IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC., ALLERGAN USA, INC., ALLERGAN SALES, L.L.C., ENDO PHARMACEUTICALS SOLUTIONS INC., and SUPERNUS PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 09-cv-511 (GMS)
WATSON LABORATORIES, INC.—FLORIDA, SANDOZ INC., and PADDOCK LABORATORIES, INC.,	)	
Defendants.	)	

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiffs Allergan, Inc., Allergan USA, Inc., Allergan Sales, LLC, Endo Pharmaceuticals Solutions Inc., and Supernus Pharmaceuticals, Inc. (collectively, "the plaintiffs") allege that pharmaceutical products proposed by defendants Watson Laboratories, Inc.—Florida, Sandoz, Inc., and Paddock Laboratories, Inc. (collectively, "the defendants") infringe the asserted claims of the patents-in-suit. (D.I. 1.) The court held a seven-day bench trial in this matter on May 2 through May 10, 2011. (D.I. 204-210.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patents-in-suit and whether the defendants' proposed products infringe the patents-in-suit. (D.I. 201-203.)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that: (1) all asserted claims of the patents-in-suit are invalid due to obviousness; (2) the asserted claims of the patents-in-suit are not

invalid due to anticipation; (3) claim 1 of the '978 Patent and claim 1 of the '449 Patent are not invalid due to indefiniteness; (4) claim 1 of the '359 Patent is not invalid due to written description; (5) the defendants' proposed products infringe the asserted claims of the patents-in-suit; and (6) each of the parties' Rule 52(c) motions are granted in part and denied in part. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiffs Allergan, Inc., Allergan USA, Inc., and Allergan Sales, LLC (collectively, "Allergan") are corporations organized and existing under the laws of the State of Delaware, with their principal place of business at 2525 Dupont Drive, Irvine, California 92612.

2. Plaintiff Endo Pharmaceutical Solutions, Inc. ("Endo") is a corporation organized and existing under the laws of the State of Delaware and has its headquarters at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317.

3. Plaintiff Supernus Pharmaceuticals, Inc. ("Supernus") is a Delaware corporation having its principal place of business at 1550 East Gude Drive, Rockville, Maryland 20850.

4. Allergan, Endo, and Supernus will be collectively referred to as "Allergan" or "plaintiffs."

5. Defendant Watson Laboratories, Inc.—Florida ("Watson") is a Florida corporation with its principal place of business at 4955 Orange Drive, Davie, Florida 33314.

6. Defendant Sandoz, Inc. ("Sandoz") is a corporation organized and existing under the laws of the State of Colorado, having its principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.

7. Defendant Paddock Laboratories, Inc. ("Paddock") is a corporation organized and existing under the laws of the State of Minnesota, with headquarters at 3940 Quebec Avenue North, Minneapolis, Minnesota 55427.

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 194, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also reordered and renumbered some paragraphs, corrected some spelling and formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in the Discussion and Conclusions of Law section of this opinion, preceded by the phrase "the court finds" or "the court concludes."

8. Watson, Sandoz, and Paddock will be collectively referred to as "defendants."

9. The court has subject matter jurisdiction, as well as personal jurisdiction over all parties.

B. Background

10. Trospium chloride (a quaternary ammonium compound with the chemical name of spiro [8-azoniabicyclo[3,2,1]octane-8, 1'-pyrrolidinium]-3-[(hydrozydiphenyl-acetyl)-oxy] chloride (1α,3β,5α)-(9C1)) is an antagonist at muscarinic cholinergic receptors.

11. In the 1990s, trospium chloride (hereafter, "trospium"), oxybutynin, and tolterodine were the three main pharmaceutical treatments for overactive bladder ("OAB"), a condition which affects approximately thirty-three million people in the United States.

12. In 2002, Ditropan (oxybutynin) and Detrol (tolterodine) were the two mainstay OAB treatments and were once-a-day formulations approved by the Food and Drug Administration (the "FDA").

13. Unlike oxybutynin and tolterodine, trospium is a quaternary ammonium compound, rendering it permanently positively charged.

14. Though trospium had been used in the immediate release formulation of OAB pharmaceutical products for years, SANCTURA XR® is the only product that uses a quaternary ammonium compound in its once-a-day formulation.

C. The Patents-in-Suit

15. United States Patent Number 7,410,978 ("the '978 Patent"), entitled "Once Daily Dosage Forms Of Trospium," naming Argaw Kidane, Henry H. Flanner, Padmanabh Bhatt, and Arash Raoufinia as inventors, was issued on August 12, 2008.

16. United States Patent Number 7,759,359 ("the '359 Patent"), entitled "Method Of Treating Bladder Dysfunction With Once-a-Day Trospium Salt Formulation," naming Argaw Kidane, Henry H. Flanner, