations include some of the same coating ingredients is no guarantee that they will have exactly the same functional properties. Plaintiffs assert that the composition of a preparation (including its fillers, binders, and excipients) can affect both the dissolution profile of a preparation and its dissolution storage stability. JA 1518:10-19; JA 1519:7-1520:1; JA 3234; JA 3395. In this case, Plaintiffs argue, there are numerous qualitative and quantitative differences between Example 1 and Example 4 that could affect dissolution storage stability. JA

[32] These "other prior art references" considered by the Examiner did not include the '777 Patent, although the '777 Patent was disclosed to the Examiner during prosecution of the '161 Patent. JA 91:8-14; JA 4407.

1516:12-1517:21; JA 3411. For example, Example 4 has a conventional enteric coat comprised of HPMCP, with mineral oil as the plasticizer. *Id.* In contrast, Example 1 has a semi-enteric delayed release coat comprised of HPMCP/HPMC with triethyl citrate and diethyl phthalate as the plasticizers.[33] JA 3159; *see also* JA 3411. Plaintiffs argue that the Examiner was incorrect in assuming that preparations containing some of the same coating ingredients would have the same dissolution storage stability. Plaintiffs note that the Examiner ultimately issued the '161 Patent after considering the '777 Patent.

In support of their arguments, Plaintiffs offer three forms of evidence. First, Plaintiffs showed that the *pre-storage* dissolution profile of Example 4 differs significantly from the *pre-storage* dissolution profile of Example 1. JA 4302; JA 1495:18-1496:6; JA 1517:16-1518:1; JA 3399. Second, Plaintiffs relied on testimony from their expert, Dr. McGinity, and Mylan's expert, Dr. Buckton, explaining generally that dissolution storage stability problems are complicated and can be influenced by numerous factors. JA 993:14-994:19; JA 1424:4-23, JA 1474:2-24, JA 1483:5-1488:11; JA 3230; JA 3233-41; JA 3286-88; JA 3394-97; JA 3892.

Finally, Plaintiffs relied on the *Murthy* reference, a comprehensive review article on dissolution storage stability issues. JA 1481:21-1482:4; JA 3230-43. *Murthy* explains that formulation variables (*i.e.*, the type of ingredients and their amounts) are "critical parameters that have [a] significant impact on the outcome of dissolution stability." JA 1484:3-1485:4; JA 3234; JA 3395. *Murthy* further explains that excipients such as binders, disintegrants, and fillers (*i.e.*, diluents or bulking agents), can all impact dissolution storage stability. JA 1485:5-13; JA 3234-35; JA 1485:14-22; JA 3235. In addition, each coating material or combination of coating materials can have a unique effect on dissolution stability, and processing conditions such as coating parameters, coating conditions, drying conditions, and curing are important in determining whether a product maintains stable dissolution during storage. JA 1483:5-13; JA 3233-34; JA 1485:23-1486:9; JA 3235-36. Finally, *Murthy* explains that packaging and environmental factors (such as temperature, light, and oxygen) can all impact dissolution storage stability. JA 1486:10-24; JA 3238-39. *Murthy* states that, because the "cause[s] [of] dissolution changes are often complex and not well understood," each formulation "has to be evaluated on a case-by-case basis." JA 1487:22-1488:11; JA 3230; JA 3240; JA 3397.

b. Analysis

As an initial matter, the Court notes that Defendants have a difficult burden of proof on inherency. The '161 Patent sets forth a series of specific parameters for dissolution storage stability. Defendants cannot just show that Example 4 probably meets those limitations. *See In re Robertson*, 169 F.3d at 745. They are required to show, by

[33] In addition, Example 4 of the '777 Patent has a precoat of HPMC, while Example 1 of the '161 Patent has as stabilizing coat of HPMC and talc. JA 3159; *see also* JA 3411. Finally, the active ingredient in Example 4 of the '777 Patent is minocycline hydrochloride, while it is doxycycline hyclate in Example 1 of the '161 Patent. JA 3159; JA 1586.

clear and convincing evidence, that Example 4 *necessarily* meets those limitations every time. *See Transclean Corp.*, 290 F.3d at 1373. Defendants' burden of proof is made more difficult by the fact that they are relying on the '777 Patent, prior art that was considered by the Examiner before he issued the '161 Patent. *See Glaxo Group*, 376 F.3d at 1348 (Defendants' "burden is 'especially difficult' when the infringer attempts to rely on prior art that was before the patent examiner during prosecution"). For the reasons set forth below, the Court finds that Defendants did not meet this burden.

Defendants' evidence of inherency was lacking. Whether the formulation in Example 4 necessarily meets the dissolution storage stability limitations in Example 1 is an empirical question: it either meets those limitations or it does not. One would expect the answer to this question to lie in empirical data; in this case, test results showing that Example 4 meets the dissolution storage stability limitations set forth in Example 1. *See In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997) (citing *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) ("[W]hether a claim limitation is inherent in a prior art reference is a factual issue on which evidence may be introduced.") Failing actual test results, one would expect to see references to publications establishing, as a general matter, that preparations with the same coating ingredients have the same dissolution storage stability. Defendants, however, did not conduct a single test, cite to a single data point, or introduce a single reference to any publication.

