UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
TAMPA DIVISION

SHIRE DEVELOPMENT, LLC, SHIRE PHARMACEUTICAL DEVELOPMENT, INC., COSMO TECHNOLOGIES LIMITED and NOGRA PHARMA LIMITED,

Plaintiffs,

v. Case No: 8:12-cv-1190-T-36AEP

MYLAN PHARMACEUTICALS, INC. and MYLAN, INC.,

Defendants.
_____/

OPINION AND ORDER

I. *INTRODUCTION*

This cause came before the Court at a four-day bench trial held from September 26 to September 29, 2016. Following the trial, the parties submitted proposed Findings of Fact and Conclusions of Law (Docs. 499, 500). Upon due consideration of the testimony, exhibits received into evidence, argument of counsel, and the applicable law, and being fully advised in the premises, the following, issued pursuant to Federal Rule of Civil Procedure 52(a), constitutes the Court's findings of fact and conclusions of law on the issue of patent infringement.[1]

Shire filed this patent infringement case pursuant to the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355. Plaintiffs[2] (collectively "Plaintiff" or

[1] Throughout these Findings of Fact and Conclusions of Law, the Court may adopt, without attribution, language proposed by one side of the dispute. In all such instances, the findings or conclusions in question have become the Court's, based on the Court's review of the evidence and the law. To the extent that any of the Court's findings of fact may be considered conclusions of law, or vice versa they should be considered as such.

[2] Plaintiffs are Shire Development LLC, Shire Pharmaceutical Development, Inc., Cosmo Technologies Limited, and Nogra Pharma Limited.

"Shire") sued Defendants [3](collectively "Defendant" or "Mylan")[4] over Mylan's Abbreviated New Drug Application ("ANDA") seeking the Food and Drug Administration's ("FDA") approval to manufacture, use, and sell a generic equivalent of a Shire pharmaceutical product named Lialda® ("Lialda"). Shire seeks a declaratory judgment of infringement of U.S. Patent No. 6,773,720 (the "'720 Patent"), entitled "Mesalazine controlled release oral pharmaceutical compositions." Mylan denies that its ANDA Product infringes the '720 Patent.

II. *FINDINGS OF FACT*

A. *The Parties*

1. Shire Development LLC is a limited liability company organized and existing under the laws of the State of Delaware, having its principal place of business at 725 Chesterbrook Boulevard, Wayne, Pennsylvania 19087. *See* Statement of Admitted Facts, Doc. S-502, ¶ 1. Shire Pharmaceutical Development Inc. is a corporation organized and existing under the laws of the State of Maryland, having its principal place of business at 1801 Research Boulevard, Rockville, Maryland 20850. *Id*. at ¶ 2. Cosmo Technologies Limited ("Cosmo") is a company organized and existing under the laws of Ireland, having its principal place of business at 2, Duncairn Terrace, Bray Co., Wicklow, Ireland. *Id*. at ¶ 3. Giuliani International Limited (now known as Nogra Pharma Limited) is a company organized and existing under the laws of Ireland, having its principal place of business at 33 Sir John Rogerson's Quay, Dublin 2, Ireland. *Id*. at ¶ 4.

2. Cosmo Technologies Limited is the owner of the '720 patent on assignment from Cosmo S.P.A. Nogra Pharma Limited is an exclusive licensee of the '720 patent and has granted Shire Pharmaceutical Development Inc. an exclusive sublicense. *Id*. at ¶ 16.

[3] Defendants are Mylan Pharmaceuticals, Inc. and Mylan, Inc.
[4] For convenience, the Court will refer to plaintiffs and defendants in the singular, except where otherwise noted.

3. Mylan Pharmaceuticals Inc. is a corporation organized and existing under the laws of the state of West Virginia having a place of business at 491 Chestnut Ridge Road, Morgantown, West Virginia 26505. *Id*. at ¶ 5. Mylan Inc. is a corporation organized and existing under the laws of the state of Pennsylvania having a place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania 15317. *Id*. at ¶ 6. Mylan Pharmaceuticals is a wholly-owned subsidiary of Mylan Inc. *Id*. at ¶ 7.

B. ***Background***

4. Shire is the holder of New Drug Application ("NDA") No. 22-000, which relates to delayed release mesalamine tablets, 1.2 g. *Id*. at ¶ 8. On January 16, 2007, the United States Food and Drug Administration ("FDA") approved the marketing of the delayed release mesalamine tablets, 1.2 g, described in NDA No. 22-000. *Id*. at ¶ 9. The delayed release mesalamine tablets, 1.2 g, described in NDA No. 22-000 are sold in the United States by Shire using the trademark Lialda®. *Id*. at ¶ 10. Lialda is a delayed-release mesalamine tablet used to treat ulcerative colitis.

5. U.S. Patent No. 6,773,720 ("the '720 patent"), entitled "Mesalazine controlled release oral pharmaceutical compositions," was issued by the United States Patent and Trademark Office ("USPTO") on August 10, 2004. *Id*. at ¶ 11. U.S. Patent Application No. 10/009,491 ("the '491 application"), from which the '720 patent issued, was filed in the USPTO on June 8, 2000. *Id.* at ¶ 12. In the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" ("Orange Book"), the '720 patent is listed in the entry for Lialda®. The '720 patent expires on June 8, 2020. *Id*. at ¶ 13.

6. Mylan Pharmaceuticals submitted Abbreviated New Drug Application ("ANDA") No. 20-3574 to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA")

(codified at 21 U.S.C. § 355(j)), seeking approval to engage in the commercial manufacture, use, or sale of mesalamine delayed-release tablets, 1.2 g ("Mylan's ANDA Product" or "Mylan's Product") prior to expiration of the '720 patent. *Id.* at ¶ 17. The ANDA contains data for the purpose of establishing bioequivalence to Lialda®. It identifies Lialda® as the Reference Listed Drug and provides data for an exhibit batch of Mylan's ANDA Product, labeled 1042070 (the "exhibit batch"). *Id.* at ¶ 20. The exhibit batch of Mylan's ANDA Product is representative of the product that Mylan will sell, if approved by the FDA. *See* Tr. Day 2 am (Testimony of Dr. Deshmukh) and Tr. Day 1 pm (Testimony of Mr. Pananchukunnath).

7. The November 24, 2015 Resubmission and Amendment to ANDA No. 20-3574 provided data for three validation batches of Mylan's ANDA Product, labeled 3040706, 3040780, and 3040826 (collectively, "validation batch"). *See* Doc. S-502 at ¶ 21. Mylan did not change the formulation composition, drug product manufacturing process, or controls between its exhibit batch and validation batch. *See* Tr. Day 2 am (Testimony of Dr. Deshmukh). Mylan's November 24, 2015 Resubmission and Amendment to ANDA No. 20-3574 reports to FDA that "[t]here are no changes to the formulation composition, Drug Product manufacturing process or controls." *See* Doc. S-502 at ¶ 22. Thus, data and representations in Mylan's original ANDA submission, such as its Product Development Report and dissolution data, also apply to Mylan's validation batch. *See* Tr. Day 2 am (Testimony of Dr. Deshmukh).

8. Mylan Pharmaceuticals submitted a certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) in ANDA No. 20-3574 that the '720 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Mylan's ANDA Product. *See* Doc. S-502 at ¶ 24. By letters dated April 12, 2012, Mylan Pharmaceuticals provided notification of paragraph IV certifications regarding the '720 patent pursuant to 21 U.S.C. §

355(j)(2)(B)(i)-(iv) of the FDCA and 21 C.F.R. § 314.95 in connection with ANDA No. 20-3574. *Id.* at ¶ 25.

9. On May 25, 2012, Shire filed this suit for declaratory relief against Mylan Pharmaceuticals and Mylan Inc. alleging infringement of the '720 patent. *Id.* at ¶ 26. Shire asserts that Mylan's commercial manufacture, use, sale or offer for sale in the United States and importation into the United States of Mylan's ANDA Product would infringe claims 1 and 3 of the '720 patent. *Id.* at ¶ 29.

10. On August 27, 2012, Mylan filed counterclaims, including *inter alia*, for a declaratory judgment that the '720 patent is not infringed. *Id.* at ¶ 27. It denies that its ANDA Product, if manufactured, used, sold, or offered for sale in the United States or imported into the United States would infringe claims 1 and 3 of the '720 patent. *Id.* at ¶ 30. Mylan dismissed its invalidity claims and defenses prior to trial. *Id*. at ¶ 31.

C. *The '720 Patent*

11. The '720 Patent at issue in this case contains 4 claims. Shire alleges infringement of Claims 1 and 3 of the '720 Patent. Claim 1 is the '720 Patent's only independent claim. It provides:

Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid, comprising:

> a. an inner lipophilic matrix consisting of substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, dior triglycerids, waxes, ceramides, and cholesterol derivatives with melting points below 90° C[ ], and wherein the active ingredient is dispersed both in said lipophilic matrix and in the hydrophilic matrix;
>
> b. an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins,

> pectins, starches and derivatives, alginic acid, and natural or synthetic gums;
>
> c. optionally other excipients; wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

Claim 3, which is dependent on Claim 1, provides: "Compositions as claimed in [c]laim 1, in the form of tablets, capsules, minitablets". *See* the '720 Patent, Plaintiff's Ex. PTX-001.

D. *Mylan's ANDA Product*

12. Mylan knew of the '720 Patent during the development of its ANDA Product. *See* Tr. Day 1 pm (Testimony of Mr. Pananchukunnath); Tr. Day 2 pm (Testimony of Mr. Amminabavi).

13. Mylan admits that its ANDA Product is an oral pharmaceutical containing as an active ingredient 5-amino-salicylic acid. Doc. S-502 at ¶ 32. 5-amino-salicylic acid is also known as mesalamine or mesalazine. *Id.* at ¶ 33. Mylan also admits that its ANDA Product contains active ingredient in an amount of 85.59% by weight of the total composition. *Id.* at ¶ 34. Mylan's ANDA Product is in the form of a tablet. *Id.* at ¶ 35.

14. Mylan's ANDA Product contains two Hydroxypropyl Methylcellulose ("HPMCs"), Carboxymethyl Cellulose Sodium ("CMC"), and Sodium Starch Glycolate ("SSG"), each of which is identified in the '720 Patent as "examples of hydrogels which can be used according to the invention". *See* Tr. Day 1 pm (Testimony of Mr. Pananchukunnath). Mylan's ANDA Product also contains stearic acid and palmitic acid, two lipophilic substances identified in the '720 Patent.

15. Mylan uses a double-granulation process to manufacture its ANDA product. *See* Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 1 pm (Testimony of Mr. Pananchukunnath). Granulation is a process in which ingredients are combined

in order to form granules. There are four general stages to Mylan's manufacturing process: (1) First Granulation (referred to as "Intragranular Part I"); (2) Second Granulation (referred to as "Intragranular Part II"); (3) Blending; and (4) Compression. *See* Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 pm (Testimony of Dr. Sinko); Tr. Day 1 pm (Testimony of Mr. Pananchukunnath).

16. In Mylan's First Granulation, the following ingredients are dispensed in the amounts indicated (mg/tablet), sifted, uniformly mixed, and granulated: (i) Mesalamine (1200 mg/tablet); (ii) SSG (16 mg/tablet); (iii) CMC (16 mg/tablet); and (iv) Eudragit (30 mg/tablet). *See* Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko). Mylan's First Granulation produces granules that contain a mixture of Mesalamine, SSG, CMC, and Eudragit, as well as "fines" (i.e., small particles) of these same ingredients. *Id*.

17. In Mylan's Second Granulation, the granules and fines from the First Granulation are mixed and granulated again with: (i) HPMC E-15 (30 mg/tablet); (ii) HPMC E-50 (35 mg/tablet); (iii) a higher quantity of CMC (20 mg/tablet); (iv) a higher quantity of SSG (20 mg/tablet); and (v) CSD (15 mg/tablet). *See* Tr. Day 3 am (Testimony of Dr. Sinko). As a result, the ingredients of the Second Granulation are added around the granules formed in the First Granulation. *See* Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 2 am (Testimony of Dr. Deshmukh). The ingredients added during Mylan's Second Granulation–HPMC E-15, HPMC E-50, SSG, CMC, and CSD–are also mixed with the fines of, *inter alia*, Mesalamine produced in the First Granulation step. *See* Tr. Day 3 am (Testimony of Dr. Sinko).

18. After the Second Granulation step, Stearic Acid NF (which contains a mixture of stearic acid and palmitic acid) is blended into a final mixture, which is then compressed into tablets.

See Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko). During the Compression step, Stearic Acid NF is forced into the granules via pores. *Id*. As a result, Stearic Acid NF is distributed throughout the granules in the final tableted Product. *Id.*

III. *CLAIM CONSTRUCTION*

At the request of the parties, and following claim construction briefing and a *Markman* hearing on December 22, 2014, *see Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 979 (Fed. Cir. 1995), the Court issued an Order dated March 23, 2015 (Doc. 233), construing certain disputed claims of the ′720 Patent. The Court's claim constructions are as follows:

Claim Term	**Construction**[5]
"lipophilic"	"poor affinity towards aqueous fluids"
"hydrophilic"	"having affinity for water"
"inner lipophilic matrix"	"a macroscopically homogeneous structure in all its volume that is separate from the outer hydrophilic matrix and that has poor affinity towards aqueous fluids"
"outer hydrophilic matrix"	"a macroscopically homogeneous structure in all its volume that is separate from the inner lipophilic matrix and that has an affinity for water"
"dispersed"	plain and ordinary meaning[6]
"other excipients"	"excipients, not including coatings, other than those substances forming the inner lipophilic matrix and those compounds forming the outer hydrophilic matrix"
"% by weight of the total composition"	"% by weight of the inner lipophilic matrix, the outer hydrophilic matrix, optionally other excipients, and the active ingredient"
"selected from the group consisting of"	"an exclusionary term specifying that the element contains only what is expressly set forth in a recited list, but does not exclude substances or compounds unrelated to said element"

[5] Order, Doc. 233 (Mar. 23, 2015).
[6] *See also* Tr. Day 3 am (Testimony of Dr. Sinko).

Claim Term	Construction[5]
"consisting of [substances/compounds]"	"consisting of two or more [substances/compounds]"[7]

Additionally, the parties agreed on the meaning of the following claim terms:

Claim Term	Agreed Meaning
"matrix"	"a macroscopically homogeneous structure in all its volume"[8]
"controlled-release oral pharmaceutical compositions"	"a pharmaceutical composition suitable for oral administration whereby the dissolution rate of active ingredient is not immediate"[9]
"with melting point(s) below 90° C"	"each of which begins to change from solid to liquid at a temperature below 90°C"[10]

IV. *THE LAW OF INFRINGEMENT*

Pursuant to 35 U.S.C. § 271, it is an act of infringement "to submit [an ANDA] for a drug claimed in a patent or the use of which is claimed in a patent ... if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug ... claimed in a patent ... before the expiration of such patent." 35 U.S.C. § 271(e)(2). Within the Hatch–Waxman context, the act of infringement that gives rise to a case or controversy has been noted as "artificial," as the specific infringing composition has not yet been made, used, or sold. *Glaxo, Inc. v. Novopharm, Ltd*., 110 F.3d 1562, 1569 (Fed. Cir. 1997) (citing *Eli Lilly & Co. v. Medtronic, Inc*., 496 U.S. 661, 675, 677, 110 S.Ct. 2683, 110 L.Ed.2d 605 (1990)). In these cases, "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Id*. at 1570. That said,

[7] Doc. 175-2 at 2; 175-3 at 1.
[8] Doc. 175-2 at 2; Ex. 3 and Doc. 175-3 at 1.
[9] Doc. 175-2 at 2; Doc. 175-3 at 15.
[10] Doc. 175-2 at 2; Doc. 175-3 at 1.

"[w]hat is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Id*.

Patent infringement is a question of fact, and a patent is infringed if a single claim is infringed. *Cephalon, Inc. v. Watson Pharms., Inc*., 707 F.3d 1330, 1340, (Fed. Cir. 2013); *Intervet Am. ., Inc. v. Kee–Vet Labs., Inc.*, 887 F.2d 1050, 1055 (Fed. Cir. 1989). The infringement analysis involves two steps. "First, the court determines the scope and meaning of the patent claims asserted ... and then the properly construed claims are compared to the allegedly infringing device." *Cybor Corp. v. FAS Techs., Inc*., 138 F.2d 1448, 1454 (Fed. Cir. 1998). "To prevail, the plaintiff must establish by a preponderance of the evidence that the accused device infringes one or more claims of the patent either literally or under the doctrine of equivalents." *Bayer AG v. Elan Pharm. Research Corp*., 212 F.3d 1241, 1247 (Fed. Cir. 2000) (citing *Insituform Techs., Inc. v. Car Contracing, Inc.*, 161 F.3d 668, 692 (Fed. Cir. 1998)).

A. *Literal Infringement*

"To prove literal infringement, a plaintiff must show that the accused device contains each and every limitation of the asserted claims." *Presidio Components, Inc. v. Am. Technical Ceramics Corp*., 702 F.3d 1351, 1358 (Fed. Cir. 2012) (citing *Uniloc USA, Inc. v. Microsoft Corp*., 632 F.3d 1292, 1301 (Fed. Cir. 2011)). This may be done with direct or circumstantial evidence, and a patentee need not present direct evidence of infringement. *02 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd*., 449 Fed. Appx 923, 928 (Fed. Cir. 2011) (citing *Lucent Techs., Inc. v. Gateway, Inc*., 580 F.3d 1301, 1318 (Fed. Cir. 2009); *Symantec Corp. v. Computer Assocs. Int'l, Inc*., 522 F.3d 1279, 1293 (Fed. Cir. 2008)). Further, it is improper to compare the accused product with a preferred embodiment in the Examples of the patent, instead of with the claims. *See SRI Int'l v. Matsushita Elec. Corp. of Am*., 775 F.2d 1107, 1121 (Fed. Cir. 1985) (citations omitted). "If any

claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Id*. (quoting *Bayer AG*, 212 F.3d at 1247).

B. *The Doctrine of Equivalents*

An accused product that does not literally infringe a claim may still infringe under the doctrine of equivalents if each limitation of the claim is met in the accused product either literally or equivalently. *Cybor Corp. v. FAS Techs., Inc.,* 138 F.3d 1448, 1459 (Fed. Cir. 1998) (citations omitted). To find infringement under the doctrine of equivalents, there must be "a showing that the difference between the claimed invention and the accused product was insubstantial." *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co*., 559 F.3d 1308, 1312 (Fed. Cir. 2009) (citation omitted). A plaintiff may do so "by showing on a limitation by limitation basis that the accused product performs substantially the same function in substantially the same way with substantially the same result as each claim limitation of the patented product." *Id*. (citing *Warner–Jenkinson Co., Inc. v. Hilton Davis Chem. Co*., 520 U.S. 17, 39–40, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997)).

C. *Contributory and Induced Infringement*

To succeed on a theory of contributory or induced infringement, Plaintiff must first show direct infringement of the ′720 Patent. *Lucent*, 580 F.3d at 1317; *see also Glenayre Elecs., Inc. v. Jackson*, 443 F.3d 851, 858 (Fed. Cir. 2006).

35 U.S.C. § 271(c) provides as to contributory infringement:

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

Id. at § 271(c).

To establish contributory infringement under § 271(c) in the ANDA context, a plaintiff must establish (i) direct infringement, (ii) knowledge of the listed patents, and (iii) that the defendant intended its generic drug to be bioequivalent to the plaintiff's product. *Wyeth v. Sandoz, Inc.*, 703 F. Supp. 2d 508, 521-23 (E.D.N.C. 2010) (citing § 271(c)).

Induced infringement requires: (i) direct infringement, and (ii) that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement. *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 765-66 (2011); *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1304–05 (Fed. Cir. 2002). Intent to induce infringement is based on an objective analysis. *Aventis Pharm., Inc. v. Barr Labs., Inc.*, 411 F. Supp. 2d 490, 518 (D.N.J. 2006), *aff'd*, 208 Fed. Appx 843 (Fed. Cir. 2006) (per curiam). Evidence of intent can be proved by direct or circumstantial evidence. *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988). "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b).

V. INFRINGEMENT ANALYSIS AND CONCLUSIONS OF LAW[11]

A. *Trial Testimony*

At trial, Shire presented the testimony of two of Mylan's 30(b)(6) witnesses: Manoj Pananchukunnath, who was vice president and head of global scientific affairs at Mylan and was involved in the formulation of Mylan's ANDA Product; and Doctor Abhijit Deshmukh, a Mylan formulation scientist, who was the Global Head of Scientific Affairs for the solid oral dosage business at Mylan. Shire also presented the testimony of Nagaraj Amminabavi, a senior manager at the formulation development department of Mylan, who was involved in the formulation development of Mylan's ANDA Product and Mayur Loya, an assistant manager at Mylan

[11] The Court's infringement analysis contains additional findings of fact.

Laboratories. Additionally, Shire presented expert testimony and analyses of Mylan's ANDA Product through: (1) Ms. Vivian A. Gray, a consultant and chemist to the pharmaceutical industry for dissolution testing;[12] (2) Alan John Paul, Ph.D., an expert in analytical chemistry and materials characterization of pharmaceutical materials;[13] (3) Professor Stephen W. Hoag, Ph.D., an expert in pharmaceutical formulation and process design and testing;[14] (4) Professor Steven R. Little, Ph.D., a scientist and professor of chemical engineering and an expert in controlled-release formulation and testing;[15] and (5) Professor Patrick J. Sinko, Ph.D., an expert in pharmaceutical science and formulation.[16]

Shire's expert witnesses presented and analyzed the results of tests conducted on Mylan's ANDA Product and its related properties: (a) dissolution testing and imaging; (b) scanning electron microscopy ("SEM") imaging; (c) time-of-flight secondary ion mass spectrometry ("ToF-SIMS") imaging; and (d) drop penetration testing.

To rebut Shire's infringement case, Mylan presented the testimony of Luigi Moro, a 30(b)(6) witness for Cosmo and its Chief Scientific Officer, and the expert testimony of Neil E. Spingarn, Ph.D., an analytical chemist.[17] Dr. Spingarn testified only on the ToF-SIMS analyses; he did not address dissolution testing and imaging, SEM imaging, or drop penetration testing.[18] Further, Dr. Spingarn did not conduct any testing on Mylan's ANDA Product.[19]

The following admissions were announced at the commencement of the trial, and therefore, required no proof. Mylan's ANDA Product contains stearic acid. Mylan's ANDA

[12] Tr. Day 1 am (Testimony of Ms. Gray); PX-30-318.
[13] Tr. Day 1 pm (Testimony of Dr. Paul); PX-40-707.
[14] Tr. Day 2 am (Testimony of Dr. Hoag); PX-601-361.
[15] Tr. Day 2 pm (Testimony of Dr. Little); PX-613-796.
[16] Tr. Day 3 am (Testimony of Dr. Sinko); PX-617-797.
[17] Tr. Day 4 am (Testimony of Dr. Spingarn).
[18] Tr. Day 4 am (Testimony of Dr. Spingarn).
[19] Tr. Day 4 am (Testimony of Dr. Spingarn).

Product contains palmitic acid. The stearic acid in Mylan's ANDA Product has a melting point below 90° C. The palmitic acid in Mylan's ANDA Product has a melting point below 90° C. Mylan's ANDA Product contains two hydrogenated fatty acid substances. Stearic acid is a hydrogenated fatty acid. Palmitic Acid is a hydrogenated fatty acid.[20]

B. *The Claim Limitations*

Claim 1 of the ′720 Patent has several claim limitations, all of which must be met in order for the Court to make a finding of literal infringement. First, Claim 1 requires "controlled-release oral pharmaceutical compositions" that have 5–amino–salicylic acid (mesalamine) as the active ingredient. And Claim 1 requires the mesalamine to be present in an amount of 80–95% by weight of the total composition. The ANDA Product must have an "inner lipophilic matrix" that consists of one or more of the listed lipophilic substances and the lipophilic excipients used to form the lipophilic matrix must have a melting point below 90° C. Claim 1 also requires an "outer hydrophilic matrix" consisting of one of the listed hydrophilic substances. Finally, Claim 1 requires that mesalamine be dispersed in each of the matrices and that each matrix is macroscopically homogeneous in all its volume.

1. Controlled Release

"Controlled release" means the dissolution rate of the active ingredient is not immediate.[21] Dr. Little defined "immediate" release as taking approximately 45 minutes to release about 75% of the active ingredient.[22] Further, he testified that if less than 75% of the active ingredient is released after two hours, then the formulation is controlled release.[23]

[20] Tr. Day 1 am, pp 73-74.
[21] Tr. Day 2 pm (Testimony of Dr. Little).
[22] *Id*.
[23] *Id.*

Mylan asserts that the five examples in the '720 Patent show that mesalamine is released at a rate of not more than 60-70% within four hours and not more than 90% within eight hours.[24] But Mylan's internal testing of its Exhibit Batch Report shows that on average, over 90% of the mesalamine is dissolved at four hours. Mylan contends that this information undermines the credibility of the opinions of Dr. Little and Dr. Sinko. These experts concluded that the dissolution profile of the Mylan ANDA Product is consistent with the dissolution profile of the two matrix formulations described in the '720 Patent without accounting for the aforementioned differences. The Court finds the testimony of Dr. Little and Dr. Sinko to be credible.

Ms. Vivian A. Gray, an expert in dissolution testing,[25] designed and carried out a dissolution test on three of Mylan's tablets that: (1) measured the percentage of mesalamine released from each tablet over time; and (2) captured digital images of each tablet in dissolution.[26] Each of the three tablets was placed in a vessel (labeled "Vessel 2," "Vessel 4," and "Vessel 5") and subjected to three stages of dissolution media: (1) 0.1 N hydrochloric acid ("Acid Stage"); (2) 6.4 pH phosphate buffer ("Buffer Stage 1"); and (3) 7.2 pH phosphate buffer ("Buffer Stage 2")[27] which corresponded to the pH exposure in the intestinal fluid.[28] Ms. Gray used ultraviolet spectrophotometry to measure the amount of mesalamine dissolved in each of the vessels at specified time points, ultimately calculating the percentage of mesalamine dissolved from each of the Mylan tablets over time.[29] Ms. Gray obtained twenty-nine measurements over the course of her eleven-hour experiment: (1) two samples in the Acid Stage; (2) two samples in Buffer Stage 1; and (3) twenty-five samples in Buffer Stage 2.[30] Ms. Gray then obtained the average percent-

[24] *See* '720 Patent.
[25] Tr. Day 1 am (Testimony of Ms. Gray); PX-30-318.
[26] Tr. Day 1 am (Testimony of Ms. Gray).
[27] *Id*.
[28] *Id*.; *see also* Tr. Day 2 pm (Testimony of Dr. Little).
[29] Tr. Day 1 am (Testimony of Ms. Gray).
[30] *Id*.

dissolved for each of the three tablets.[31] Ms. Gray's dissolution test confirms that the coating on Mylan's Product delays release until the appropriate pH conditions, after which the uncoated tablet core releases about 40-42% at 150 minutes and about 85% release at over 300 minutes.[32] Ms. Gray testified that the data and images obtained in her dissolution test accurately reflect the dissolution of Mylan's Product, and Mylan offered no expert testimony in rebuttal.[33]

Dr. Little, an expert in controlled-release formulation and testing,[34] analyzed: (i) the '720 Patent; (ii) the composition and manufacture of Mylan's product as described in Mylan's ANDA; (iii) Dr. Paul's ToF-SIMS and SEM imaging; and (iv) Ms. Gray's dissolution testing and images.[35] Dr. Little concluded that Mylan's Product, specifically its uncoated tablet core, is a controlled-release oral pharmaceutical composition.[36] Dr. Little further concluded that this controlled release is attributable to two spatially separate (i.e., inner and outer) and compositionally separate (i.e., lipophilic and hydrophilic) matrices in Mylan's tablet core.[37]

Dr. Sinko is an expert in pharmaceutical science and formulation.[38] In forming his opinions, Dr. Sinko reviewed: (i) the '720 Patent, (ii) the Court's claim constructions, (iii) the Mylan ANDA formulation and manufacturing process, (iv) Mylan development documents, (v) scientific literature, (vi) testimony from Mylan's corporate witness, and (vii) the testing and opinions of Shire's experts.[39] Based on this information and data, Dr. Sinko concluded that Mylan's Product is an oral pharmaceutical composition that is controlled release.[40]

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[31] *Id.*; PX-32-322.4-.6.
[32] Tr. Day 2 pm (Testimony of Dr. Little).
[33] Tr. Day 1 am (Testimony of Ms. Gray); PX-33-800.1-800.786; PX-34-800.787-800.1618; PX-35-800.1619-800.2375.
[34] Tr. Day 2 pm (Testimony of Dr. Little); PX-613-796.
[35] Tr. Day 2 pm (Testimony of Dr. Little).
[36] *Id.*
[37] *Id.*
[38] Tr. Day 3 am (Testimony of Dr. Sinko); PX-617-797.
[39] Tr. Day 3 am (Testimony of Dr. Sinko).
[40] *Id*.

And Mylan's ANDA states that its Product was "designed with a combination of delayed and controlled release dosage attributes," and that this "dual functionality" is built through a delayed-release coating and "extended release tablet core."[41] The data contained in Mylan's ANDA Product shows that release from the tablet core of its Product is not immediate, taking between three and four hours to release 75% of its mesalamine.[42]

After considering the evidence, testimony and documents, the Court finds that Shire has met its burden to prove by a preponderance of the evidence that Mylan's ANDA Product is a controlled-release oral pharmaceutical composition. This aspect of Claim 1 is met.

2. *The Matrices*

The Court construed the term "inner lipophilic matrix" to mean a "macroscopically homogeneous structure in all is volume that is separate from the outer hydrophilic matrix that has poor affinity towards aqueous fluids."[43] The Court construed the term "outer hydrophilic matrix" to mean "a macroscopically homogeneous structure in all its volume that is separate from the inner lipophilic matrix and that has an affinity for water."[44]

(A). *Separate Matrices*

The Court construed the matrices as "separate."[45] "[C]onsidering 'matrix' is properly construed as 'a macroscopically homogen[e]ous structure in all its volume,' the construction of 'inner lipophilic matrix' requires the inner volume to be separate from the outer volume." *Shire Dev., LLC v. Watson Pharm., Inc.*, 787 F.3d 1359, 1367 (Fed. Cir. 2015). "The lack of overlap of

[41] Tr. Day 2 pm (Testimony of Dr. Little); PX-614-477.2.
[42] *Id.*; *see also* Tr. Day 3 am (Testimony of Dr. Sinko).
[43] Doc. 233 at 18.
[44] Doc. 233 at 10.
[45] Doc. 233 at 8.

the components of the two Markush groups[46] supports the requirement that the volumes be separate." *Id*.

