IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

APTALIS PHARMATECH, INC. AND IVAX INTERNATIONAL GMBH,	)	
Plaintiffs,	)	
v.	)	Civ. No. 14-1038-SLR
APOTEX INC. AND APOTEX CORP.,	)	
Defendants.	)	

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OPINION

Dated: December 8, 2016
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of Abbreviated New Drug Application ("ANDA") No. 206703 by defendants Apotex Inc. and Apotex Corp. (collectively "defendants") seeking to produce and market generic versions of AMRIX® ("AMRIX"). (D.I. 1) On August 11, 2014, plaintiffs Adare Pharmaceuticals, Inc. (formerly Aptalis Pharmatech, Inc.) and Ivax International GmbH (collectively "plaintiffs") brought this action alleging infringement of U.S. Patent Nos. 7,790,199 ("the '199 patent") and 7,829,121 ("the '121 patent").[1] (D.I. 1) Defendants answered the complaint and counterclaimed on September 12, 2014. Plaintiffs answered the counterclaims on October 6, 2014. (D.I. 10; D.I. 18) The court held a *Markman* hearing on May 27, 2015 and issued a claim construction order on June 18, 2015 construing one disputed limitation. (D.I. 81) The court held a final pretrial conference on October 29, 2015 and a two-day bench trial on November 16 and 17, 2015 on the issue of infringement.[2] The parties have since completed post-trial briefing. The 30-month stay of FDA final approval on Actavis's ANDA expires on December 30, 2016. (D.I. 101 at 6) The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

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[1] Both patents are listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book") for plaintiffs' extended release cyclobenzaprine hydrochloride product, AMRIX. (D.I. 1)

[2] The parties stipulated to limit the trial to this issue. (D.I. 19)

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Technology at Issue

1. The patents-in-suit

The '199 patent issued on September 7, 2010,[3] and the '121 patent issued on November 9, 2010,[4] both titled "Modified Release Dosage Forms of Skeletal Muscle Relaxants" (collectively, "the patents-in-suit"). The patents-in-suit share a common specification.[5] (JTX 1, 2) The background of the invention explains that "[m]uch effort has been devoted to developing matrix tablet based and multi-particulate capsule based drug delivery systems for oral application." (1:29-32; *see also* 1:53-59) The specification is directed to oral formulations of the skeletal muscle relaxant drug cyclobenzaprine hydrochloride ("cyclobenzaprine") having extended release coatings. More specifically, it discloses "a modified release, multi-particulate dosage form of a skeletal muscle relaxant comprising one or more bead populations which provides an extended release profile of the active under in vitro conditions closely mimicking the profile simulated from pharmaco-kinetic modeling." (3:58-63) "[T]he core particle may be formed by granulating and dry milling and/or by extrusion and spheronization of a pharmaceutical composition containing the active." (4:9-14; *see also* 5:21-30) Extended release "[b]eads can be produced by applying a functional membrane comprising a water insoluble polymer alone or in combination with a water soluble

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[3] The application leading to the '199 patent was filed on September 24, 2008, and is a continuation of parent U.S. Patent No. 7,387,793 ("the '793 patent").

[4] The application leading to the '121 patent was filed on September 24, 2008, and is a divisional of the '793 patent.

[5] All references are to the '199 patent unless otherwise indicated.

polymer onto [immediate release b]eads." (4:15-17) The extended release formulation "provides for therapeutically effective plasma profiles over an extended period of time." (4:24-26, *see also* 4:36-54, 4:58-5:9) The specification describes the manufacture:

> The active core of the dosage form of the present invention may be comprised of an inert particle or an acidic or alkaline buffer crystal, which is coated with a drug-containing film forming formulation and preferably a water-soluble film forming composition to form a water-soluble/dispersible particle. Alternatively, the active may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing the drug substance.

(5:17-24, *see also* 6:23-33, 6:54-56) "The membrane coatings can be applied to the core using any of the coating techniques commonly used in the pharmaceutical industry, but fluid bed coating is particularly useful." (7:11-13) Claim 1 of the '199 patent recites:

> A pharmaceutical dosage form comprising a population of extended release beads, wherein said extended release beads comprise:
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> an active-containing core particle comprising cyclobenzaprine hydrochloride as the active; and
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> **an extended release coating comprising a water insoluble polymer membrane surrounding said core**, wherein said water insoluble polymer membrane comprises a polymer selected from the group consisting of ethers of cellulose, esters of cellulose, cellulose acetate, ethyl cellulose, polyvinyl acetate, neutral copolymers based on ethyl acrylate and methyl methacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, pH-insensitive ammonia methacrylic acid copolymers, and mixtures thereof;
>
> wherein the total amount of cyclobenzaprine hydrochloride in the pharmaceutical dosage form is 30 mg;
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> wherein following a single oral administration of the pharmaceutical dosage form, the pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) of 19.851±5.8765 ng/mL of cyclobenzaprine HCl and an AUC_{0-168} of 736.60±259.414 ng·hr/mL.

(10:23-45) (emphasis added). Plaintiffs assert that defendants infringe claims 1, 2 and 5 of the '199 patent; and claims 14, 16 and 17 of the '121 patent ("the asserted claims"). (D.I. 94 ¶ 8)

2. The accused ANDA product

Defendants' generic products are available in two strengths, 15 mg and 30 mg. The products consist of a matrix system containing a water-insoluble polymer used to provide extended release of cyclobenzaprine. The tablets are manufactured by mixing and compressing the formulation. (JTX 5, 27, 29) In FDA correspondence, defendants explained that the generic product and AMRIX use "[d]istinct drug release mechanisms and formulation strategy." Moreover, "the pellets encapsulated inside [AMRIX use a] membrane-reservoir system to control the drug release rate. In comparison, [defendants' products use a] polymeric matrix-based dosage form to modulate drug release." (JTX 5 at 241)

B. Infringement

1. Standard

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). To prove direct infringement, the patentee must establish that one or more claims of the patent read on the accused device literally or under the doctrine of equivalents. *See Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). First, the court must construe the

asserted claims to ascertain their meaning and scope, a question of law. *See id.* at 976-77; *see also Teva Pharms. USA, Inc. v. Sandoz, Inc.*, _ U.S. _, 135 S. Ct. 831, 837 (2015). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1337 (Fed. Cir. 2015) (citing *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998)).

"Direct infringement requires a party to perform each and every step or element of a claimed method or product." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1320 (Fed. Cir. 2009) (quoting *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007)). "If any claim limitation is absent . . ., there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *Ferring B.V. v. Watson Labs., Inc.-Florida*, 764 F.3d 1401, 1411 (Fed. Cir. 2014) (citing *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1552 (Fed. Cir. 1989) ("One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim.")). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted).

2. Analysis

At bar, the only issue is whether defendants' extended release cyclobenzaprine products meet the single disputed claim limitation – "extended release coating

comprising a water insoluble polymer membrane surrounding" the active ingredient particles.[6, 7] (D.I. 101 at 6)

a. Claim construction

During the claim construction exercise, the parties presented competing proposals for the limitation "extended release coating." Plaintiffs characterized the various extended release coatings as being "configured in a slightly different way," but working "in fundamentally the same way." Plaintiffs proposed: "Material or materials on the surface of another material or materials that delay the release of a drug in order to maintain the drug at therapeutically effective concentrations over an extended period of time." (D.I. 52 at 4, 11) Defendants characterized the various extended release coatings as "film coatings" and other techniques including "embedding the drug within a matrix."[8] (D.I. 59 at 5) Defendants argued that "membrane" was synonymous with "film" and proposed: "A continuous outer film applied onto the surface of the active containing core to provide an extended release of the active core." Defendants cited to the applicants' discussion of "individual beads" during the prosecution history of the

[6] The parties agreed to limit the trial to arguments based on this limitation. (D.I. 19)

[7] Plaintiffs' reliance on *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), to argue that the particular type of extended-release formulation that is used is not a key aspect of the invention does not inform the present infringement analysis. The Federal Circuit analyzed whether certain patents (parent patents to the current patents-in-suit) were invalid for obviousness. In that context, the Federal Circuit explained that "[e]ven if the [prior art references] teach the claimed physical drug delivery system and dissolution profile, they reveal nothing about the critical limitation at issue[,] a therapeutically effective PK profile," and plaintiffs "acknowledged that the structure of the drug delivery system and the dissolution profile are not novel aspects of the claimed invention." *Id.* at 1075.

[8] This is the only use of the word "matrix" in the claim construction briefing.

parent patent[9] as support for the term "continuous," concluding that a person of ordinary skill would understand the disputed limitation "to require a coating that surrounds each individual drug-containing core." (*Id.* at 11) While defendants represented at the claim construction hearing that their ANDA product was a "matrix" formulation, plaintiffs maintained that defendants' manufacturing process resulted in drug cores covered with polymer material. (D.I. 105 at 36, 49)

Before the claim construction hearing, the parties agreed that "water insoluble polymer membrane surrounding said core" meant "a water insoluble polymer covering that surrounds the active core."[10] (D.I. 52 at 1, n.1) Neither party, however, presented the concept of membrane and matrix systems (on which defendants now heavily depend),[11] or specifically addressed how the agreed upon construction using the terms "covering" and "surround" would affect the overall interpretation of the full claim limitation "an extended release coating comprising a water insoluble polymer membrane surrounding said [active] core." The court construed "extended release coating" as "a layer of any substance that is applied onto the surface of another, the purpose of which is to delay the release of a drug in order to maintain the drug at therapeutically effective concentrations over an extended period of time."[12] (D.I. 81)

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[9] Discussed further below.

[10] Interestingly, defendants proposed such construction, i.e., that a "membrane" was a "covering" rather than "a continuous outer film," their proposed construction for "coating." (D.I. 50) "Covering" means "something that covers or conceals" and "covers" means "to lay or spread something over" or "to place or set a cover or covering over." "Surround" means "to enclose on all sides." *Merriam-Webster Unabridged* (2016).

[11] Discussed further below.

[12] The court disagrees with plaintiffs' assertion that the defenses presented by defendants are directed to "types of dosage forms" instead of whether they contain an "extended-release coating." (D.I. 99 at 49) The arguments outlined below (regardless

b. Prosecution history[13]

The prosecution history of the parent patent, the '793 patent (briefly cited during the claim construction exercise), informs the court's infringement analysis. Specifically, the first office action in that prosecution rejected pending claims 1,[14] 2, 6-9 and 11 as anticipated by U.S. Patent No. 4,839,177 ("the '177 patent"). According to the examiner, the '177 patent "disclose[d] a controlled drug release system comprising the

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of the nomenclature used) are properly directed to whether defendants' extended release products comprise an active-containing core particle surrounded by a water insoluble polymer membrane, as construed by the parties and the court.

[13] Plaintiffs argue that a review of the prosecution history is not warranted as it is not based on the disputed claim limitation. Although the discourse with the examiner was directed to the applicants' addition of (and arguments regarding) the phrase "multi-particulate pharmaceutical dosage forms," the explanations inform the understanding of "extended release coatings." The whole of the patent prosecution history is pertinent to the interpretation of claim limitations. *Ruckus Wireless, Inc. v. Innovative Wireless Sols., LLC*, 824 F.3d 999, 1002-03 (Fed. Cir. 2016) (citation omitted) ("The ordinary meaning [of claim terms] may be determined by reviewing various sources, such as the claims themselves, the specification, the prosecution history, dictionaries, and any other relevant evidence.").

[14] Which recites:

> A pharmaceutical dosage form of a skeletal muscle relaxant providing a modified release profile comprising a population of extended release (ER) beads,
>
> wherein said ER beads comprise
>
> an active-containing core particle (IR (immediate release) bead) comprising a skeletal muscle relaxant; and
>
> an ER (extended release) coating comprising a water insoluble polymer membrane surrounding said core,
>
> wherein said dosage form when dissolution tested . . . exhibits a drug release profile substantially corresponding to the following pattern:
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> . . . ;
>
> thereby providing therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions in humans.

(JTX 4 at 9)

following: (1) a deposit core comprising an active substance and (2) a support platform coating applied to said deposit core." (JTX 4 at 617; JTX 3) The examiner concluded that "[s]ince the essential elements of the '177 composition are identical to the instant compositions (that is, an extended release capsule comprising a muscle relaxant, diazepam, coated with an insoluble polymer), the composition would inherently have the same physiochemical properties as the compositions set forth in the instant application." (JTX 4 at 618) In response, the applicants amended the preamble of claim 1 to recite: "A multi-particulate pharmaceutical dosage form of a skeletal muscle relaxant providing a modified release profile comprising a population of extended release (ER) beads pharmaceutical dosage form." The applicants argued that the '177 patent was "directed to tablet cores and not [to] multi-particulate pharmaceutical dosage forms" and that the amendment to claim 1 clarified "that the pharmaceutical dosage form is multi-particulate." (*Id.* at 633, 635)

The examiner disagreed, stating that the '177 patent taught "a multi-particulate form," since "the composition comprises a plurality of 'granulates' that can be interpreted as being tantamount to particulates." (*Id.* at 660) In response, the applicants argued (without further amending claim 1) that the examiner's

> broad reading of the '177 patent fails to account for the fact that the extended release beads in the present application are each **individually coated** with an extended release coating surrounding the core of each core particle in the extended release beads. The identification of granulates that are compressed into a tablet form is insufficient to anticipate or render obvious the multi-particulate dosage form set forth in the claims of the pending application. By contrast, the beads of the present application maintain their individuality and perform as individual entities. Each of the beads is individually coated with an extended release coating. The granulates of the '177 patent, by contrast, are compressed into a monolithic structure, wherein the individual particles do not act or perform individually. Furthermore, the uncoated deposit core in the '177

> patent fails to act as an immediate release component and the coated deposit core is not a true sustained-release component.

(*Id.* at 677) The examiner maintained his rejection of the claims as anticipated by the '177 patent, stating that using the broadest reasonable interpretation, the limitation "multi-particulate" in the preamble of the claim is not given patentable weight. Further, the composition disclosed by the '177 patent discloses a "deposit core" (an immediate release component) and a coating (an extended release portion). (*Id.* at 685-86)

In response, the applicants amended claim 1 to recite "an active-containing core particle comprising a skeletal muscle relaxant selected from the group consisting of cyclobenzaprine, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof." (*Id.* at 695) The applicants explained that the

> '177 patent fails to disclose or suggest the use of the specified muscle relaxants. Furthermore, applicants maintain the position that the claims are patentably distinguishable over the '177 disclosure since claim 1 is clearly directed to a population of extended release beads that are neither disclosed nor suggested in the '177 patent. Although the Office has not given the limitation "multi-particulate" any patentable weight since it is in the preamble of the claim, applicants respectfully submit that the body of the claim clearly is directed to a multi-particulate dosage form since the body of the claim recites a population of extended release beads.

(*Id.* at 699) The examiner then withdrew the rejection over the '177 patent "[a]s a result of [a]pplicants' amended claims and arguments." (*Id.* at 710)

As noted, the applicants characterized the extended release beads as "individually coated," and which perform "individually." However, nowhere in the cited prosecution history were the terms "membrane system" or "matrix system" used – not in the '177 patent or the '793 patent, and not by the examiner or the applicants. Moreover, the phrase "multi-particulate pharmaceutical dosage form" was given a broad construction by the examiner, and the applicants did not further amend the '793 patent

to include the phrase as a claim limitation. Therefore, the court will conduct the infringement analysis consistent with the claim construction exercise as it was litigated by the parties.

c. SEM/EDS images

The parties agree that the exterior surface of defendants' product does not have an extended release coating. The infringement inquiry is whether the interior of defendants' product satisfies the disputed limitation. (D.I. 97 at 173:9-18) Plaintiffs' expert, Dr. Muzzio, presented eight SEM and eight corresponding EDS images of a fractured mini-tablet produced by defendants. (D.I. 98 at 315:22-24; JTX 10) Referencing a SEM image, he described that certain material was consistent in size with the drug particles – "the only particles in the blend that are . . . meant to be that size in any significant amount." There is "a different looking material, which is in the space between the" drug particles that is predominantly polymer, but could contain other components and even smaller drug particles. (D.I. 97 at 124:9-125:8; JTX 10 at 11) In the EDS imaging, Dr. Muzzio pointed out the drug particles, shown by the red color, where oxygen does not predominate. The other particles (including polymer) would be purple. (D.I. 97 at 128:11-18; 168:7-18; JTX 10 at 29) Dr. Muzzio did not experiment with color selection for the EDS to determine if he could have distinguished the polymer from the other particles present in the mixture – all other particles were identified by the purple color. (D.I. 97 at 156:20-24; 159:2-23)

Dr. Muzzio identified a drug particle surrounded by polymer in a SEM image. (D.I. 97 at 163:22-164:10; DTX 60) In the corresponding EDS image, Dr. Muzzio agreed that certain spots that he marked as polymer in the SEM image did not show up

as purple (used to indicate polymer) and some did. He explained that he could not determine, "based solely on morphology in the SEM" image, that certain smaller particles were drug particles. (D.I. 97 at 167-170; JTX 10 at 37) Dr. Muzzio repeatedly referred to the images (which he admits are of defendants' product) as "illustrations," explaining that the images are

> attempting to show the kind of structure that would take place here. There [are] small amounts of drug commingled with the polymer in regions that [he] . . . described as matrix. And also this is picking up X-rays that are being released by the material. X-rays tend to penetrate through small layers of material. So the X-rays would be coming from deeper into the picture. The X-rays could be picking up a signal from behind some of the particles that are on the surface. So it's meant as a qualitative illustration.