Instead, Defendants base their theory of inherency on the assumptions of two people: (1) their expert, Dr. Kibbe; and (2) the Examiner. The Court accords little weight to Dr. Kibbe's testimony, as his testimony was merely a recitation of Defendants' theory and was not supported by any extrinsic evidence. *See Motorola, Inc. v. InterDigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997) ("An expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself.").

The Court also finds evidence of the Examiner's assumptions regarding dissolution stability to be unpersuasive. Defendants explained, in meticulous detail, that the Examiner assumed that preparations with the same coating ingredients would have the same dissolution stability. However, the fact that the Examiner took this point for granted in the context of a patent prosecution does not relieve Defendants of proving the underlying fact of inherency by clear and convincing evidence at trial. Moreover, the fact that the Examiner made this assumption about *other* prior art references is hardly clear and convincing evidence with respect to the '777 Patent. In fact, the Examiner did *not* make this assumption about the '777 Patent itself, even though this reference was included in the materials that he considered.[34] As the Examiner is presumed to have

[34] The '777 Patent was not the basis of any of the Examiner's rejections. Defendants infer from this that the Examiner did not really consider the '777 Patent. However, an equally plausible explanation is that the Examiner considered the '777 Patent and concluded that it was not a valid basis for a rejection. Because courts are required to give deference to qualified government agencies, the Court rejects Defendants' inference that the Examiner did not consider the '777

properly done his job, and the Examiner ultimately issued the '161 Patent, the Examiner's opinion weighs against Defendants' inherency argument. *Therasense, Inc.*, 649 F.3d at 1288-90. The Court therefore concludes that Defendants failed to introduce any persuasive evidence of inherency.

Plaintiffs, in contrast, presented at least some evidence that the dissolution storage stability of the two preparations is not identical. First, the *Murthy* reference — the only scientific publication cited by either party — states that dissolution storage stability can be affected by a multitude of factors, including the quantity of the functional ingredients and the quantity and quality of the excipients. Second, Defendants do not dispute (or even address) the fact that the *pre-storage* dissolution profiles of Example 4 and Example 1 are different. The fact that the two preparations, when initially manufactured, have different rates of release does not necessarily mean that they will have different dissolution stability properties (as dissolution profiles are just a starting point from which to calculate dissolution stability). However, it does suggest, as a general matter, that preparations with the same structural elements can have different functional properties, and that small changes in composition can have a large impact on dissolution. Finally, Plaintiffs' theory is consistent with the evidence that was introduced elsewhere in the case demonstrating that dissolution storage stability can be affected by many different factors. *See, e.g.*, JA 993:14-994:19; JA 1424:4-23; JA 1474:2-24; JA 1483:5-1488:11; JA 3230; JA 3233-41; JA 3286-88; JA 3394-97; JA 3892.

For the forgoing reasons, the Court finds that Defendants failed to prove, by clear and convincing, evidence that the '777 Patent inherently disclosed the dissolution storage stability limitations of the '161 Patent. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1346 (Fed. Cir. 2008) (no anticipation where the prior art did not disclose every claim limitation because it "[did] not offer any *in vivo* dissolution data nor state the pharmacokinetic profile of its own formulations.") (internal quotation marks omitted).

2. The '777 Patent Does Not Anticipate the Migration Limitation

Anticipation analysis requires a comparison of prior art against the patent claims, as those claims are construed by the Court. *Allergan*, 2011 WL 4000820, at *10 ("[T]he finder of fact must compare the construed claims against the prior art"); *see Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). In this case, each claim of the '161 Patent includes a stabilizing coat limitation. JA 1588-89 ("wherein a stabilizing coat is provided between each core element and its modified release coating so that"). The Court construed the stabilizing coat limitation to mean "a layer . . . which keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented so that" the dissolution stability limitations are met. *Warner Chilcott Labs. Ireland*, 2011 WL 2971155, at *7.

Patent. *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1288-90 (Fed. Cir. 2011) (en banc) (when prior art that was before the PTO is relied on by the patent challenger, "he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job . . . to issue only valid patents.").

Defendants did not offer any evidence to establish that the precoat in Example 4 "keeps the migration of core materials to a minimum such that the interaction of core materials with coating materials is reduced or prevented." As noted in the infringement analysis, the Court will not assume that an intermediate coat serves this function by virtue of its presence. *See, e.g.*, JA 81:17-82:2; *see also* JA 66:10-15. While Dr. Kibbe testified that Example 4 describes the use of an HPMC precoat between the core and modified release coating, Defendants admit that this precoat is not used to improve dissolution stability. JA 1389:15-19. Rather, the "precoat" is applied to provide a "smooth surface" on which to apply the delayed release coating. JA 1389:23-1390:2; JA 4321 col. 19, ll. 4-6 ("This [precoating] provides a smooth surface on the precursors for subsequent pH sensitive polymer coating"). Based solely on this information, the Court is unable to conclude that the precoat in Example 4 minimizes the migration of core materials.

As such, the Court finds that Defendants failed to prove by clear and convincing evidence that the '777 Patent anticipates the migration limitation of the '161 Patent.

3. The '777 Patent Does Not Anticipate the Limitations that Require that the Active Ingredient Be an Acid Salt of Doxycycline

Plaintiffs also argue that the '777 Patent does not anticipate claims 20-24 of the '161 Patent, which require that the active ingredient be an acid salt of doxycycline. *See* JA 1589; JA 3408. Doxycycline hyclate is mentioned only once in the '777 Patent at column 3, lines 53-68: "In contrast to minocycline hydrochloride and its isomers and analogs, doxycycline hyclate does not contain an alkyl amino group at either the 7- or the 9-position." JA 3152, col. 3, ll. 53-68; JA 1515:8-16; JA 3409. This reference to doxycycline hyclate is made to expressly distinguish it from minocycline hydrochloride, and it is unrelated to the '777 Patent disclosure. JA 1515:8-24; JA 1520:2-14; JA 3408-09; JA 3412. As such, the Court concludes that the '777 Patent does not clearly and unequivocally disclose the claimed invention, without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the '777 Patent. JA 1406:1-3; JA 1515:8-24; JA 1520:2-14; JA 3412.

4. The '777 Patent Anticipates the Tablet Limitation

Plaintiffs argue that the '777 Patent does not anticipate claims 16 and 20-22 of the '161 Patent, which require that the modified release preparation be provided as a plurality of coated core elements compressed to form a tablet. *See* JA 1589; JA 3408. The Court disagrees. The '777 Patent expressly contemplates compressing multi-coated beads into a tablet. *See* JA 4319 ("The multi-coated compositions . . . [can also] be formed . . . into tablet oral dosage unit forms by conventional means known to one of ordinary skill in the pharmaceutical arts, e.g. compressing or pressing."); JA 4321. Thus, the '777 Patent anticipates the tablet limitation.

However, the '777 Patent does not specify the type of excipients to use in creating a tablet. As such, there is no guarantee that a person of ordinary skill in the art could create a tablet that met the dissolution storage stability limitations of the '161 Patent

without undue experimentation. *See* JA 1426:14-20; JA 1484:9-1485:22; JA 3234-35. Accordingly, this provide further support for the proposition that the '777 Patent does not inherently disclose the dissolution storage stability limitations.

5. Conclusion

For the forgoing reasons, the Court finds that Defendants have not shown, by clear and convincing evidence, that claims 1-3, 5, 10, 16, and 20-22 of the '161 Patent are anticipated by the '777 Patent.

B. OBVIOUSNESS

The Court finds that Defendants have not shown by clear and convincing evidence that the asserted claims of the '161 Patent are obvious under 35 U.S.C. § 103(a).

Obviousness under 35 U.S.C. § 103(a) is a legal question based on underlying factual determinations. *Eisai Co. Ltd. v. Dr. Reddy's Labs.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008) (citing *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1478-79 (Fed. Cir. 1997)). An obviousness analysis measures the difference between the claimed invention and the prior art to determine whether "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. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006) (citing *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006)). The factual underpinnings, often referred to as the *Graham* factors, include (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) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

An obviousness analysis also involves an evaluation of the "teaching, suggestion, or motivation" test ("TSM test"), which requires patent challengers to show that "some motivation or suggestion to combine the prior art teachings" can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc. ("KSR")*, 550 U.S. 398, 407 (2007) (internal quotations omitted). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 418. Rather, "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." *Id.* The Supreme Court emphasized that this is a flexible test that should be applied using common sense. *Id.* at 419 ("The obviousness analysis cannot be confined by a formalistic conception of the words, teachings, suggestion, and motivation").

A patent may be proved obvious by showing that the combination of elements was "obvious to try." *KSR*, 550 U.S. at 421. Where there are a "finite number of identified, predictable solutions" to a particular problem, courts should assume that a person of

ordinary skill in the art will "pursue the known options." *Id.* If a person of ordinary skill can implement a predictable variation of the known options, Section 103 likely bars patentability. *Id.* at 417. However, when prior art gives "no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," an invention is not obvious to try. *Bayer Schering Pharm. AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (stating the number of options must be "small or easily traversed").

Finally, "[a] factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 550 U.S. at 421. 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 "virtually every claimed invention is a combination of old elements").

The Court will address: (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 factors.

1. Level of Ordinary Skill in the Art

Obviousness is judged from the perspective of a hypothetical person of ordinary skill in the art, who is "a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421. 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 be an individual with a Ph.D. in pharmaceutical sciences or chemistry with at least four years of practical experience in solid oral dosage form development. *See Astrazeneca AB v. Mylan Labs., Inc. (In re Omeprazole Patent Litig.)*, 490 F. Supp. 2d 381, 517 (S.D.N.Y. 2007).

2. Scope and Content of the Prior Art

Under *Graham*, the Court must define the scope and content of the prior art as of April 12, 2002, the filing date of the '161 Patent. JA 1579. Prior art is limited to "analogous" references "from the same field or endeavor" or, if not, from the same field or endeavor, art that is "reasonably pertinent to the particular problem with which the inventor is involved." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

In this case, the prior art includes: (1) the monograph for Prior Art Doryx Capsules in the 43rd edition of the Physician's Desk Reference ("43rd PDR"); (2) Japanese Patent Application 562-226926 ("JP '926"); (3) U.S. Patent No. 5,413,777 ("the '777 Patent"); (4) International Patent Application WO 99/03453 ("WO '453"); (5) European Patent Application 0475536 ("EP '536"); (6) U.S. Patent No. 5,283,065 ("the '065 Patent"); and (7) the 1993 *Murthy* article entitled "Current Perspectives on the Dissolution Stability of

Solid Oral Dosage Forms" ("*Murthy*"). Defendants introduced the first six references; Plaintiffs introduced the *Murthy* reference. There were no objections to any of the prior art references.

3. Differences Between the Claimed Subject Matter and Prior Art

The parties agree that the problem facing the hypothetical person of ordinary skill in the art is the "problem of improving dissolution stability" in Prior Art Doryx Capsules. Mylan's Post-Trial Brief ("Mylan's Br.") at 35; *see also* Impax's Post-Trial Brief ("Impax's Br.") at 37; Pls' Br. at 45. The '161 Patent differs from Prior Art Doryx in three important respects: the '161 Patent contains dissolution storage stability limitations, the '161 Patent contains a stabilizing coat limitation, and the '161 Patent contains limitations relating to the percentage of coated cores that should be included in the tablet.

The Court finds that: (a) the dissolution storage stability limitations are not rendered obvious by the prior art; (b) the stabilizing coat limitation is not rendered obvious by the prior art; and (c) the limitations relating to the percentage of coated cores in the tablet are not rendered obvious by prior art. Each of these findings is explained in greater detail below.

a. The Dissolution Storage Stability Limitations Are Not Rendered Obvious by the Prior Art

Defendants argue that the dissolution storage stability limitations of the '161 Patent (claims 1-3, 5, 10, 16, and 20-22) are rendered obvious by Prior Art Doryx in combination with any of the '777 Patent, JP '926, WO '453, and EP '536 (the "four references"). Because none of the four references relate, in any way, to long-term dissolution stability, the Court finds that these claims are not rendered obvious by the prior art.

Defendants admit that the prior art does not disclose the dissolution storage stability limitations of the '161 Patent. *See* Impax's Br. at 38; Mylan's Br. at 37 (The "prior art does not expressly disclose the dissolution stability limitations recited in the asserted claims of the '161 patent."). Indeed, none of the four references are directed to dissolution storage stability and none of the references contain long-term dissolution storage stability data for any of their preparations.[35]

Instead, Defendants simply assert that the dissolution storage stability limitations of the '161 Patent "would be inherent in the prior art because the prior art uses the same ingredients in about the same amounts." Mylan's Br. at 37. This conclusion is flawed for several reasons. First, Defendants did not introduce a shred of evidence that any of the four references have the same dissolution stability properties as the '161 Patent.

[35] Although JP '926 provides data on the dissolution properties of the preparation one month after manufacturing, it does not provide any long-term dissolution storage stability data. JA 1510:24-1511:9; JA 3577.

Second, contrary to Defendants' assertion, the prior art does not use "the same ingredients in about the same amounts." None of Defendants' four prior art references share the same core ingredient as the '161 Patent: doxycycline hyclate.[36] And the coating materials in the four cited references have, at most, one or two ingredients in common with the '161 Patent. *See, e.g.*, JA 1586 (the '161 Patent lists hydroxypropyl cellulose as one of many possible coating ingredients) and JA 4389 (EP '536 lists low substituted hydroxypropyl cellulose as one of five coating ingredients). To conclude that compositions comprised of dozens of ingredients have the same dissolution stability properties because they have one or two ingredients in common is much too large a leap to take without any supporting evidence.

Finally, even if it were true that the prior art used the "the same ingredients in about the same amounts," that is still no guarantee that the four references would have the same dissolution stability properties as the '161 Patent. As the *Murthy* reference explains in detail, every preparation must be evaluated on a case-by-case basis because even a small change in the amount of one ingredient can impact a preparation's dissolution stability profile. *See* JA 3234.

Because the prior art offers absolutely no guidance on dissolution storage stability to a person of ordinary skill in the art, the dissolution storage stability limitations of the '161 Patent are not rendered obvious by the prior art.

b. The Stabilizing Coat Limitation Is Not Rendered Obvious by the Prior Art

Defendants argue that the stabilizing coat limitation of the '161 Patent (claims 1 and 21) is rendered obvious by the combination of Prior Art Doryx (the 43rd PDR) and four prior art references that discuss the use of intermediate coats: '777 Patent, JP '926, WO '453, and EP '536. The Court disagrees.

While Defendants are correct that Prior Art Doryx and the general concept of intermediate coats were independently known in the prior art, Defendants failed to "identify a reason that would have prompted a person of ordinary skill in the [art] to combine the[se] elements." *KSR*, 550 U.S. at 418. The record reflects that there were a multitude of possible solutions to dissolution stability problems known in the art. The use of intermediate coats was not one of these solutions. In fact, Defendants do not point to a single prior art reference that uses an intermediate coat to improve long-term dissolution stability. Moreover, combining Prior Art Doryx with any of these four references would have created new problems. The Court therefore finds that the stabilizing coat limitation is not rendered obvious by any of the four individual references or by the prior art as a whole.

[36] The '777 Patent mentions doxycycline, but only to distinguish it from minocycline. JA 1515:8-16; 3152 col. 3, ll. 53-68; JA 3409. EP '536 mentions "doxycycline" in a long list of potential active ingredients, but does not mention doxycycline hyclate. *See* JA 1504:12-23.

i. A Person of Ordinary Skill in the Art Attempting to Solve the Dissolution Stability Problem Faced Many Possible Choices

The parties agree that the problem facing the hypothetical person of ordinary skill in the art was the "problem of improving dissolution stability" in the Prior Art Doryx Capsule. Mylan's Br. at 35; *see also* Impax's Br. at 37; Pls' Br. at 45. Finding a solution to this problem would have required clearing several difficult hurdles. A skilled artisan attempting to solve a dissolution stability problem would not only have to develop a solution to the dissolution stability problem itself, but would also have to find a solution that did not destroy any of the benefits conferred by the Prior Art Doryx Capsule (*i.e.*, the reduction of gastric upset and the improvement in bioavailability). Further, because the Patentees never identified the source of the dissolution stability problem, a person of ordinary skill in the art would be required to solve the problem without knowing what caused it. *See* JA 1418:17-21; JA 5595. The Court finds that Defendants failed to show that a person of ordinary skill in the art would have overcome these considerable hurdles.

The *Murthy* article — the only cited reference that discusses dissolution storage stability — makes clear that there are a plethora of factors that impact dissolution storage stability. *Murthy* explains that formulation variables (*i.e.*, the type of ingredients and their amounts) are "critical parameters that have [a] significant impact on the outcome of dissolution stability." JA 1484:3-1485:4; JA 3234; JA 3395. *Murthy* further explains that excipients such as binders, disintegrants, and fillers (*i.e.*, diluents or bulking agents), can all impact dissolution storage stability. JA 1485:5-13; JA 3234-35; JA 1485:14-22; JA 3235. In addition, each coating material or combination of coating materials can have a unique effect on dissolution stability, and processing conditions such as coating parameters, coating conditions, drying conditions, and curing are important in determining whether a product maintains a stable dissolution profile during storage. JA 1483:5-13; JA 3233-34; JA 1485:23-1486:9; JA 3235-36. Finally, *Murthy* explains that packaging and environmental factors (such as temperature, light, and oxygen) can all impact dissolution storage stability. JA 1486:10-24; JA 3238-39. *Murthy* states that, because the "cause[s] [of] dissolution changes are often complex and not well understood," each formulation "has to be evaluated on a case-by-case basis." JA 1487:22-1488:11; JA 3230; JA 3240; JA 3397. Notably, *Murthy* does not mention the use of an intermediate layer to address dissolution storage stability problems. JA 1488:22-1489:2.

The Patentees' attempts to identify the cause of the dissolution storage stability problem further illustrates the difficulty that a person of ordinary skill in the art would have in developing a solution. In 1990, Faulding scientists observed that the pellets in the Doryx Capsule had an increased rate of drug release in acid after storage. JA 3290; JA 1471:23-1472:20; JA 3386. Faulding was unable to determine the precise cause of the dissolution storage stability problem. JA 1416:3-19; JA 1472:25-1473:12; JA 3291; JA 3387. In October 1993, Faulding's scientists compiled a list of possible reasons for the instability of the dissolution profile of the Doryx Capsule. JA 3287-88; JA 1473:20-

1474:1; JA 1474:5-12; JA 1474:25-1475:3. Their list contained 74 possible causes of instability, and included potential problems relating to formulation variables, excipients, coating materials, and processing conditions. JA 3286-88; JA 1474:13-24. For each of the 74 possible causes included on the list, one can imagine that there would be one or more possible solutions.