Shire contends that the matrices in the Mylan ADNA Product have spatially and compositionally separate volumes. It presented the testimony of Dr. Paul, an expert in analytical chemistry and materials characterization of pharmaceutical materials.[47] Dr. Paul used SEM imaging to assist in the identification of granular features in Mylan's Product.[48] SEM is a high-resolution imaging technique that is routinely used in the physical characterization of pharmaceutical materials.[49] Dr. Paul performed SEM imaging on cross-sectional areas of tablets from Mylan's exhibit batch and Mylan's validation batch.[50] He also used ToF-SIMS imaging to map the location of mesalamine and excipients in and around the same granular features identified in his SEM analyses.[51] Additionally, Dr. Paul performed ToF-SIMS on ten cross-sectional areas from three tablets of Mylan's Product (two tablets from the exhibit batch; one tablet from the validation batch).[52] In conjunction with the SEM imaging, Dr. Paul's ToF-SIMS chemical imaging mapped the location of mesalamine and excipients relative to granular features in Mylan's ANDA Product.[53] Dr. Paul generated overlay images of the SEM and ToF-SIMS images for each of the areas that showed granular features.[54] He also generated ToF-SIMS overlay images that showed the location of certain ingredients relative to each other in the same area.[55]

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[46] "A Markush group is a listing of specified alternatives of a group in a patent claim." *Abbott Labs. v. Baxter Pharm. Prods.*, 334 F.3d 1274, 1280 (Fed. Cir. 2003).
[47] Tr. Day 1 pm (Testimony of Dr. Paul); PX-40-707.
[48] Tr. Day 1 pm (Testimony of Dr. Paul).
[49] *Id*.
[50] *Id.*; PX-41-700.351.
[51] Tr. Day 1 pm (Testimony of Dr. Paul).
[52] *Id.*
[53] *Id.*
[54] *Id.*; PX-55-700.004; PX-56-700.013; PX-57-700.033; PX-58-700.007.
[55] Tr. Day 1 pm (Testimony of Dr. Paul); PX-54-700.121; PX-53-700.122.

ToF-SIMS imaging of Mylan's Product shows an outer volume (defined by the presence of the two HPMCs) that is spatially separate from an inner volume (defined by the absence of the two HPMCs) dispersed within.[56] Shire's experts testified that Mylan's outer and inner volumes exhibit separate compositional characteristics due to different distribution of excipients, i.e., hydrophilic excipients concentrated in the outer volume.[57] Hydrophilic excipients HPMC E-15 and HPMC E-50 are located exclusively in Mylan's outer volume.[58] Hydrophilic excipients SSG and CMC exist in higher concentrations in the outer volume of Mylan's Product.[59] Mylan's expert, Dr. Spingarn, agreed that Dr. Paul's ToF-SIMS images show more SSG and CMC outside the granule (than inside).[60] Images of the Mylan ANDA Product in dissolution show that the inner and outer volumes of Mylan's Product exhibit separate compositional characteristics attributable to the presence of separate matrices: an inner lipophilic matrix and an outer hydrophilic matrix.[61]

Mylan argues that the evidence does not support a conclusion that there are separate matrices in its ANDA Product. Although Dr. Little and Dr. Sinko testified that Mylan's Product has separate matrices based on Dr. Paul's ToF-SIMS images showing fatty acids and HPMCs[62], Mylan contends that Dr. Paul himself disagreed with that opinion. Dr. Paul testified that he could not tell from his own ToF-SIMS images whether palmitic acid and stearic acid are separate from the HPMCs in Mylan's Product. [63] Mylan also argues that because SSG and CMC, which are

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[56] Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko); PX-53-700.097; PX-54-700.095; PX-53-700.125; PX-54-700.123; PX-53-700.165; PX-54-700.163; PX-53-700.054; PX-54-700.052; PX-53-700.388; PX-54-700.389; PX-53-700.417; PX-54-700.416; PX-53-700.405; PX-54-700.404; PX-53-700.427; PX-54-700.426.
[57] Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko).
[58] Tr. Day 1 pm (Testimony of Dr. Paul); (Testimony of Dr. Little); PX-54-700.095.
[59] Tr. Day 1 pm (Testimony of Dr. Paul); Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 3 pm (Testimony of Dr. Sinko); Tr. Day 2 pm (Testimony of Dr. Little).
[60] Tr. Day 4 am (Testimony of Dr. Spingarn); PX-53-700.388; PX-54-700.389 (Validation Batch, Area 1); Tr. Day 4 am (Testimony of Dr. Spingarn); PX-53-700.107; PX-54-700.106 (Exhibit Batch, Area 1).
[61] *See infra* ¶¶ 82-106.
[62] Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko).
[63] Tr. Day 1 pm (Testimony of Dr. Paul).

supposed to make up the "outer hydrophilic matrix" appear throughout the ANDA Product and inside and outside the inner volume of the granule, the evidence does not support that the matrices are separate, either spatially or compositionally.[64]

But Ms. Gray's images in dissolution show that the inner and outer volumes of Mylan's Product exhibit separate compositional characteristics. The outer volume exhibits increased viscosity in the hydrated gel layer and the inner volume resists the penetration of aqueous solvent. And ToF-SIMS imaging shows that the distribution of stearic acid and palmitic acid in the inner volume is spatially separate from the HPMCs, CMC, and SSG in the outer volume.[65] The spatially separate distribution of these ingredients results in the compositionally separate characteristics exhibited over the inner and outer volumes of Mylan's Product and observed in Ms. Gray's dissolution images.[66] Mylan's expert, Dr. Spingarn, offered no rebuttal testimony.

After considering the evidence, testimony and documents, the Court finds that Shire has proven by a preponderance of the evidence that the Mylan ANDA Product contains separate matrices. This aspect of Claim 1 is met.

(B). *Macroscopically Homogeneous in All its Volume*

The Court construed both the inner lipophilic matrix and the outer hydrophilic matrix as being "macroscopically homogeneous in all its volume."[67] Shire contends that the inner lipophilic matrix in the Mylan ANDA Product is the macroscopically homogeneous distribution of stearic

[64] *See* Doc. 500 ("Mylan's Proposed Findings of Fact and Conclusions of Law") at 21-22.
[65] Tr. Day 1 pm (Testimony of Dr. Paul); PX-54-700.121; Tr. Day 2 pm (Testimony of Dr. Little); PX-53-700.097; PX-54-700.095.
[66] Tr. Day 2 pm (Testimony of Dr. Little); PX-54-700.121; PX-53-700.097; PX-54-700.095; Tr. Day 3 am (Testimony of Dr. Sinko); PX-53-700.097; PX-54-700.095; PX-53-700.122; PX-54-700.121; PX-34-800.1210 (enlarged).
[67] Doc. 233 at 10.

acid and palmitic acid in the inner volume.[68] It further contends that HPMCs form a macroscopically homogeneous structure in the outer volume of Mylan's Product.[69]

In support, Shire offered the testimony of Dr. Sinko and Dr. Paul. They explained that when viewing the ToF-SIMS images together, in consideration of the entire tablet, the inner lipophilic matrix is macroscopically homogeneous. [70] Dr. Sinko explained that the distribution of stearic acid and palmitic acid within Mylan's inner volume forms a structure because it is fixed in space.[71] Because there is so little room for excipients, this structure does not need to be physically connected in order to form a matrix.[72] And the patent examples do not describe a physically connected structure.[73] But Shire did not provide any macroscopic images at trial. To determine whether the matrices are macroscopically homogeneous in all their volume, Dr. Sinko and Dr. Paul testified that one would need to "zoom out," "extrapolate," or "imagine drawing back to the scale of the tablet."[74]

Mylan's expert, Dr. Spingarn, opined that the evidence does not show macroscopic homogeneity precisely because the images are not macroscopic.[75] Dr. Spingarn further testified that "extrapolating" or "zooming out" based on microscopic images is insufficient to predict macroscopic homogeneity.[76] He testified that "[n]o scientist can say, well, on a small image it's not homogeneous but if I made it bigger it would look homogeneous."[77] Mylan argues that the images do not show homogeneity, and even if they did, they would not prove this claim of the

[68] Doc. 499 (Shire's ¶ 89; Tr. Day 2 pm (Testimony of Dr. Little), Tr. Day 3 am (Testimony of Dr. Sinko), Tr. Day 3 pm (Testimony of Dr. Sinko).
[69] Tr. Day 1 pm (Testimony of Dr. Paul); Tr. Day 3 am (Testimony of Dr. Sinko).
[70] Tr. Day 3 am (Testimony of Dr. Sinko); *see also* Tr. Day 1 pm (Testimony of Dr. Paul).
[71] Tr. Day 3 pm (Testimony of Dr. Sinko).
[72] Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 3 pm (Testimony of Dr. Sinko).
[73] Tr. Day 3 pm (Testimony of Dr. Sinko).
[74] Tr. Day 1 pm (Testimony of Dr. Paul); Tr. Day 3 am (Testimony of Dr. Sinko).
[75] Tr. Day 4 am (Testimony of Dr. Spingarn).
[76] *Id*.
[77] *Id*.

element because all of the images are *microscopic*. And Dr. Spingarn, in reviewing the ToF-SIMs images, noted that because there were "bright spots next to dark spots" representing the distribution of SSG and CMC in Mylan's tablet, the outer matrix was not homogeneous.[78] Ultimately, it was Dr. Spingarn's position that no one could look at any of the microscopic images and determine whether they represented macroscopic homogeneity.