(D.I. 97 at 129:14-23) He testified that he did not rely on the EDS images in his infringement analysis. (*Id.* at 130:1-2)

Defendants' expert, Dr. Klibanov, opined that the SEM images did not allow unequivocal distinguishing between drug particles, polymer particles, and other particles. He agreed with Dr. Muzzio's preliminary identification of particles based on size, but stated that "proof can only come from a technique that identifies the particles given their chemical composition," such as EDS. (D.I. 98 at 315-316; JTX 10) Addressing a particular EDS image, he then reasoned that he (and a person of skill in the art) looking at such image would not conclude that a covering of pink particles is on the surface of the red particles, i.e., that the pink particles "surround" the surface of drug particles. Instead, a person of ordinary skill in the art would see "a random mixture of drug particles, red particles, and polymer particles, pink particles[, which] is a hallmark of a matrix system." He concluded that "there [are] no drug particles surrounding

polymer particles, and there [are] no polymer particles . . . surrounding drug particles." (D.I. 98 at 317:9-319:19; JTX 10 at 29)

d. Other evidence

Dr. Muzzio explained that there are many methods to make extended release drugs, which methods use "some type of a substance" to "slow down the contact between gastrointestinal fluids and drug," thereby slowing "down the drug being released." (D.I. 97 at 72) Defendants' products use a water insoluble polymer. (*Id.* at 75:23-25) Dr. Muzzio described that in a matrix formulation (like the ANDA products), "the drug particles are . . . embedded in the matrix form by the remaining material." The ingredients of the matrix hold the tablet together. (*Id.* at 76:24-77:14) He explained that dry coatings allow the application or deposit of a fine powder on the surface of another material. When powders are blended in a mixer, "preferential adhesion and sticking of powders onto the surfaces of other powders . . . happens as a result of electrostatic charging, sticking, or friction of fine cohesive powders." (*Id.* at 105-108) Dr. Muzzio walked through defendants' manufacturing method, explaining that the formulation of polymer (especially adapted for dry coating applications) and cyclobenzaprine forms a "sticky" mixture. The mixture is compressed and tableted, with individual particles held together by Van der Waals and electrostatic forces in the final tablets.[15] (*Id.* at 110-121; JTX 5, 27, 29; PTX 24)

Dr. Muzzio concluded that the structure of defendants' ANDA product is "drug particles . . . embedded in a matrix that is predominantly polymer." He interpreted this

[15] Much of the specific information regarding the manufacturing process is redacted, but all evidence has been considered by the court.

to be a "water insoluble polymer applied by the [manufacturing] process to the surface of the drug particles," resulting in "thin regions of material sandwiched between" drug particles, which are "layers." (D.I. 97 at 133) He explained that "the drug particles are embedded in a matrix made mainly of particles. That means when you look at the polymers in that matrix, there are polymers covering the particle surface." As to the term "surrounding," he explained that the polymer "covers a significant fraction of the drug particle surface, and the probability of the matrix being present in any location around the perimeters is more or less the same. So in the average situation, there will be matrix material at different places around each drug particle." (*Id.* at 136:3-18)

Defendants' expert described extended release membrane and matrix systems by reference to literature references (D.I. 98 at 275-290).

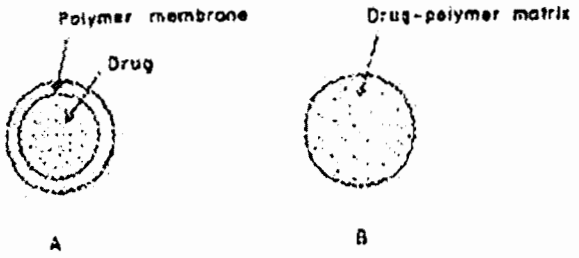

Fig 8. Schematic representation of systems using dissolution. A, encapsulated formulation where drug release is determined by thickness and dissolution rate of the polymer membrane; B, matrix formulation where drug release is determined by dissolution rate of the polymer.