Given the complexity of dissolution storage stability problems, and the lack of information about the cause of the problem in the Doryx Capsule, the Court finds that a person of ordinary skill in the art in April 2002 would be faced with a litany of possible paths and dead-ends, none of which would have any greater likelihood of success than the others. In other words, this is not a case in which there were a "finite number of identified, predictable solutions" to the problem. *KSR*, 550 U.S. at 421. Rather, this is a case where the prior art gives no indication as to "which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d at 903.

It would be extremely difficult for Defendants to argue that a person of ordinary skill in the art would focus on just one of the many possible solutions noted above. But Defendants do not make this argument. Defendants argue that a skilled artisan would ignore every single one of these potential solutions, known in the prior art, and would instead focus on references that have nothing to do with improving dissolution stability.

For the reasons set forth below, the Court finds that a person of ordinary skill in the art would not be motivated to combine Prior Art Doryx with any of the four references cited by Defendants. None of the references give any indication that their preparations could be used to improve dissolution stability. Furthermore, combining these references with Prior Art Doryx would have resulted in other problems, such that a person of ordinary skill in the art would not have considered using these formulations.

ii. The '777 Patent Does Not Render the Stabilizing Coat Limitation Obvious

The '777 Patent is entitled "Pulsatile Once-A-Day Delivery Systems for Minocycline." JA 3136-65. The '777 Patent concerns pulsatile pharmaceutical delivery systems that maintain certain therapeutic blood levels of minocycline for up to 24 hours. JA 3151 col. 1, ll. 29-34; JA 1492:8-22; JA 1430:24-1431:9. Blood levels of minocycline are maintained through the use of a formulation that delivers an immediate pulse of minocycline using quick release granules, followed by a second pulse of minocycline using delayed release granules. JA 1493:9-15.

The '777 Patent does not render the stabilizing coat limitation obvious for several reasons. First, the '777 Patent is not directed to dissolution storage stability and does not include any dissolution storage stability data. JA 1389:15-19; JA 1494:2-20; JA 1495:9-13. Although the '777 Patent mentions an optional intermediate coat in one of its 24 examples, this intermediate coat is applied to provide a "smooth surface" for the application of the outer coating, not to impart dissolution storage stability. JA 1389:23-1390:2; JA 4321 col. 19, ll. 4. Second, the '777 Patent does not pertain to formulations

containing doxycycline hyclate. JA 1515:8-13; JA 1515:18-24. Doxycycline hyclate is mentioned only once in the '777 Patent, and that is to distinguish it from minocycline hydrochloride. JA 1515:8-21.

Finally, a person of ordinary skill in the art would not have considered a combination involving the '777 Patent because that combination would have resulted in bioavailability problems. One of the goals of the '161 Patent was to maximize the absorption of doxycycline hyclate by ensuring that the active ingredient was released in the upper small intestine. The conventional enteric coating in the '777 Patent would prevent the drug from being released for a much longer period of time (at 2 hours, only slightly more than 10% of the drug is released). JA 1431:24-1432:4; JA 1495:14-1496:10; JA 3141; JA 3399. Because the goal of the '777 Patent and the goal of the '161 Patent diverge with respect to such a crucial aspect of drug delivery, a person of ordinary skill in the art would not have considered the '777 Patent pertinent to a doxycycline hyclate formulation. *See In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 437-38.

Accordingly, the '777 Patent, alone or in combination with any other prior art references, viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, does not render obvious the stabilizing coat limitation of the '161 Patent.

iii. JP '926 Does Not Render the Stabilizing Coat Limitation Obvious

JP '926 is a Japanese patent application entitled "Long-Acting Compound Granular Agent." JA 3558-88; JA 4461-91. Like the '777 Patent, JP '926 concerns a pulsatile drug delivery system in which a first pulse of drug is delivered using fast acting granules, and a second pulse is delivered using slow acting granules. JA 1506:9-17; JA 1445:24-1446:7. JP '926 is directed at resolving a manufacturing problem. JA 1507:5-7. The inventors of JP '926 believed that, during the application of the enteric coating onto the core, the solvent used to apply the enteric coating penetrated into the core and dissolved some of the active ingredient. JA 1506:18-1507:4; JA 1451:14-20; JA 3566. As a result, when dissolution testing was conducted immediately after manufacture (as opposed to after storage), drug was released faster than expected. JA 3565-66; JA 1506:18-1507:4. JP '926 describes the use of an intermediate layer to prevent the solvent from permeating into the core during application of the enteric coating. JA 3563; JA 3536.

JP '926 does not render the stabilizing coat limitation obvious for several reasons. First, JP '926 does not concern dissolution storage stability. JA 1507:5-7; JA 1512:7-12. The limited stability testing provided in JP '926 was conducted only one month after manufacturing. JA 3577; JA 1510:19-1511:4; JA 1511:19-21. This differs markedly from the six months of accelerated storage testing that a person of ordinary skill in the art would be required to conduct to produce long term stability data. *See* JA 1511:22-1512:1. Second, none of the active ingredients claimed in JP '926 are tetracyclines. JA 1445:12-16. Third, the fast acting granules in JP '926, which release up to 80% of the

drug immediately in the stomach, would cause gastric upset if combined with a doxycycline hyclate core. JA 1446:8-23. Finally, the slow acting granules in JP '926, which take much longer to release the drug, would cause bioavailability problems if combined with a doxycycline hyclate core. JA 1507:8-24; JA 1446:24-1447:16. Thus, a person of ordinary skill in the art would not have considered JP '926 pertinent to a doxycycline hyclate formulation.

