UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO. 12-60862-CIV-MIDDLEBROOKS/BRANNON

SHIRE DEVELOPMENT LLC,
SHIRE PHARMACEUTICAL
DEVELOPMENT INC.,
COSMO TECHNOLOGIES LIMITED and
GIULIANI INTERNATIONAL LIMITED,

Plaintiffs,

v.

WATSON PHARMACEUTICALS, INC.,
WATSON LABORATORIES, INC. –
FLORIDA, WATSON PHARMA, INC., and
WATSON LABORATORIES, INC.,

Defendants.
_____/

OPINION AND ORDER

THIS CAUSE comes before the Court upon the Federal Circuit's Mandate issued September 1, 2015, which remanded this case for further proceedings in accordance with the Federal Circuit Opinion. (DE 305). Plaintiffs[1] (collectively, "Plaintiffs" or "Shire") assert that Defendants[2] (collectively, "Defendants" or "Watson") infringe claims 1 and 3 of United States Patent 6,773,720 (the "'720 Patent"). I held a bench trial on the remaining issues for disposition

[1] Shire Development LLC, Shire Pharmaceutical Development Inc., Cosmo Technologies Limited, and Nogra Pharma Limited (f/k/a Giuliani International Limited).
[2] Watson Pharmaceuticals, Inc. (n/k/a Actavis, Inc.) ("Watson Pharmaceuticals"), Watson Laboratories, Inc. – FL (n/k/a Actavis Laboratories FL, Inc.) ("Watson Florida"), Watson Pharma, Inc. (n/k/a Actavis Pharma, Inc.) ("Watson Pharma"), and Watson Laboratories, Inc. ("Watson Laboratories") (collectively, "Watson").

from January 25 through January 27, 2016, with closing arguments held on March 23, 2016. Based on the evidence presented, I make the following finds of fact and conclusions of law.[3]

I. Procedural Background

'720 Patent. The '720 Patent is listed in the FDA's publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the "Orange Book") as covering Lialda®. Shire Development is the owner of New Drug Application ("NDA") No. 22000, and is FDA-approved for the manufacture and sale of mesalamine delayed-release tablets containing 1.2 g mesalamine, which are commercialized under the tradename Lialda®. Lialda® is indicated for the induction of remission in adults with active, mild-to-moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.

Complaint. On May 8, 2012, Plaintiffs filed this action for infringement of the '720 Patent against Defendants under the Hatch-Waxman Act (the "Hatch-Waxman Act" or the "Act"), 35 U.S.C. § 271.

The Hatch-Waxman Act permits a generic drug manufacturer to obtain approval to market a generic version of a previously approved pharmaceutical product without conducting expensive and time-consuming tests to establish the safety and effectiveness of that product. In place of these safety and efficacy tests, the generic manufacturer must submit an Abbreviated New Drug Application ("ANDA") to the Federal Drug Administration ("FDA") and demonstrate that its product is bioequivalent to the branded product. 21 U.S.C. § 355(j)(2)(A)(iv). The Hatch-Waxman Act requires that an ANDA applicant submit a "Paragraph IV" certification in its ANDA, certifying that the product it seeks FDA approval to market will not infringe any valid

[3] To the extent that any findings of fact constitute conclusions of law, they are hereby adopted as such; to the extent that any conclusions of law constitute findings of fact, they are also so adopted.

U.S. patent. *Id.* § 355(j)(2)(A)(vii)(IV). The Act also requires that an ANDA applicant submit a detailed notice to the patent owner, known as a "Paragraph IV notice," explaining the factual and legal basis for the opinion that the patent is invalid or that the generic product will not infringe the patent. *Id.* § 355(j)(2)(B); *see also* 21 C.F.R. § 314.95(c)(6). The patent owner may file a suit for patent infringement within forty-five days of receipt of a Paragraph IV notice. If the owner files suit, then the FDA may not approve the ANDA for thirty months or until a United States court finds for the defendant based on non-infringement, patent invalidity, or patent unenforceability. *Id.* § 355(j)(5)(B)(iii).

Defendant Watson Florida submitted Watson's ANDA number 203817 ("ANDA Product") to the FDA seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of Watson's ANDA Product. Watson's ANDA Product is a generic mesalamine delayed-release tablet and contains 1.2 g mesalamine as the active ingredient.

Watson's ANDA included a "Paragraph IV" certification seeking FDA approval before the expiration of the '720 Patent. On March 26, 2012, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv), Watson sent the Paragraph IV certification to Cosmo Technologies Limited, Young & Thompson, Shire US Inc., and "Shire." Watson's notice indicates that Watson Florida seeks FDA approval to market Watson's ANDA Product before the '720 Patent expires.

Plaintiffs filed their Complaint against Defendants on May 8, 2012, within forty-five days of receipt of the Paragraph IV notice letters, and filed an Amended Complaint (DE 43) on August 3, 2012. Plaintiffs allege infringement of one or more claims of the '720 Patent against all Defendants (Count I), and induced and/or contributory infringement of the '720 Patent by Watson Pharmaceuticals (now Actavis) (Count II). With regard to Count II, Plaintiffs allege that Watson Pharmaceuticals knowingly induced Watson Pharma, Watson Laboratories, and/or

Watson Florida to infringe and/or contributed to Watson Pharma's, Watson Laboratories', and/or Watson Florida's infringement of the '720 Patent. They also allege that Watson Pharmaceuticals actively induced, encouraged, aided, or abetted Watson Pharma's, Watson Laboratories', and/or Watson Florida's preparation, submission, and filing of Watson's ANDA with a Paragraph IV certification to the '720 Patent. Plaintiffs assert that these acts constitute infringement under 35 U.S.C. § 271.

On August 23, 2012, Defendants filed their Answer. (DE 52). Within the Answer, Watson Florida asserts two counterclaims for declaratory relief: (1) a declaration that their ANDA Product would not infringe any claim of the '720 Patent, (*see* DE 52 at 15-16); and (2) a declaration that the '720 Patent and its claims are invalid under 35 U.S.C. § 112, for lack of written description and lack of enablement, to the extent the claims are alleged to cover any products set forth in the Watson ANDA. (*See* DE 52 at 16-17).

Claims at Issue. Plaintiffs are asserting infringement of only claims 1 and 3 of the '720 Patent. Claim 1 is the '720 Patent's only independent claim, and provides:

> 1. 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-, di- or triglycerids, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the 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.

'720 Patent at col.6 11.7-30.

Claim 3, which is dependent on claim 1, recites: "Compositions as claimed in claim 1, in the form of tablets, capsules, mintablets." (*Id.*).[4]

2013 Markman Hearing and Trial. At the request of the Parties, and following claim construction briefing and a *Markman* hearing on December 20, 2012, I issued an Order dated January 16, 2013 (DE 147), construing certain disputed claims of the '720 Patent.

I held a non-jury trial from April 8 through April 12, 2013, with closing arguments conducted on April 26, 2013 ("2013 Trial"). Following the 2013 Trial, I entered an Opinion and Order (DE 246, "2013 Order"), finding that Watson's ANDA Product infringed claims 1 and 3 of the '720 Patent. Specifically, I found that Watson's ANDA Product met the limitations of the claims that were at issue. I further found that the claims were not invalid under 35 U.S.C. § 112 for lack of a written description or enablement. I held that Shire was entitled to injunctive relief.

Federal Circuit Appeal. Following the 2013 Order, Watson appealed to the United States Federal Circuit. On appeal, Watson challenged the 2013 constructions of the claim terms "inner lipophilic matrix" and "outer hydrophilic matrix," and, thus, my subsequent infringement finding. Watson did not otherwise challenge the 2013 claim construction Order or appeal any of the other factual findings supporting the infringement determination in the 2013 Order.

[4] Because claim 3 is dependent on claim 1, it necessarily contains all of the limitations of claim 1. Thus, Watson's ANDA Product can only infringe claim 3 if it infringes claim 1. Said differently, if Watson's ANDA Product does not infringe claim 1, it cannot infringe claim 3.

On March 28, 2014, the Federal Circuit issued an opinion, affirming my construction of the term "matrix," but reversing my construction of "inner lipophilic matrix" and "outer hydrophilic matrix." *Shire Dev. LLP v. Watson Pharms. Inc.*, 746 F.3d 1326 (Fed. Cir. 2014) [hereinafter *Watson I*].

Shire appealed the Federal Circuit's Order in *Watson I* to the U.S. Supreme Court, arguing that the Federal Circuit did not give proper deference to my factual findings underlying claim construction. Petition for a Writ of Certiorari, *Shire Dev., LLC, v. Watson Pharms., Inc.*, 135 S. Ct. 1174 (2015) (No. 14-206). The Supreme Court granted Shire's petition for certiorari, vacated *Watson I*, and remanded for proceedings consistent with *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831 (2015). *Shire Dev., LLC v. Watson Pharms., Inc.*, 135 S. Ct. 1174 (2015).

The parties engaged in supplemental briefing on remand to the Federal Circuit, and the Federal Circuit re-issued its opinion on June 3, 2015. *Shire Dev., LLC v. Watson Pharms., Inc.*, 787 F.3d 1359 (Fed. Cir. 2015) [hereinafter *Watson II*]. In *Watson II*, the Federal Circuit held *Watson I* did not implicate factual findings to which it owed deference under *Teva*. The Federal Circuit then reaffirmed its reversal of my construction of "inner lipophilic matrix" and "outer hydrophilic matrix," as well as the reversal of the associated infringement finding.

2016 Trial. I held a bench trial on January 25 through January 27, 2016, to adjudicate the remaining issue—whether the accused Watson tablet[5] infringes the claimed "inner lipophilic matrix" and "outer hydrophilic matrix" limitations of the asserted claims, when those terms are construed in accordance with the Federal Circuit's Mandate.

[5] The formulation for which Watson currently seeks FDA approval remains the same as the formulation from the 2013 Trial. *See* 2016 Trial Tr. Day 1 at 200:20-24, Sinko Direct.

II. Law of Infringement

Pursuant to 35 U.S.C. § 271(e)(2), 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.

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

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Additionally, 35 U.S.C. § 271(c) provides for 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).

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). It is well established that 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."[6] *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000) (citing *Insituform Techs., Inc. v. Car Contracting, Inc.*, 161 F.3d 668, 692 (Fed. Cir. 1998)).

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. *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 449 F. App'x 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).

[6] Shire originally argued that Watson's ANDA Product infringed literally and under the doctrine of equivalents. However, Shire orally waived its doctrine of equivalents argument the morning of the 2016 Bench Trial. Accordingly, I will only consider whether Watson's ANDA product literally infringes the '720 Patent.

III. Claim Construction in light of the Federal Circuit Mandate

a. Prior Constructions

Following the *Markman* Hearing, in my January 16, 2013 Order (DE 147), I construed the following terms:[7]

Claim Term	2013 Construction
"inner lipophilic matrix"	a matrix including at least one lipophilic excipient, where the matrix is located within one or more other substances
"outer hydrophilic matrix"	a matrix of at least one hydrophilic excipient, where the matrix is located outside the inner lipophilic matrix

Applying these constructions, I found that Watson's ANDA Product contained both an inner lipophilic matrix and outer hydrophilic matrix. Defendant Watson appealed my construction of these terms, and the Federal Circuit reversed my constructions. *See Watson II*, 737 F.3d at 1365.

b. Federal Circuit Mandate

The Federal Circuit upheld my construction of "matrix" as "a macroscopically homogenous structure in all its volume." *Watson II*, 787 F.3d at 1365. With respect to the claim constructions of "inner lipophilic matrix" and "outer hydrophilic matrix," the Parties disagree about what the Federal Circuit held.

For the reasons discussed below, I find that the Federal Circuit held that: (1) each matrix must exhibit "lipophilic" or "hydrophilic" properties, respectively, and (2) the matrices must be "separate" from each other. *Id.* at 1365-68.

[7] I construed additional disputed and agreed upon claim terms in the claim construction Order (DE 147), which were not disturbed on appeal. Accordingly, I incorporate the definition and discussion of those terms by reference. *See* 2013 Order at 5-6.

c. The Lipophilic Matrix Must Exhibit Lipophilic Characteristics and the Hydrophilic Matrix Must Exhibit Hydrophilic Characteristics

The Federal Circuit held that the inner matrix must exhibit lipophilic characteristics and the outer matrix must exhibit hydrophilic characteristics. *Watson II*, 787 F.3d at 1365-66 (Section III.A of the opinion). Specifically, the Federal Circuit held that the adjective "lipophilic" means that "the matrix—not just an excipient within the matrix—must exhibit the stipulated-to lipophilic properties." *Id.* The Federal Circuit explained that "the '720 patent teaches that this occurs when 'the main component of the matrix structure' is lipophilic." *Id.* (citing PTX001 at 1:17-18).

For the meaning of "lipophilic characteristics," the Federal Circuit looked to the patent specification. *See Watson II*, 787 F.3d at 1365. Specifically, the Federal Circuit cited to the passage describing lipophilic characteristics as providing "some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids." *Id.* at 1367 (referring to '720 Patent at col.1 ll. 17-20). The Federal Circuit also observed that the Parties stipulated that "lipophilic" means "poor affinity towards aqueous fluids." *See Watson II*, 787 F.3d at 1365.

The intrinsic record also provides insight into the meaning of "hydrophilic characteristics," even though the Federal Circuit does not provide express guidance as it does for "lipophilic characteristics." For example, the '720 Patent's specification describes "high resistance to the progress of the solvent" caused by the presence of "strongly hydrophilic groups" that "remarkably increases viscosity inside the hydrated layer." ('720 Patent at col.1 ll.22-26). In another passage, the '720 Patent describes hydrophilic characteristics as the formation of "a high viscosity swollen layer." (*Id.* at col.2 ll.60-64). Furthermore, the specification states that the substances that constitute the hydrophilic matrix are known as "hydrogels." (*Id.* at col.3 ll.18-23; *see also id.* at col.3 l.57-col.4 l.5) (describing the dissolution characteristics of the outer

hydrophilic matrix)). Additionally, the Parties have stipulated that "hydrophilic" means "having an affinity to water." (2013 Order at 6).

d. The Lipophilic and Hydrophilic Matrices Must Be Separate

The Federal Circuit also held that the inner lipophilic matrix and the outer hydrophilic matrix must be "separate." *Watson II*, 787 F.3d at 1366-68. The Federal Circuit held that "[t]he prosecution history, the structure of the claim itself, the ordinary meaning of the claim terms, including the Markush group limitations, and the patent's description of the invention compel a claim construction which requires that the inner lipophilic matrix is *separate* from the outer hydrophilic matrix." *Id.* at 1366 (emphasis added).

The ordinary meaning of the claim terms provides one basis for the Federal Circuit's holding of separate matrices. *Watson II*, 787 F.3d at 1366-67. For example, the Federal Circuit observed that the individual words "inner" and "outer" define "mutually exclusive spatial characteristics," and the words "lipophilic" and "hydrophilic" define "mutually exclusive compositional characteristics." *Id.* at 1366. Under the Federal Circuit's reasoning, "*one* matrix cannot be both inner and outer in a relation to a second matrix. Nor can *one* matrix be both hydrophilic and lipophilic." *Id.* at 1367 (emphasis added). Consequently, a single structure may not serve as both a lipophilic matrix and a hydrophilic matrix. *See id.* at 1366-67. Thus, the Federal Circuit concluded that the ordinary meaning of the claim terms requires "the inner volume to be separate from the outer volume." *Id.*

The Federal Circuit further concluded that the "lack of overlap" between the two Markush groups[8] in the claim "supports the requirement that the *volumes* be separate." *Watson II*, 787 F.3d at 1367 (emphasis added).

In addition, the Federal Circuit found that the description of the invention in the specification also provides support for its holding that the matrices be separate. *Watson II*, 787 F.3d at 1367. The Federal Circuit explained that the examples in the '720 Patent describe "discrete lipophilic matrix granules" compressed with the hydrophilic matrix. *Id.* Thus, the "discrete" granules are one example of an inner volume that is spatially separate from an outer volume (*i.e.*, the extragranular space). *Id.* at 1367.

The Federal Circuit also explained that the specification describes separate compositional characteristics. *Watson II*, 787 F.3d at 1367. For an illustration of "compositional" lipophilic characteristics, the Federal Circuit cited the specification, which describes "some resistance to the penetration of solvent due to the poor affinity towards aqueous fluids." *Id.* Additionally, as described above, the specification describes compositional hydrophilic characteristics as "remarkably increase[d] viscosity inside the hydrated layer" or "a high viscosity swollen layer."' ('720 Patent at col.1 ll.21-26; *id.* at col.2 l.61). Therefore, the Federal Circuit's statement that the inner lipophilic matrix "cannot have hydrophilic properties" means that it cannot exhibit the characteristics described in the patent as "hydrophilic." *Watson II*, 787 F.3d at 1367.

In addition, the Federal Circuit explained that claim constructions that could encompass a single matrix structure of lipophilic and hydrophilic excipients would be too broad. *Watson II*, 787 F.3d at 1367-68. The Federal Circuit observed that "any arbitrarily selected volume in a

[8] "A Markush group lists specified alternatives in a patent claim, typically in the form: a member selected from the group consisting of A, B, and C." *Watson II*, 787 F.3d at 1363 n.3 (citing *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005)).

single mixed matrix would satisfy the district court's construction of 'inner lipophilic matrix' because that volume would necessarily contain 'at least one lipophilic excipient' and it would be 'inside' the surrounding volume." *Id.* at 1367. Again, the Federal Circuit reasoned that a *single* structure cannot serve as both a lipophilic matrix and a hydrophilic matrix. *Id.* The Federal Circuit concluded that the claims "require *two* matrices with a defined spatial relationship." *Id.* at 1368 (emphasis added).

e. Construction of "inner lipophilic matrix" and "outer hydrophilic matrix" on Remand

Governed by the Federal Circuit's Mandate on remand, I face a limited task. On remand, I must follow the Federal Circuit's Mandate as the law of the case. *Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 576 F.3d 1348, 1356 (Fed. Cir. 2009) ("The mandate rule requires that the district court follow an appellate decree as the law of the case."). Here, the Federal Circuit's Mandate states:

> [W]e reverse the district court's constructions of 'inner lipophilic matrix' and 'outer hydrophilic matrix,' and its subsequent infringement determination, and we remand for proceedings consistent with this opinion.

Watson II at 1368. Thus, the "proceedings" described by the Mandate require me to determine whether the Watson product contains an "inner lipophilic matrix" and an "outer hydrophilic matrix," consistent with the Federal Circuit's Opinion.

At the 2016 Trial, Shire argued that the proper construction of "inner lipophilic matrix" and "outer hydrophilic matrix" are apparent from the Federal Circuit's Opinion. Specifically, Shire contends that the Federal Circuit simply imposed two additional requirements on the previous constructions of "inner lipophilic matrix" and "outer hydrophilic matrix": the two

matrices must exhibit their respective lipophilic or hydrophilic characteristics, and the two matrices must be separate. (2016 Trial Tr. Day 1 at 12:7-20, Shire Opening).

In contrast, Watson urges me to adopt an entirely new construction of "inner lipophilic matrix" and "outer hydrophilic matrix." Watson argues that "lipophilic matrix" means a "dispersion of an active ingredient within a continuous phase of water insoluble material which forms a lipophilic structure with an active ingredient packed into the interstices of that structure." (2016 Trial Tr. Day 1 at 51:3-6, Watson Opening). Similarly, Watson argues that "hydrophilic matrix" means a "dispersion of active ingredient and a sufficiently large amount of swelling hydrophilic materials known as hydrogels, which, upon coming into contact with liquid swell to form and maintain a gel layer around the dosage form." (*Id.* at 53:10-14, Watson Opening). Watson contends that these two constructions are consistent with the ordinary and customary meaning of "lipophilic matrix" and "hydrophilic matrix," and that these constructions are consistent with the Federal Circuit's requirements. (*Id.* at 52:3-7, Watson Opening).

I am not convinced by Watson's argument that the newly-proposed constructions should be adopted. For starters, Watson did not argue on appeal that the 2013 constructions were incorrect due to their failure to account for the plain meaning set forth in its new constructions. Additionally, Watson's constructions are different than it proposed to the Federal Circuit on appeal. (Br. of Defs.-Appellants at 35). On appeal, Watson argued that the inner lipophilic matrix should be construed as "a lipophilic matrix that is separate and distinct from, and contained within, an outer hydrophilic matrix." (Br. of Defs.-Appellants at 35). Similarly, Watson argued that the outer hydrophilic matrix should be construed as "a hydrophilic matrix that is separate and distinct from, and external to, an inner lipophilic matrix." (*Id.*).

Notably, Watson's construction of these terms on appeal align—for the most part— with Shire's proposed constructions on remand; namely, that "the respective matrices themselves need to be 'lipophilic' (*i.e.* have a 'poor affinity towards aqueous fluids') or 'hydrophilic,' (*i.e.* have an 'affinity to water')." (*Id.* at 43).

I find that the Federal Circuit's treatment of the proper constructions of these terms forecloses any new constructions. *See Engel Industries, Inc. v. Lockformer Co.*, 166 F.3d 1379 (Fed. Cir. 1999) ("An issue that falls within the scope of the judgment appealed from but is not raised by the appellant in its opening brief is necessarily waived. Unless remanded by this court, all issues within the scope of the appealed judgment are deemed incorporated within the mandate and thus are precluded from further adjudication."). Here, the remand was narrow, and for the purpose of determining whether Watson's ANDA Product meets the Federal Circuit's requirements that: (1) the inner lipophilic matrix must exhibit lipophilic characteristics, (2) the outer hydrophilic matrix must exhibit hydrophilic characteristics, and (3) the matrices must be separate.

Accordingly, "inner lipophilic matrix" and "outer hydrophilic matrix" are construed as follows:

Claim Term	**2016 Construction on Remand**
"inner lipophilic matrix"	a matrix including at least one lipophilic excipient, where the matrix exhibits lipophilic characteristics and is located within, and separate from, the outer hydrophilic matrix
"outer hydrophilic matrix"	a matrix of at least one hydrophilic excipient, where the matrix exhibits hydrophilic characteristics and is located outside of, and separate from, the inner lipophilic matrix.

On remand, I must determine whether Watson's product satisfies these additional limitations.

IV. Infringement Analysis

Having determined the proper construction of "inner lipophilic matrix" and "outer hydrophilic matrix," I must now determine, as a matter of fact, whether Shire has proven that Watson's product has an "inner lipophilic matrix" and "outer hydrophilic matrix" when properly construed.

In determining whether Watson's ANDA Product contains an "inner lipophilic matrix" and "outer hydrophilic matrix," as Shire argues, I must consider whether the ANDA Product has: (1) two separate matrices; (2) an inner lipophilic matrix that exhibits lipophilic characteristics; and (3) an outer hydrophilic matrix that exhibits hydrophilic characteristics.

a. Undisturbed Findings of Fact

Claim 1 requires a "[c]ontrolled-release oral pharmaceutical composition[] containing as an active ingredient 5-amino-salicylic acid." ('720 Patent at col.6 ll.7-8). Claim 1 also requires active ingredient "in an amount of 80 to 95%." (*Id.* at col.6 ll.27-28). Watson does not dispute that its ANDA Product is a controlled-release oral pharmaceutical composition in the form of a tablet (2013 Order at 13-15), which contains 5-amino-salicylic acid as an active ingredient (*Id.* at 12 n.12), in an amount of 80-95% by weight of the total composition. (DE 325-1, Joint Pretrial Stip., at ¶ 29).

Additionally, I made the following undisturbed findings in my 2013 Order (DE 246) that are relevant to my consideration of whether Watson's ANDA Product contains an "inner lipophilic matrix" and "outer hydrophilic matrix" as those terms are now defined:[9]

1. Magnesium stearate in the granules forms a macroscopically homogeneous structure in all of its volume. (*Id.* at 16).

2. Sodium starch glycolate in the extragranular volume forms a macroscopically homogenous structure in all its volume. (*Id.* at 23).

3. Active ingredient mesalamine is dispersed in both the "inner lipophilic matrix" and "outer hydrophilic matrix" of Watson's ANDA Product. (*Id.* at 24-26).

4. The magnesium stearate located in the granules of the Watson ANDA Product slows the release of mesalamine. (*Id.* at 22).

5. The sodium starch glycolate located in the extragranular space will affect the release of mesalamine. (*Id.* at 18 n.25).

b. Inner Lipophilic Matrix and Outer Hydrophilic Matrix are Separate

As discussed above, the Federal Circuit held that the constructions of "inner lipophilic matrix" and "outer hydrophilic matrix" require separate matrices. *Watson II*, 787 F.3d at 1366. The Federal Circuit explained that "the matrices are defined by mutually exclusive spatial characteristics—one inner, and one outer—and mutually exclusive compositional characteristics—one hydrophilic, one lipophilic." *Id.* at 1366. The Federal Circuit described "spatial characteristics" in terms of different volumes. *Id.* at 1367 ("the construction of 'inner lipophilic matrix' requires the inner volume to be separate from the outer volume."); *see also id.* (the Markush group "supports the requirement that the volumes be separate"). The Federal Circuit described "compositional characteristics" in terms of the characteristics of the matrices

[9] Additional relevant findings of fact to the infringement determination were made in the 2013 Order, and remain the law of the case. (2013 Order).

described by the patent. *See also id.* ("[t]he specification explains that a lipophilic matrix 'opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids'").

For the reasons discussed below, the Watson ANDA Product contains a spatially and compositionally separate inner lipophilic matrix and outer hydrophilic matrix.

i. Spatially Separate

I previously found that Watson's ANDA Product contains two volumes: (1) granules, and (2) the space outside of the granules (the "extragranular space"). (2013 Order at 16-17, 18 at n.25, 23). I based this finding on evidence from Dr. Bugay, who conducted Scanning Electron Microscopy ("SEM") and Energy Dispersive X-Radiation ("EDX") analysis on the uncoated, core tablets used in Watson's ANDA Product. (*Id.* at 16; PTX 42, SEM-EDX Images). I also considered Watson's manufacturing process, which results in compressed tablets made up of granular and extragranular regions. (2013 Order at 11-12).

At the 2016 Trial, Dr. Steven Little testified that Dr. Bugay's images depicted inner and outer volumes that were spatially separate: "You can see discrete regions that are granules here that are different than and separate from the extragranular space . . . so they are spatially separate." (2016 Trial Tr. Day 1 at 73:5-9; *see also id.* 72:21-73:9, 83:6-14, Little Direct). Similarly, Dr. Patrick Sinko testified that the images show the granules and extragranular space "are spatially separate, so they are physically separate . . . ." (*Id.* at 230:8-9, Sinko Direct). Additionally, Watson's expert, Dr. Park, acknowledged that Watsons's ANDA Product was divided into granular and extragranular volumes. (2016 Trial Tr. Day 2 at 283:25-239:18, Park Cross).

Additionally, Shire presented evidence from Dr. Yang that further shows Watson's ANDA Product contains two separate volumes. (2016 Trial Tr. Day 1 at 152:7-20). Dr. Yang microtomed[10] a Watson ANDA tablet, and examined the cross-sectioned surface with an optical microscope. Dr. Yang observed two spatially separate structures, which he identified as "Type 1" and "Type 2." "Type 1" structures were generally oval or circular in shape and had a darker coloring. "Type 2" structures were generally between the "Type 1" structures and were irregularly shaped with lighter coloring. (*Id.* at 144:9-15; 147:25-148:21). Dr. Sinko later testified that the "Type 1" and "Type 2" structures were the "granular" and "extra-granular" regions, respectively. *See id.* at 217:10-218:16 ("[Dr. Yang] called them type one and type two . . . I typically refer[] to them [as] granular and extra-granular. But basically, it is the same thing.").

Accordingly, Shire's proposed inner lipophilic and outer hydrophilic matrices are defined by mutually exclusive spatial characteristics, as the volume making up the inner lipophilic matrix—the interior of the granules—is spatially separate from the volume making up the outer hydrophilic matrix—the extragranular space.

ii. Exhibit Separate Characteristics

I must next consider whether the spatially separate volumes—the inner granules and the extragranular space—exhibit separate characteristics. Evidence presented at trial shows that the separate inner and outer volumes contain different distributions of excipients that result in separate characteristics. This separate distribution of excipients accounts for the separate characteristics (*i.e.* lipophilic and hydrophilic) exhibited by each of the matrices.

[10] A microtome is an advanced cutting instrument, which Dr. Yang used to obtain a very smooth surface, upon which he conducted a drop penetration test. (2016 Trial Tr. Day 1 at 144:2-8, Yang Direct).

I previously found the hydrophilic sodium starch glycolate exists in clusters or aggregates, indicating higher concentration, in the extragranular spaces of Watson's ANDA tablet, as compared to the granular spaces. (2013 Order at 23). Additionally, based on Dr. Bugay's SEM/EDX images, Dr. Sinko testified that there are no aggregates of sodium starch glycolate inside the granule. (2016 Trial Tr. Day 2 at 75:18-76:1, Sinko Redirect). Dr. Sinko testified that sodium starch glycolate is more "potent than the mag stearate outside" and that "it's separate because it overwhelms the behavior of the mag stearate." (2016 Trial Tr. Day 1 at 224:3-21, Sinko Direct).

As I previously found, the magnesium stearate would impact release in the granules, but not in the extragranular space. (2013 Order at 18 n. 25). Further, I found that, while the sodium starch glycolate outside of the granules would affect release of mesalamine, the sodium starch glycolate within the granules would not affect the release. (*Id.*). This differential in the distribution of excipients results in two separate volumes that exhibit separate characteristics: the granules exhibit lipophilic characteristics whereas the extragranular regions exhibit hydrophilic characteristics. (*Id.* at 72:16-73:24, Little Direct; *id.* at 228:20-230:16, Sinko Direct).

Additionally, Dr. Little testified at the 2016 Trial that he observed two volumes that exhibit two separate characteristics during his dissolution studies of the Watson ANDA Product.[11] First, the outer regions of the Watson ANDA tablet began to swell, erode, and disintegrate. (2016 Trial Tr. Day 1 at 82:20-83:14, Little Direct). As this occurred, intact granules were released. (*Id.*). Dr. Little explained that the swelling, erosion, and disintegrating behavior of the extragranular regions is due to the outer hydrophilic matrix of sodium starch glycolate. (*Id.* at 82:10-15). In contrast, the granules that were released throughout the

[11] I addressed Dr. Little's experimental method in my 2013 Order, and those findings were undisturbed on appeal. (DE 246 at 14-15).

dissolution observation did not swell, but instead persisted in the buffer. Dr. Little explained that the persistence of the granules is due to the magnesium stearate within the inner volume of the granules. (*Id.* at 86:16-87:20). Dr. Little testified that "the two different behaviors that we see are different, they are separate. So you see a hydrophilic behavior, and then what is inside is you see these granules that are exhibiting lipophilic behavior." (*Id.* at 82:20-85:11).

Dr. Yang also presented experimental evidence of two volumes exhibiting compositionally separate matrices. Dr. Yang performed a water penetration test to assess whether the Watson ANDA Product contained separate volumes that exhibit different capacities to resist the penetration of water. (*Id.* at 140:14-141:12, Yang Direct). A drop penetration test is a routine test used to study the interactions between solid and liquid. (*Id.* at 141:6-12, Yang Direct; *see also* 2016 Trial Tr. Day 1 at 218:17-21, Sinko Direct (drop penetration test is a standard characterization tool recognized by pharmaceutical industry)).

As described above, Dr. Yang microtomed a tablet, within which he identified ten "Type 1" and ten "Type 2" locations. (2016 Trial Tr. Day 1 at 147:25-149:19, Yang Direct). Then, Dr. Yang used a microgoniometer to place picoliter-sized drops of distilled water on each type of structure. (*Id.* at 150:11-152:2, 161:6-7). The microgoniometer measured the penetration rate of the drops deposited on the "Type 1" and "Type 2" regions. (*Id.* at 155:10-156:4). On average, the "Type 1" granules exhibited a water penetration rate that was *6.8-times slower* than the "Type 2" extragranular regions. (*Id.* at 152:4-154:15; PTX 512 at 8). Thus, Dr. Yang's experimental data also shows that the "Type 1" and "Type 2" structures exhibit separate compositional characteristics regarding affinity for water.

Accordingly, I find that the inner volume of the granules and the extragranular volume—which make up the volume of Shire's proposed "inner lipophilic matrix" and "outer hydrophilic matrix," respectively—exhibit compositionally separate characteristics.

c. Inner Lipophilic Matrix Exhibits Lipophilic Characteristics

I must next determine whether the Watson ANDA Product contains an inner lipophilic matrix that exhibits lipophilic characteristics. As described above, the Federal Circuit explained that the '720 Patent described "lipophilic properties" as "some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids." ('720 Patent at col.1 ll.17-20; *Watson II*, 787 F.3d at 1365). Additionally, the Parties stipulate to a construction of "lipophilic" that means "having a poor affinity toward aqueous fluids." (2013 Order at 6). The '720 Patent also describes that the inner lipophilic matrix slows the release of mesalamine. ('720 Patent col.4 l.1-5). The inquiry, therefore, is whether the inner volume of the granules—which is the volume that meets the "separate" requirement—exhibits these lipophilic characteristics.

My undisturbed findings of fact support that the distribution of magnesium stearate in the volume of the granules exerts resistance to the penetration of solvent. First, it is undisputed that magnesium stearate is a lipophilic substance. (2013 Order at 12 n.9, 16 n.19). Additionally, I previously found that "magnesium stearate located in the granules will have an effect on the release of mesalamine." (*Id.* at 18 n.25; *see also id.* at 22 n.31). Furthermore, I found that the effect on release by magnesium stearate was linked to its lipophilic characteristics: "[magnesium stearate is] known to perform the function of slowing drug release by virtue of [its] lipophilic nature." (*Id.* at 22). In fact, the only way that magnesium stearate controls release is due to its lipophilic characteristics. (2016 Trial Tr. Day 1 at 215:19-216:5, Sinko Direct).

Furthermore, testimony showed that magnesium stearate may impart lipophilic characteristics to a composition even in low concentrations. Dr. Sinko testified that "very low concentrations [of magnesium stearate] have been known to have significant effects on tablet formulations." (*Id.* at 208:23-209:8). Dr. Sinko discussed scientific literature recognizing that fluid completely failed to penetrate a blend containing 5% magnesium stearate. (*Id.* at 209:12-22, 210:25-211:24). Dr. Sinko also discussed references where a concentration of 0.5% magnesium stearate would have "a pretty significant effect increasing that complete dissolution time by . . . eight, ten, plus fold." (*Id.* at 211:25-213:17). Defendant's expert Dr. Park also acknowledged that "being lipophilic is a reason that magnesium stearate may retard the release . . . ." (2016 Trial Tr. Day 2 at 197:22-25, Park Cross).

Additionally, Dr. Yang's experimental testing confirms that the granules exhibit a poor affinity for aqueous fluids. As described above, Dr. Yang found that the absorption rate of water was 6.8 times slower into the Type 1 structure (the granules) compared to the absorption rate of water into the Type 2 structure (the extragranular region). (2016 Trial Tr. Day 1 at 154:12-15, 155:12-18, 156:17-157:2, Yang Direct; *id.* at 214:8-14, 219:11-17, Sinko Direct).

Although magnesium stearate is present with other excipients inside of the granule—specifically, povidone, copovidone, and microcrystalline cellulose—those other excipients are not responsible for the lipophilic characteristics observed in the granules. During the first trial, Shire presented the testimony of Watson's expert Dr. Leo Trevino, who performed a dissolution test on Watson's milled granules. (2013 Order at 22 n.31; 2013 Trial Tr. Day 3 at 205:20-207:13, Sinko Direct). These granules contained mesalamine and the same excipients (povidone, copovidone, and microcrystalline cellulose) as the granules in the final compressed Watson ANDA Product. However, the granules Dr. Trevino tested lacked magnesium stearate and

sodium starch glycolate. (*Id.* at 10:7-11:3, Trevino Direct; *id.* at 206:6-207:4, Sinko Direct). In the absence of magnesium stearate and sodium starch glycolate, Dr. Trevino's test showed near-immediate release of mesalamine from the milled granules. (*Id.* at 207:5-13, Sinko Direct). Similarly, Dr. Little performed a dissolution experiment with pure mesalamine and observed that the mesalamine dissolved within seconds to minutes. (2016 Trial Tr. Day 1 at 84:18-22, 86:3-15, Little Direct; *see also* 2013 Order at 14-15). Given these results, Drs. Little and Sinko concluded that something in the Watson granules besides the intragranular excipients (povidone, copovidone, and microcrystalline cellulose) was slowing the release of the mesalamine. (2013 Order at 15; 2013 Trial Tr. Day 2 at 39:22-40:2, Little Cross; 2016 Trial Tr. Day 1 at 86:16-87:20, Little Direct; *id.* at 214:15-24, 216:19-217:9, Sinko Direct).[12]

Dr. Little's dissolution experiment—discussed above and in the 2013 Order—also provides evidence that the inner volume of the Watson ANDA Product exhibits resistance to the penetration of solvent. (2013 Order at 14-15; 2016 Trial Tr. Day 1 at 86:12-15, Little Direct). Dr. Little testified that the granules released from the Watson ANDA Product did not swell—thus, they did not exhibit hydrophilic characteristics—as they would if the sodium starch glycolate in the granules had any effect. (*Id.* at 82:23-83:14, 85:8-11, Little Direct; 2013 Order at 15 n.25). Rather, the granules resisted the penetration of the aqueous buffer and persisted for as long as 86 minutes. (2013 Order at at 15; 2016 Trial Tr. Day 1 at 84:13-17, 86:12-15, 87:16-20, Little Direct; *id.* at 214:15-24, 216:17-217:9, Sinko Direct). Based on the high solubility of mesalamine and Dr. Trevino's test showing that the other hydrophilic ingredients had no effect

[12] This evidence also supports that the other excipients, besides magnesium stearate, in the granules are functionally unrelated to the lipophilic matrix. This is discussed in more detail in Section IV. e.

on release, Dr. Little concluded that magnesium stearate is responsible for the granules' resistance to dissolution. (*Id.* at 83:15-19, 86:16-87:20, Little Direct).

In response to this evidence, Watson argues that there is not enough lipophilic substance in the inner volume of the granules to produce lipophilic characteristics. Watson relies on Dr. Park's testimony for support, who found that that the amount of magnesium stearate "is so small, you cannot exhibit lipophilic property based on such a small amount." (2016 Trial Tr. Day 2 at 157:17-21, Park Direct). However, Dr. Park did not cite any experiments or studies to confirm his opinion. Indeed, his opinion was contradicted by Shire's expert Dr. Sinko, who testified that "the primary issue is . . . the potency of the chemical." (2016 Trial Tr. Day 1 at 209:1-4, Sinko Direct). Dr. Sinko testified that it was well-known in the scientific literature that low levels of magnesium stearate could produce marked lipophilic effects. (*Id.* at 209:5-8, 209:12-211:24, 211:25-213:17, Sinko Direct; *see also id.* at 99:3-8, Little Cross (testifying that magnesium stearate "is one of the most lipophilic things I can imagine, so from a chemical structure standpoint, from how it resists penetration of water, it has been shown in .5 percent before to cause release inhibiting [e]ffects like that, resisting penetration of water . . .")). Additionally, such literature is consistent with the '720 Patent itself, which discloses granules containing only 2.4% lipophilic substances by weight. ('720 Patent, col. 5 ll. 30-45).

In a similar argument, Watson contends that the lipophilic or hydrophilic substance must constitute the "main component" of the respective lipophilic or hydrophilic matrix, and that "main component" should be understood quantitatively. (2016 Trial Tr. Day 1 at 42:21-23, Watson Opening; *see also* 2016 Trial Tr. Day 2 at 126:19-25, Park Direct). In support, Watson looks to a passage from the Federal Circuit citing the portion of the specification describing inert matrices where "the main component of the matrix structure" opposes some resistance to the

penetration of the solvent. *Watson II*, 787 F.3d at 1365-66 (citing '720 Patent, col. 1 ll.17-20). However, the Federal Circuit cited this passage to support its holding that the matrix exhibit lipophilic properties—not necessarily to support a holding that lipophilic substances must be present in a certain quantitative amount.

To the contrary, the Federal Circuit only held that the inner lipophilic matrix must exhibit lipophilic characteristics and be separate from the outer hydrophilic matrix. Defining the claims according to specific percentages of individual ingredients would contravene the Federal Circuit's emphasis on the characteristics of the matrices themselves, as opposed to the characteristics of the excipients. *See Watson II*, 787 F.3d at 1365-66 ("Thus, a 'lipophilic *matrix*' is more than just a matrix with at least one lipophilic *excipient*—the matrix itself must exhibit lipophilic characteristics.").

I find that magnesium stearate is the "main component" of the inner lipophilic matrix. According to both Drs. Sinko and Little, the "main component" is the structure responsible for the lipophilic or hydrophilic behavior. (2016 Trial Tr. Day 1 at 76:16-77:1, Little Direct; 2016 Trial Tr. Day 2 at 12:4-13, Sinko Cross). The quantity of a component alone is not a reliable indicator of the characteristics of the entire composition. (*See* 2016 Trial Tr. Day 2 at 12:9-13, Sinko Cross: "To say it quantitatively to me, I utterly disagree . . . I would say it has nothing to do strictly with quantity."). Both Dr. Sinkos and Little testified that some excipients, such as magnesium stearate, are "potent" in the sense that low quantities of individual components can lead to significant lipophilic characteristics. (2016 Trial Tr. Day 1 at 208:23-209:8, Sinko Direct; *id.* at 99:3-8, Little Cross). Thus, the "main component" of the inner lipophilic matrix—the magnesium stearate—exhibits the required lipophilic characteristics.

For the foregoing reasons, I find that the interior volume of the granules exhibits lipophilic characteristics and does not exhibit hydrophilic characteristics. This inner volume is separate from the outer volume. Accordingly, the Watson ANDA Product contains an inner lipophilic matrix—the volume within the granules—which exhibits lipophilic characteristics.

d. Outer Hydrophilic Matrix Exhibits Hydrophilic Characteristics

I must next determine whether the Watson ANDA Product also contains an outer hydrophilic matrix that exhibits hydrophilic characteristics. As described above, the specification describes "hydrophilic characteristics" such as "remarkably increase[d] viscosity inside the hydrated layer" or "a high viscosity swollen layer." ('720 Patent col.1 ll.21-26; *id.* at col.2 ll.60-64). Additionally, the Parties have stipulated that "hydrophilic" means "having an affinity to water." (2013 Order at 6). Here, the volume of the hydrophilic matrix—the extragranular space—displays the characteristics described by the '720 Patent. These characteristics are due to sodium starch glycolate's affinity towards aqueous fluids. (2016 Trial Tr. Day 1 at 75:12-77:7, 88:6-10, Little Direct; *id.* at 224:25-225:25, Sinko Direct).

Sodium starch glycolate has an affinity toward aqueous fluids and is recognized in the pharmaceutical industry as having dramatic swelling properties. (2016 Trial Tr. Day 2 at 172:22-173:6, Park Direct; *id.* at 224:16-22, 233:20-234:2, 245:8-17, Park Cross). Upon contact with aqueous fluids, sodium starch glycolate takes in water to swell, which further slows the penetration of the fluids into the composition. (2013 Order at 18 n.25; 2016 Trial Tr. Day 1 at 76:5-15, 77:18-78:13, 79:7-17, 81:3-83:14, Little Direct; *id.* at 225:20-25, 226:15-25, 227:23-228:19, Sinko Direct). In fact, sodium starch glycolate is known in the art as a "hydrogel," the class of hydrophilic compounds mentioned in the '720 Patent. (2016 Trial Tr. Day 2 at 191:8-16, 224:16-22, Park Cross).

The hydrophilic effect of sodium starch glycolate can be observed in the Watson ANDA tablet during dissolution. Based on Dr. Bugay's images, Dr. Sinko testified that the "vast majority" of sodium starch glycolate would exist outside of the granules, given its high molecular weight. (*Id* at 76:6-13, Sinko Redirect). In addition, Dr. Sinko testified that sodium starch glycolate occupied between 50-80% of the extragranular region. (*Id.* at 81:12-21).[13]

Dr. Little explained that during the first phases of dissolution, the Watson ANDA tablet swelled to the point that the coating was broken and eventually removed. (2016 Trial Tr. Day 1 at 81:3-82:9, Little Direct). Dr. Little observed a hydrated layer at 32 and 42 minutes that is indicative of the swelling that would be expected from a hydrophilic matrix of sodium starch glycolate. (*Id.* at 82:20-83:5). As the dissolution continued, the tablet's hydrated layer continued to swell, erode, disintegrate, and release granules—further evidence of a hydrophilic matrix. (*Id.* at 83:6-14, 83:23-84:7). Dr. Little testified at the 2013 Trial, and on remand, that this behavior—swelling upon contact with buffer, erosion of the hydrated layer, release of granular structures, and further disintegration of the hydrated layer—aligns with the '720 Patent's description of the behavior of the outer hydrophilic matrix. (2013 Trial Tr. Day 2 at 61:5-62:17, 63:5-12, Little Cross; 2016 Trial Tr. Day 1 at 75:12-76:15, 78:14-80:9, Little Direct).

For the foregoing reasons, I find that the extragranular volume exhibits hydrophilic characteristics and does not exhibit lipophilic characteristics. This outer volume is separate from the inner volume. Accordingly, the Watson ANDA Product contains an outer hydrophilic matrix—the extragranular volume—which exhibits hydrophilic characteristics.