(DTX 10[16] at 1668) In a membrane system, particles of drug are coated with varying thicknesses of slowly soluble polymers. (*Id.*) The "drug is concentrated in the core, and

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[16] Charles S L Chiao and Joseph R Robinson, Chapter 94: *Sustained-Release Drug Delivery Systems, in Remington: The Science and Practice of Pharmacy* (Alfonso R Gennaro, ed., 19th ed. 1995).

must traverse a polymeric membrane or film which slows down the release rate. . . . Drug release through a membrane is controlled by the thickness and the porosity of the membrane, as well as the solubility of the drug in the gastrointestinal fluids." (DTX 9[17] at 561; *see also* DTX 12[18] at 391, DTX 13[19] at 70) In a matrix system, the "drug is embedded in an inert polymer" by mixing the drug and polymer and then compressing the mixture into a tablet. "Drug release rate from insoluble polymer matrices is controlled by the pore size and number of pores, and tortuosity of the matrix. . . . The release mechanism will also depend greatly on how the drug is dispersed within the system (dissolved, molecularly dissolved, or dispersed)." (DTX 9 at 556-60; *see also* DTX 10 at 1667-69; DTX 6[20] at 290-93; DTX 11[21] at 193-97) "Membrane-controlled delivery systems differ from the matrix formulations in that the rate-controlling part of the system is a membrane through which the drug must diffuse, rather than diffusing through the whole matrix." (DTX 9 at 561)

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[17] Emma L. McConnell and Abdul W. Basit, Chapter 31: *Modified-release oral drug delivery, in Aulton's Pharmaceutics*, 4th ed. (Michael E. Aulton and Kevin M. G. Taylor, eds., 4th ed. 2013).

[18] Ho-Wah Hui, and Joseph R. Robinson, Chapter 9: *Design and Fabrication of Oral Controlled Release Drug Delivery Systems, in Controlled Drug Delivery: Fundamentals and Applications* (Joseph R. Robinson and Vincent H. L. Lee, eds., 2nd ed. 1987)

[19] Wei-Youh Kuu, Ray W. Wood, and Theodore J. Roseman, Chapter 2: *Factors Influencing Kinetics of Solute Release, in Treatise on Controlled Drug Delivery: Fundamentals, Optimization, Applications* (Agis Kydonieus, ed., 1992).

[20] Pardeep K. Gupta and Joseph R. Robinson, Chapter 6: *Oral Controlled-Release Delivery, in Treatise on Controlled Drug Delivery: Fundamentals, Optimization, Applications* (Agis Kydonieus, ed., 1992).

[21] Jorge Heller, Chapter 4: *Use of Polymers in Controlled Release of Active Agents, in Controlled Drug Delivery: Fundamentals and Applications*, (Joseph R. Robinson and Vincent H. L. Lee, eds., 2nd ed. 1987).

Dr. Klibanov characterized the patent as describing a "membrane system" and defendants' product as a "matrix system."[22] (D.I. 98 at 291-304) He explained that he used the court's construction of "extended release coatings" and, particularly, the court's reference to the specification,[23] which "explain[ed] that extended release coatings are indeed membrane coatings that can be applied to the core." (*Id.* at 305-308) He opined that defendants' manufacturing process results in "a random and pretty uniform mixture," and in tablets that are "a matrix extended release system, which has no coating and no layer." A "person of ordinary skill in the art . . . would not characterize the polymer particles in [defendants'] products as a coating or as forming a layer. It just scientifically simply makes no sense." (*Id.* at 310) Dr. Kilbanov explained that the court's construction provides that the layer of substance be "applied onto" the surface of another, which defendants' manufacturing process does not do. In his opinion, a person of ordinary skill would just as easily characterize the matrix system of defendants' tablets as layering drug particles onto the polymer particles versus layering polymer particles onto the drug particles. (*Id.* at 291-92, 311) He reasoned (based on the court's construction and explanation) that "a person of ordinary skill in the art would understand that membrane coatings are used in membrane . . . extended release systems that" he previously described, not in "matrix extended release systems, like" those used in defendants' ANDA products. (*Id.* at 312)

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[22] Dr. Muzzio testified that "the way in which [defendants] practice[] the patent . . . is consistent with" the language of the disputed limitation and that the patent describes "matrix formulations," as well as membrane formulations. (D.I. 97 at 85-86)