Accordingly, JP '926, alone or in combination with any other prior art references, viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, does not render obvious the stabilizing coat limitation of the '161 Patent.

iv. WO '453 Does Not Render the Stabilizing Coat Limitation Obvious

WO '453 is an international patent application entitled "Novel Pharmaceutical Formulation with Controlled Release of Active Substances." JA 3169-218.

WO '453 does not render the stabilizing coat limitation of the '161 Patent obvious for several reasons. First, WO '453 is directed to ***chemical*** stability, not dissolution storage stability. JA 1501:24-1505:3. Although WO '453 mentions the use of optional intermediate coatings, WO '453 states that these intermediate coatings may be used to "cover the irregularities on the core surface and to reduce the necessary amount of gastro-resistant coating." JA 3176; JA 3175; JA 1499:8-22; JA 3401. WO '453 does not concern dissolution stability and does not present any dissolution storage stability data. JA 1440:21-24; JA 1502:4-6. Second, WO '453 is concerned with resolving chemical stability issues for acid-sensitive drugs such as omeprazole and lansoprazole. JA 1441:6-8. Doxycycline hyclate is not an acid sensitive drug. JA 1438:15-17. Finally, the conventional enteric coatings described in WO '453 are designed to release less than 10% of the drug after 2 hours in acidic media, which would cause bioavailability problems if combined with a doxycycline hyclate core. JA 3201; JA 1441:19-25; JA 1564:3-5; JA 1564:19-21; JA 3402. Thus, a person of ordinary skill in the art would not have considered WO '453 pertinent to a doxycycline hyclate formulation.

Accordingly, WO '453, alone or in combination with any other prior art references, viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, does not render obvious the stabilizing coat limitation of the '161 Patent.

v. EP '536 Does Not Render the Stabilizing Coat Limitation Obvious

EP '536 is a European patent application entitled "Spherical granules having core and their production." JA 3219-29. Defendants rely only on Examples 2 and 11 of EP '536.

EP '536 does not render the stabilizing coat limitation of the '161 Patent obvious for several reasons. First, like WO '453, EP '536 concerns the chemical stability of acid sensitive drugs. JA 1438:9-11. EP '536 is not directed to dissolution storage stability

and does not include any dissolution storage stability data. JA 1438:9-11; JA 1438:23-25; JA 1505:3-5. Second, the modified release coatings in Examples 2 and 11 of EP '536 are conventional enteric coatings that would cause bioavailability problems if combined with a doxycycline hyclate core. JA 1565:10-14; JA 1505:24-1506:8; JA 1503:21-1504:11; JA 3403. Finally, the cores of Examples 2 and 11 contain magnesium carbonate, and even Dr. Kibbe admits that magnesium should not be co-administered with doxycycline hyclate. JA 4335; JA 1429:3-19. Thus, a person of ordinary skill in the art would not have considered EP '536 pertinent to a doxycycline hyclate formulation.

Accordingly, EP '536, alone or in combination with any other prior art references, viewed in light of the creativity and background knowledge of a person of ordinary skill in the art, does not render obvious the stabilizing coat limitation of the '161 Patent.

vi. Conclusion

It is eminently clear that Defendants' obviousness attack is entirely hindsight driven. 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 '161 Patent, picked and chose from the already-narrowed list of references that Defendants' lawyers provided, and worked backwards using improper hindsight. *See* JA 1403:14-1404:11. Not only is this legally incorrect, but upon examination, the prior art in no way suggests that a person of ordinary skill in the art would have had a reasonable expectation of success if they had simply added an intermediate coat to Prior Art Doryx. Because Defendants completely failed to "identify a reason that would have prompted a person of ordinary skill in the [art] to combine the[se] elements," *KSR*, 550 U.S. at 418, the Court finds that the stabilizing coat limitation is not rendered obvious by any of the individual references or by the prior art as a whole. *See In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 447-48.

c. The Limitations Relating to the Percentage of Coated Cores in the Tablet Are Not Rendered Obvious by the Prior Art

Defendants argue that the limitations in the '161 Patent concerning the percentage of coated core elements (by weight) in the claimed tablet (claims 17-19) are rendered obvious by the '777 Patent alone or in view of Example 12 of the '065 Patent. The Court finds that these claims are not rendered obvious by the prior art.