The Court appreciates Dr. Spingarn's criticism that there were no macroscopic images in the record, but that absence in and of itself is insufficient to completely disregard Shire's experts' testimony that the matrices are macroscopically homogeneous. There is nothing to refute the fact that Shire's experts could have reasonably inferred from the microscopic images that the matrices were macroscopically homogeneous. Further, Dr. Spingarn admitted at deposition that something could look homogenous at one level, but might not be homogeneous at another level and vice versa.[79]

After considering the evidence, testimony and documents, the Court finds that Shire has proven by a preponderance of the evidence that the Mylan ANDA Product contains matrices that are macroscopically homogeneous in all their volume. This aspect of Claim 1 is met.

(C). *Inner Lipophilic Matrix*

Having found that the inner lipophilic matrix is separate and macroscopically homogeneous, the Court now turns to whether it has a poor affinity towards aqueous fluids. "Poor affinity towards aqueous fluids" is observed over the volume of the inner lipophilic matrix.[80] The '720 Patent describes poor affinity towards aqueous fluids as resulting in: (1) "some resistance" to

[78] *Id.*
[79] Tr. Day 4 am (Testimony of Dr. Spingarn).
[80] Tr. Day 2 pm (Testimony of Dr. Little).

the penetration of water, relative to pure mesalamine;[81] and (2) slowed dissolution of mesalamine.[82] As Dr. Little explained, "poor affinity towards aqueous fluids" does not "pose an absolute resistance to the penetration of water because this is a pharmaceutical formulation. So water has to get into this formulation to dissolve the drug."[83]

The test compacts in Dr. Hoag's drop penetration test simulated the inner volume of Mylan's ANDA Product.[84] Although there were differences in porosity, fines, hardness, and granule size of the test compact, the test is still valid.[85] The test demonstrates that Mylan's inner lipophilic matrix has poor affinity towards aqueous fluids, as shown by the thirty-fold difference in water penetration rate.[86] This resistance demonstrates poor affinity to water attributable to the distribution of stearic acid and palmitic acid.[87]

Dr. Hoag's mesalamine compact was the appropriate control for assessing "poor affinity towards aqueous fluids."[88] The other excipients (CMC, SSG, and Eudragit) are unrelated to the poor affinity towards aqueous fluids exhibited over Mylan's inner volume. Although CMC and SSG are hydrophilic, they present in "much lower concentrations" than in Mylan's outer volume. Therefore, they do not affect the lipophilic behavior of Mylan's inner volume.[89] The Eudragit in Mylan's Product has no effect on dissolution of mesalamine.[90] The other excipients in the inner

[81] PX-1-1.3 at col.1 ll.17-20; Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 2 am (Testimony of Dr. Hoag); Tr. Day 3 am (Testimony of Dr. Sinko).
[82] PX-1-1.4 at col.4 ll.1-5; Tr. Day 2 pm (Testimony of Dr. Little).
[83] Tr. Day 2 pm (Testimony of Dr. Little).
[84] Tr. Day 2 am (Testimony of Dr. Hoag); Tr. Day 3 am (Testimony of Dr. Sinko).
[85] Tr. Day 2 pm (Testimony of Dr. Hoag).
[86] Tr. Day 2 am (Testimony of Dr. Hoag).
[87] Tr. Day 2 am (Testimony of Dr. Hoag); Tr. Day 3 am (Testimony of Dr. Sinko).
[88] Tr. Day 2 am (Testimony of Dr. Hoag).
[89] Tr. Day 2 pm (Testimony of Dr. Little).
[90] Tr. Day 1 pm (Testimony of Mr. Pananchukunnath); Tr. Day 3 am (Testimony of Dr. Sinko); PX-24-258.196; PX-26-260.98; PX-619-525.2-4; PX-620-527.3-5.

granule were not responsible for the related lipophilic properties, and did not change the poor affinity for aqueous fluids exhibited by the inner granular region.[91]

The CMC and SSG in Mylan's inner volume do not cause it to exhibit an affinity for water. Dr. Hoag's test compacts did not exhibit increased viscosity or swelling upon contact with water.[92] The inner volume observed in Ms. Gray's dissolution images did not swell and form that translucent layer like the outer volume.[93]

Mylan argues that Shire's theory of what constitutes the inner lipophilic matrix has been a moving target. In particular, it argues that Shire proposed that the "inner lipophilic matrix" in Mylan's Product was only the distribution of stearic acid in the inner volume of Mylan's granules while the "outer hydrophilic matrix" was only the distribution of SSG and HPMCs outside of the inner volume. Mylan argues that this infringement theory is foreclosed by Federal Circuit precedent relating to the '720 Patent and this Court's claim construction order because those ingredients alone do not form a "structure." Dr. Sinko testified that the stearic and palmitic acids located in the inner volume of Mylan's granules are not physically connected and the fatty acids in the granules are held in place by mesalamine, SSG, CMC, and Eudragit such that if one removed those ingredients from the granule there would be only a pile of the fatty acids left. [94]

And Mylan argues that the distribution of disconnected particles in a granule is not a structure and the required structure is a "whole body" made of substances from the list in part (a) of claim 1 that has the potential to "crack," leading to "accidental leakage" of the pharmaceutical ingredient.[95] Since there is no evidence in the record that a distribution of stearic and palmitic acid

[91] Tr. Day 3 am (Testimony of Dr. Sinko).
[92] Tr. Day 2 am (Testimony of Dr. Hoag).
[93] Tr. Day 2 pm (Testimony of Dr. Little).
[94] Tr. Day 3 pm (Testimony of Dr. Sinko).
[95] Doc. 500 at 11.

forms a structure that can "crack" as set forth in the '720 patent's prosecution history, Mylan contends that the stearic acid alone cannot form the inner lipophilic matrix. Further, because stearic acid is added at the end of the Second Granulation as a lubricant, Mylan argues that it cannot form the inner lipophilic matrix.

Mylan's second argument is that Shire alternatively alleged that the "inner lipophilic matrix" was the entire inner volume of the granules and the "outer hydrophilic matrix" was the entire outer volume. Mylan argues that under this theory Shire's case contradicts jurisprudence regarding Markush limitations because the inner volume includes ingredients which also exist in the outer volume. It ultimately argues that Shire has not met its burden of proof under either theory as argued in its Rule 52(c) motion, and in its proposed findings of fact and conclusions of law.[96]

But, as Shire's experts testified, the stearic acid is pushed into the granules during the manufacturing process, and is found throughout the tablet. Although Mylan uses a different sequence in its manufacturing process than the '720 Patent, the resulting tablet can still have the same characteristics as the '720 Patent. A different manufacturing process does not necessarily produce a different result, as demonstrated by the SEM and ToF-SIMS images showing stearic acid throughout the tablet. The Court is otherwise unpersuaded by Mylan's argument.