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[13] For the reasons discussed above in reference to the inner lipophilic matrix, the sodium starch glycolate acts as the "main component" in the extragranular region.

e. The Markush Groups

Having found that Watson's ANDA Product contains an inner lipophilic and outer hydrophilic matrix, I find it necessary to address a particular argument made by Watson on remand. Watson contends that the Federal Circuit found that claim 1 excludes excipients from the inner volume of the granule (or, lipophilic matrix) that are not listed in the Markush group in claim 1(a), and that claim 1 similarly excludes excipients from the outer volume (or, hydrophilic matrix) that are not listed in in the Markush group in claim 1(b). Essentially, Watson contends that the Federal Circuit Opinion forecloses a finding of infringement when the volume of the inner lipophilic matrix contains one lipophilic substance and several hydrophilic substances. (2016 Trial Tr. Day 2 at 125:20-126:18, Park Direct; *see also* March 23, 2016 Closing Statement).

Watson presented this argument to the Federal Circuit, yet the Federal Circuit remanded the case—notwithstanding the presence of non-claim 1(a) excipients in the granule, and non-claim 1(b) excipients in the extragranular space.

The Federal Circuit's Mandate did not necessitate that hydrophilic excipients cannot be in the lipophilic matrix, or that lipophilic excipients cannot be in the hydrophilic matrix. The Federal Circuit's requirement is that the Markush group limitations compel a claim construction that requires that the inner lipophilic matrix is separate from, but does not necessarily require distinct excipients from, the outer hydrophilic matrix. *Watson II*, 787 F.3d at 1366. Indeed, the Federal Circuit contemplated that there could be situations where the matrices contain excipients outside of their respective Markush groups. *See* Watso*n II*, 787 F.3d 1359, 1368 ("Whether or not a composition infringes when there is a trace of hydrophilic molecules in the inner volume

because of the mixing step inherent in the manufacturing process, *for example*, is a question for the fact finder.") (emphasis added).

In terms of the composition of the granule, neither Shire nor Watson presented evidence as to the exact amount of magnesium stearate within the granule. Evidence was presented, however, that showed that within the inner volume of the granule, magnesium stearate could not exceed a theoretical maximum of 5%. (2016 Trial. Tr. Day 2 at 11:6-23, Sinko Cross). Additional evidence showed that the remaining excipients in the volume of the granule were hydrophilic substances. (*Id.* at 4-12, Sinko Cross). However, as discussed above, the magnesium stearate is the main component of the inner volume of the granules. The other hydrophilic excipients—including the sodium starch glycolate[14]—are unrelated to the function of the inner lipophilic matrix. (*See* 2016 Trial Tr. Day 1 at 70:1-4). The purpose of the inner lipophilic matrix is to contribute to the controlled release of the mesalamine. (2013 Order at p. 18, n.25). Drs. Sinko and Little reaffirmed at the 2016 Trial that the hydrophilic compounds in the granules do not affect the overall lipophilic character of that volume—they do not have an effect on the release of mesalamine from the granule. (2016 Trial Tr. Day 1 at 70:1-4).[15]

Watson contends that the purpose of the inclusion of magnesium stearate in the ANDA Product was as a lubricant. I previously found that magnesium stearate does act as a lubricant—however, I found that magnesium stearate only exhibited the characteristic of a lubricant when it

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[14] I previously found that sodium starch glycolate within the granules was irrelevant to the release of mesalamine in my 2013 Order. (2013 Order at 18, n. 25).

[15] Notably, in addition to the inner lipophilic and outer hydrophilic matrices provided in claim 1(a) and claim 1(b), claim 1(c) provides for "optionally other excipients." Neither of the Parties has briefed or argued about how I should construe claim 1(c). However, that claim 1 appears to allow "other excipients," tends to support that other excipients within the inner volume and outer volume, which are unrelated to the function of those volumes as inner lipophilic and outer hydrophilic matrices, would be permitted.

was in the extragranular space. (2013 Order at p. 18, n.25). I found that when magnesium stearate was located within the granule it affects the release of mesalmine. *Id.*

Additionally, Watson argues that the presence of magnesium stearate in the extragranular space means that the outer hydrophilic matrix (the extragranular volume) violates the claim 1(b) Markush group. However, the magnesium stearate in the extragranular space is overwhelmed by the hydrophilic properties of the sodium starch glycolate in the extragranular space. (2016 Trial Tr. Day 1 at 224:3-21, Sinko Direct (testifying that sodium starch glycolate is more "potent than the mag stearate outside")). The sodium starch glycolate is the main component of the extragranular volume, and I previously found that sodium starch glycolate in the extragranular space will affect the release of the mesalamine. (2013 Order at p. 18, n.25).

In short, the inner lipophilic matrix is comprised of the volume within the granules. The volume within the granules contains magnesium stearate, which falls within the claim 1(a) Markush group. The inner volume exhibits lipophilic characteristics. Other excipients, not within the claim 1(a) Markush group are present within the inner volume. However, these other excipients do not affect the lipophilic characteristic of the inner volume and, thus, are unrelated to the lipophilic matrix.

Similarly, the outer hydrophilic matrix is comprised of the volume outside of the granules, or, the extragranular space. The extragranular space contains sodium starch glycolate, which falls within the claim 1(b) Markush group. The extragranular space exhibits hydrophilic characteristics. Magnesium stearate, an excipient not within the claim 1(b) Markush group, is present within the extragranular space. However, the magnesium stearate does not affect the hydrophilic characteristic of the extragranular space and, thus, is unrelated to the hydrophilic matrix.

V. Conclusion

Based upon my findings set forth above, and my undisturbed findings from the 2013 Order, Plaintiffs have established, by a preponderance of evidence, that the Watson ANDA Product meets the additional requirements established by the Federal Circuit for the claim constructions of "inner lipophilic matrix" and "outer hydrophilic matrix." Thus, Defendants have infringed claims 1 and 3 of the '720 Patent.

Additionally, as I found in the 2013 Order, Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.) knowingly induced Watson Laboratories, Inc.—Florida, Watson Pharma, Inc., and/or Watson Laboratories, Inc. to infringe and/or contributed to Watson Laboratories, Inc.—Florida's, Watson Pharma, Inc.'s, and Watson Laboratories, Inc.'s infringement of '720 Patent, claims 1 and 3. (2013 Order at 30, n.42). Each of the Defendants induced or contributed to the construction of the Watson ANDA Product and the filing of ANDA No. 203817. *Id.*

Plaintiffs are, therefore, entitled to the requested injunctive relief. Final judgment shall issue by separate order.

DONE AND ORDERED in Chambers at West Palm Beach, this 25 day of March, 2016.

DONALD M. MIDDLEBROOKS
UNITED STATES DISTRICT JUDGE

Copies to: Counsel of Record