[23] The extended release coatings are "membrane coatings [that] can be applied to the core using any of the coating techniques commonly used in the pharmaceutical industry, but fluid bed coating is particularly useful." (D.I. 81, citing 7:11-13)

As to whether defendants' products "have a covering that surrounds the active core," Dr. Klibanov opined that "in [his] judgment, [defendants'] ANDA products employ a matrix-type extended release system[, which does] not contain a membrane. And since there is no membrane, there can be no covering." (*Id.* at 313:2-7) He explained that "there is no covering that surrounds the drug particles in" defendants' products (as shown by the imaging) and,

> since there is no coating, and no layer, there is also no membrane and no covering that surrounds the drug particles. As follows from the disputed claim limitation, it says, an extended release coating comprising a water insoluble polymer membrane. So logically, it follows that a water insoluble polymer membrane is more specific than an extended release coating. So, in other words, a person of ordinary skill in the art would understand that the membrane or covering is a particular type of coating or layer given this claim limitation.

(*Id.* at 313:11-314:8) He also opined that "a person of ordinary skill in the art would understand that the word 'covering' was used to replace the word 'membrane' in the claim and, therefore, the covering and membrane mean pretty much the same thing. And because there is no membrane, there is no covering." (*Id.* at 314:12-18)

e. Conclusion on direct infringement

Regardless of the nomenclature used by the parties, the question at bar is whether plaintiffs have proven, by a preponderance of the evidence, that defendants' ANDA product has an "extended release coating comprising a water insoluble polymer membrane surrounding" the active ingredient particles. In other words, does the accused ANDA product have "a water insoluble polymer covering that surrounds [the surface of] the active core," "the purpose of which is to delay the release of a drug in order to maintain the drug at therapeutically effective concentrations over an extended period of time." (D.I. 52 at 1, n.1; D.I. 81) The construed claim limitation does not

require the concept of "continuity" or the "complete covering" of the active cores that defendants yet again seem to seek. In other words, defendants (through the matrix and membrane system classification) relegate anything other than complete individual coverage (a membrane system), to falling outside the meaning of the claimed limitation.[24] This is inconsistent with the court's interpretation of "extended release coating" and decision to not embrace defendants' construction. Moreover, such an interpretation is inconsistent with the parties' agreed upon construction of the limitation "a water insoluble polymer covering that surrounds the active core" (and the definitions of the chosen words).

With respect to infringement, the court did not find the experts' analyses of the SEM/EDS imaging particularly helpful. Dr. Muzzio's explanations and conclusions regarding defendants' manufacturing process (with reference to the composition of the formulation and particle sizes) were reasonable and consistent with the disputed claim limitations as construed by the parties and the court.[25] That is, the drug particles are embedded in sufficient polymer particles for the resulting formulation to be described as drug particles "covered by" or "surrounded" by polymer particles. In contrast, defendants' expert first characterized the patents-in-suit as covering a membrane system and the ANDA product as a matrix system. His subsequent analyses greatly

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[24] The issue of whether the claim language would exclude matrix systems was never joined, despite the prosecution history of the patents-in-suit, the prior art literature pertaining to different release systems, and defendants' consistent description of the accused ANDA product as comprising a matrix system.

[25] Defendants' attorney arguments (without citation to defendants' expert) criticizing this testimony are not credible (D.I. 101 at 31-34), as Dr. Muzzio stated that defendants' manufacturing process was different than that depicted in the polymer brochure. (D.I. 97 at 104:4-17; PTX 24)

depended on the literature's description of such systems (concluding that a matrix system does not use a membrane and equating "covering" with "membrane"), rather than focusing on the claim language (as construed by the court and the parties) and evidence regarding defendants' manufacturing process. On the record presented, the court concludes that plaintiffs have demonstrated, by a preponderance of the evidence, that defendants' product infringes.[26, 27]

III. CONCLUSION

For the foregoing reasons, the court finds that plaintiffs have proven, by a preponderance of the evidence, that defendants' ANDA products infringe the asserted claims of the '199 and '121 patents. An appropriate order shall issue.

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[26] Having found direct infringement, the court does not address doctrine of equivalents or prosecution history estoppel.

[27] In light of this conclusion, the court does not reach defendants' request for attorney fees. The court also declines to address defendants' arguments regarding plaintiffs' requests for relief enumerated in the pre-trial order (and complaint). Such requests will be addressed in due course. (D.I. 101 at 52-56)