After considering the evidence, testimony and documents, the Court finds that Shire has proven by a preponderance of the evidence that the Mylan ANDA Product contains an "inner lipophilic matrix" that has a poor affinity for aqueous fluids. This aspect of Claim 1 is met.

(D). *Outer Hydrophilic Matrix*

Having found that the matrices are separate and macroscopically homogeneous, the Court must now consider whether Mylan's Product's outer hydrophilic matrix has an affinity for water.

[96] *See* Doc. 500 at 1.

This Court has construed the term "hydrophilic" to mean "having affinity for water."[97] "Affinity for water" is observed over the volume of the outer hydrophilic matrix of the Mylan ANDA Product.[98] It is undisputed that the Mylan ANDA Product contains HPMC E-15 and HPMC E-50.[99] The '720 Patent Examples identify HPMC as a hydrophilic matrix-forming compound.[100] The distribution of these excipients in the outer volume of Mylan's Product forms an outer hydrophilic matrix.[101]

Shire presented evidence and testimony to support this position. Specifically, Mylan's witness testimony and documents describe its ANDA Product as a "hydrophilic matrix system" and that its "core matrix forms a hydrogel."[102] Mylan's ANDA characterizes the HPMC compounds in its Product as "hydrophilic release rate controlling polymers."[103] Images of the Mylan tablet in dissolution confirm that Mylan's outer volume has affinity for water as described in the '720 Patent.[104] Mylan's outer hydrophilic matrix shows increased viscosity and eventual disintegration when in contact with aqueous fluids which contributes to the controlled release of mesalamine from Mylan's Product.[105]

The two HPMCs in Mylan's Product are "prototypical hydrophilic matrix materials" known to produce the affinity for water described in the '720 Patent.[106] Each of the '720 Patent Examples discloses HPMC (hydroxypropyl methylcellulose) as an exemplary hydrophilic matrix-

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[97] Doc. 233 at 6-7.
[98] PX-1-1.4 at col.3 ll.60-64 ("[S]welling due to the distension of the polymeric chains of the hydrogels" results in "a high viscosity hydrated front."); Tr. Day 2 pm (Testimony of Dr. Little).
[99] Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 1 pm (Testimony of Mr. Pananchukunnath); PX-5-235.21; PX-604-392.19.
[100] Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko); PX-1-1.4, col.4 ll.14-16, 39-41, 58-63; *id.* at 1-5, col.5 ll.11-18, 34-36, col.6 ll.18-25.
[101] Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 3 pm (Testimony of Dr. Sinko).
[102] Tr. Day 2 pm (Amminabavi Dep.); PX-19-269.
[103] Tr. Day 3 am (Testimony of Dr. Sinko); PX-604-392.19; *see also* PX-5-235.21.
[104] Tr. Day 2 pm (Testimony of Dr. Little); PX-33-800.117; PX-34-800.925; PX-35-800.1735.
[105] Tr. Day 2 pm (Testimony of Dr. Little).
[106] Tr. Day 2 pm (Testimony of Dr. Little).

forming material.[107] Mylan's outer volume contains a "high concentration," i.e., "50 to 60 percent of the composition" of these two HPMC compounds.[108] The affinity for water exhibited by Mylan's outer hydrophilic matrix is attributable to two or more hydrophilic compounds in Mylan's outer volume, including at least HPMC E-15 and HPMC E-50.[109]

Mylan's outer volume contains SSG and CMC, which are also hydrophilic matrix-forming compounds. SSG is a starch derivative that is known to swell upon contact with water.[110] CMC is a carboxyalkyl cellulose that is also known to exhibit hydrophilic behavior.[111] SSG and CMC are more highly concentrated in Mylan's outer volume, which may also contribute to its affinity for water.[112]

The other excipients (stearic acid, palmitic acid, Eudragit, and CSD) are unrelated to the affinity for water exhibited over Mylan's outer volume. The presence of lipophilic substances in the outer volume does not result in poor affinity towards aqueous fluids or otherwise affect the affinity for water exhibited by Mylan's outer hydrophilic matrix.[113] Eudragit has no effect on the controlled release of mesalamine from Mylan's Product, and CSD would not result in the affinity for water seen in Ms. Gray's images.[114]

Mylan argues that because stearic acid – the lipophilic matrix-forming substance- exists in the extragranular space with the other excipients, the matrices are mixed, and such dual presence

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[107] PX-1-1.4 at col.4 ll.15-16, col.4 ll.39-40, col.4 ll.60-61, col.5 ll.15-16, col.5 ll.35-36; *see also id.* at col.3 ll.25-30 (identifying "hydroxyalkyl celluloses"); Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko).
[108] Tr. Day 2 pm (Testimony of Dr. Little).
[109] Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko).
[110] Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 3 pm (Testimony of Dr. Sinko); Tr. Day 1 pm (Testimony of Mr. Pananchukunnath).
[111] Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 3 pm (Testimony of Dr. Sinko); Tr. Day 1 pm (Testimony of Mr. Pananchukunnath).
[112] Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 2 pm (Testimony of Dr. Little); PX-5-235.24.
[113] Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko); Tr. Day 3 pm (Testimony of Dr. Sinko).
[114] Tr. Day 2 pm (Testimony of Dr. Little).

violates the "consisting of" limitation in Claim 1(b). It also argues that this presence renders the inner and outer matrix requirements meaningless. The Court rejects this argument. Although the matrices need to be separate, the stearic acid in the extragranular space may serve another function (e.g. lubricant).

Mylan also argues that Shire appears to equate the "inner lipophilic matrix" with the "inner volume," and the "outer hydrophilic matrix" with the "outer volume" when neither assertion is supported by the evidentiary record.[115] And Mylan contests Dr. Little's testimony regarding his analysis of Ms. Gray's dissolution testing images. It argues that Dr. Little did not test the actual tablets in the images to confirm that what is shown in the images is in fact "distribution of stearic and palmitic acids in the volume" surrounded by a "distribution of the two HPMCs and the SSG and [CMC]."[116] Mylan contends that the Court should, therefore, assign little weight if any, to Dr. Little's conclusions. The Court rejects these arguments; Dr. Gray's images were consistent with the SEM and ToF-SIMS images depicting the distribution of the various ingredients throughout Mylan's Product. Mylan's outer volume exhibits increased viscosity in the hydrated gel-like layer that appears in Ms. Gray's images as an outer "halo," whereas the inner volume resists the penetration of aqueous solvent.[117]

After considering the evidence, testimony and documents, the Court finds that Shire has proven by a preponderance of the evidence that the outer hydrophilic matrix has an affinity towards water. And Shire has proven that the Mylan ANDA Product contains an "inner lipophilic matrix" which is located inside and is spatially and compositionally separate from the outer matrix and an

[115] Doc. 500 at 25.
[116] Tr. Day 3 am (Testimony of Dr. Sinko).
[117] Tr. Day 2 pm (Testimony of Dr. Little).

"outer hydrophilic matrix" that is located inside and is spatially and compositionally separate from the inner matrix. This aspect of Claim 1 is met.