Both the '777 Patent and the '065 Patent were disclosed to the PTO by the inventors and were considered by the Examiner before he allowed the claims of the '161 Patent. JA 1579; JA 4406. The active spherical granules used in Example 12 of the '065 Patent are "extruded spheronized beads" that do not have any intermediate layer or delayed release coating. JA 4291, col. 17, ll. 18-23; JA 1430:9-23. Thus, this example is not relevant to claims 17-19 of the '161 Patent, which specify a percentage of coated core elements to be used in tablets. Moreover, Example 13 of the '065 Patent discloses a tablet containing 50 parts of active spherical granules, which teaches away from the weight limitations of claims 17-19 of the '161 Patent. *See* JA 4291-92. Similarly,

Example 20 of the '777 Patent teaches tablets that contain more than 50% coated beads. JA 4322 col. 21, ll. 56-62; JA 1406:24-1407:14. Thus, the '777 Patent also teaches away from the weight limitations of claims 17-19 of the '161 Patent.

4. Secondary Factors (Objective Indicia of Non-Obviousness)

Plaintiffs did not present any evidence of secondary factors or objective indicia of non-obviousness. However, 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. *See Winner Int'l Royalty Corp v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000).

5. Conclusion

For the forgoing reasons, the Court finds that Defendants failed to prove by clear and convincing evidence that the asserted claims of the '161 Patent are obvious under 35 U.S.C. § 103(a).

C. DEFENDANTS' REMAINING INVALIDITY ARGUMENTS

As part of their invalidity case, Defendants introduced the testimony of Dr. Tina deVries, the executive at Warner Chilcott responsible for overseeing the Doryx Tablet project.[37] Dr. deVries testified that the Prior Art Doryx Capsule and the Doryx Tablet both had a higher rate of absorption and a lower incidence of nausea than immediate release doxycycline tablets. Dr. deVries also testified that both products had a 24-month shelf life. Finally, Dr. deVries testified that Warner Chilcott developed the Doryx Tablet as part of an "anti-generic" strategy aimed at preserving the Doryx franchise. *See* JA 1305:17-21.

The Court accepts all of this evidence as true, but cannot discern any reason that it is relevant to the question of patent validity. To the extent that Defendants are arguing that the '161 Patent covered only new aspects of the Doryx Tablet (*i.e.*, the improvement to dissolution stability), that is self-evident. To the extent that Defendants are arguing that the Capsule and Tablet have identical properties, that is plainly incorrect. The Tablet improved the dissolution stability of the Capsule (among other things). Finally, the fact that a company developed a product as part of a business strategy is thoroughly unsurprising. And while it is comforting to know that Warner Chilcott did not run afoul of any antitrust laws by implementing a "pro-generic" strategy, that really has no relevance to any of the issues raised in this case.

[37] Dr. deVries held the title of Senior Director of Research and Development from 1996 to 2000, and the title of Vice President of Pharmaceutics from 2000 to 2005. JA 1279:13-24.

V. DEFENDANTS' EXCEPTIONAL CASE CLAIMS

Mylan and Impax assert that this is an exceptional case that entitles them to an award of attorneys' fees and expert fees under 35 U.S.C. § 285. The Court disagrees.

In patent actions, "[t]he court in exceptional cases may award reasonable attorney fees to the prevailing party." 35 U.S.C. § 285. Absent misconduct during the litigation, sanctions may be imposed against the patentee only if (1) the litigation is brought in subjective bad faith, and (2) the litigation is objectively baseless. *Professional Real Estate Investors v. Columbia Pictures Industries*, 508 U.S. 49, 60-61 (1993). There is a presumption that the assertion of infringement of a duly granted patent is made in good faith. *Springs Willow Fashions, LP v. Novo Indus., LP*, 323 F.3d 989, 999 (Fed. Cir. 2003). The underlying improper conduct and the characterization of the case as exceptional must be established by clear and convincing evidence. *Beckman Instruments, Inc., v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989).

The Court finds that Defendants' exceptional case claims were not established by clear and convincing evidence, as Defendants presented no evidence whatsoever of bad faith. *See Brooks Furniture Mfg. v. Dutailier Int'l, Inc.*, 393 F.3d 1378, 1381-82 (Fed. Cir. 2005).

VI. CONCLUSION

For the forgoing reasons, the Court concludes as follows. First, the Court concludes that Plaintiffs failed to prove, by a preponderance of the evidence, that Mylan's ANDA product infringes the '161 Patent. Second, the Court concludes that Plaintiffs failed to prove, by a preponderance of the evidence, that Impax's ANDA product infringes the '161 Patent. Third, the Court concludes that Defendants failed to prove, by clear and convincing evidence, that the '161 Patent is invalid as anticipated by the '777 Patent. Fourth, the Court concludes that Defendants failed to prove, by clear and convincing evidence, that the '161 Patent is obvious in light of prior art. Finally, the Court concludes that Defendants failed to establish their exceptional case claims by clear and convincing evidence. An appropriate Order accompanies this Opinion.

/s/ William J. Martini
WILLIAM J. MARTINI, U.S.D.J.

Date: April 30, 2012