3. Melting Point Below 90 degrees C

Mylan admits that stearic acid and palmitic acid are two hydrogenated fatty acids having melting points below 90° C. [118]

4. "Wherein the Active Ingredient is Dispersed Both in the Lipophilic Matrix and in the Hydrophilic Matrix"

The Court construed the term "dispersed" as its plain and ordinary meaning. [119] The Court adopts the plain and ordinary meaning of "dispersed" as "mixed".[120] Dr. Sinko concluded that mesalamine is dispersed in both the inner lipophilic matrix and the outer hydrophilic matrix of Mylan's Product.[121]

Mylan's expert witness, Dr. Spingarn, offered no opinion in rebuttal. But, Mylan contends that the patent requires that the mesalamine be "dispersed in"—not just "partly inglobated" in—both matrices.[122] Further, it argues that Mylan's manufacturing process is different than that described in the '720 Patent, and it does not produce a composition where mesalamine is dispersed in the matrices.[123] And it argues that the testimony from Dr. Sinko that the mesalamine gets "pushed into" the granule during the Compression stage[124] and from Dr. Little that the stearic and palmitic acid are "pressed into the granule"[125] is insufficient to prove infringement on Claim 1. The Court disagrees. Mylan's argument is mere semantics, and the unrebutted testimony is that

[118] Tr. Day 1 am.
[119] Doc. 233 at 12.
[120] Tr. Day 3 am (Testimony of Dr. Sinko).
[121] Tr. Day 3 am (Testimony of Dr. Sinko); PX-54-700.121; *see also* Tr. Day 1 pm (Testimony of Dr. Paul); PX-58-700.7; PX-59-700.1.
[122] Doc. 500 at 7.
[123] Doc. 500 at 8.
[124] Tr. Day 3 am (Testimony of Dr. Sinko); Day 3 pm (Testimony of Dr. Sinko).
[125] Tr. Day 2 pm (Testimony of Dr. Little).

mesalamine exists in both the inner lipophilic matrix and outer hydrophilic matrix of Mylan's Product.

After considering the evidence, testimony and documents, and the arguments made by both sides, the Court finds that Shire has shown by a preponderance of the evidence that the active ingredient mesalamine is dispersed both in the inner lipophilic matrix and in the outer hydrophilic matrix. This aspect of Claim 1 is met.

5. Optionally Other Excipients

The Court has construed "other excipients" in part (c) of claim 1 to mean "excipients, not including coatings, other than those substances forming the inner lipophilic matrix and those compounds forming the outer hydrophilic matrix."[126] Further, "percent by weight of the total composition" was construed to mean "percent by weight of the inner lipophilic matrix, the outer hydrophilic matrix, optionally other excipients, and the active ingredient."[127]

Drs. Paul, Little and Sinko all agreed that there is mesalamine, stearic acid, palmitic acid, SSG, CMC, and Eudragit in the inner volume of Mylan's granules [128] and mesalamine, stearic acid, palmitic acid, SSG, CMC, HPMCs, and CSD in the outer volume of Mylan's granules.[129] Shire contends that the excipients in the inner volume other than stearic and palmitic acid are "unrelated to the properties of the matrix."[130] As with the inner volume, Shire similarly contends that the stearic and palmitic acid in the outer volumes are "unrelated to the properties" of the matrix.[131]

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[126] Doc. 233 at 12.
[127] Doc. 233 at 19.
[128] Tr. Day 1 pm (Testimony of Dr. Paul); Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko).
[129] Tr. Day 1 pm (Testimony of Dr. Paul); Tr. Day 2 pm (Testimony of Dr. Little); Tr. Day 3 am (Testimony of Dr. Sinko).
[130] Tr. Day 3 am (Testimony of Dr. Sinko).
[131] Tr. Day 3 pm (Testimony of Dr. Sinko).

Dr. Sinko opined that the stearic acid and palmitic acid distributed in the outer volume are "optionally other excipients" under part (c) of claim 1, and, therefore, are excipients other than those forming the "inner lipophilic matrix."[132] He further opined that SSG and CMC in the inner volume are "optionally other excipients" under part (c) of claim 1, and, therefore, are excipients other than those forming the "outer hydrophilic matrix."[133]

Mylan argues that under the Court's claim construction, stearic and palmitic acid cannot be "other excipients" because Shire contends that they form the "inner lipophilic matrix" in Mylan's Product and that SSG and CMC cannot be "other excipients" because Shire contends that they form the "outer hydrophilic matrix" in Mylan's ANDA Product.

Based on the evidence, testimony and documents, the Court finds that Shire has proven by a preponderance of the evidence that stearic acid and palmitic acid are optionally other excipients when they exist in the outer hydrophilic matrix. And SSG, and CMC are optionally other excipients when they exist in the inner lipophilic matrix. Shire met its burden by demonstrating that the stearic and palmitic acid when found in the outer matrix, and the other excipients besides stearic and palmitic acid when found in the inner matrix are unrelated to the properties of the respective matrix. This aspect of Claim 1 is met.

C. *Induced and Contributory Infringement*

Having found direct infringement, the court now directs its attention to induced and contributory infringement. "The only difference in the analysis of a traditional infringement claim and a claim of infringement under section 271(e)(2) is the timeframe under which the elements of infringement are considered." *Wyeth*, 703 F. Supp. 2d at 519 (quoting *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1331 (Fed. Cir. 2003) (per curiam)).

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[132] *Id*.
[133] *Id.*

As to induced infringement, the asserted claims cover the FDA-approved uses. *See* 21 U.S.C. § 355(j)(2)(A). Mylan seeks to "piggyback" on the FDA approval of Lialda® with the same active ingredient and a drug dissolution profile covered by the asserted claims. Because Mylan shows that the ANDA drug is safe and effective with the studies that Shire conducted to prove the safety and efficacy of Lialda®, Mylan is "forbidden from obtaining such approval" for a use that is not covered by Shire's approved NDA, "unless it files its own ... full safety and efficacy data." *Warner–Lambert Co. v. Apotex Corp.,* 316 F.3d 1348, 1360 (Fed. Cir. 2003) (emphasis omitted). Mylan did not present a new use supported by new studies to show that the hypothetical new use is safe and effective. Rather, the record shows that the proposed use of the ANDA Product infringes the asserted patent claims because the FDA-approved uses are covered by the asserted claims. Thus, the record shows that the uses for which Mylan seeks approval are covered by Shire's asserted claims.

As to contributory infringement, when Mylan filed the ANDA, it knew of the patents-in-suit and knew that sale of its generic would cause infringement of the asserted claims. Moreover, Mylan intended its generic drug to be the interchangeable bioequivalent of Lialda®. This knowledge and development shows that Mylan's product is "especially made" for "use in practicing a patented process" that is a "material part of the invention." *See* 35 U.S.C. § 271(c). Mylan designed the ANDA Product to treat ulcerative colitis, the same disorder that the FDA has approved for treatment using Lialda®. In light of the undisputed evidence of the identical indications for the drugs and the properly construed asserted claims, no substantial noninfringing uses exist.

Shire has proven by a preponderance of the evidence that Mylan Inc. knowingly induced Mylan Pharmaceuticals Inc. to infringe and contributed to Mylan Pharmaceuticals' infringement of claims 1 and 3 of the '720 Patent.

VI. CONCLUSION

Based on the Court's findings set forth above, Shire has established by a preponderance of the evidence that Mylan's ANDA Product infringes Claims 1 and 3 of the '720 Patent, literally. And Shire has established secondary liability by Mylan Pharmaceuticals Inc. on the theory of induced and contributory infringement. Shire is entitled to the following relief:

1. A judgment declaring that the submission and filing of Mylan's ANDA with a paragraph IV certification was an act of infringement of the '720 Patent by Mylan.

2. A judgment declaring that the commercial manufacture, use, sale, offer for sale and/or importation into the United States of Mylan's Product prior to the expiration of the '720 Patent will constitute an act of infringement of the '720 Patent by Mylan.

3. A judgment declaring that Mylan Inc. has, is, and will induce and/or contribute to Mylan Pharmaceuticals Inc.'s infringement of the '720 Patent.

4. An order that the effective date of any approval of Mylan's ANDA shall be no earlier than the expiration date of the '720 Patent.

5. A judgment permanently enjoining Mylan from engaging in the commercial manufacture, use, sale, offer for sale and/or importation in the United States of Mylan's Product until the expiration of the '720 Patent.

6. A judgment declaring that Mylan's claims of invalidity are dismissed with prejudice.

For the foregoing reasons, Mylan's Motion for Judgment on Partial Findings (Doc. 478) is DENIED. A Final Judgment in favor of Shire will issue by separate Order.

DONE AND ORDERED in Tampa, Florida on January 27, 2017.

Charlene Edwards Honeywell

Charlene Edwards Honeywell
United States District Judge

Copies to:
Counsel of Record and Unrepresented Parties, if any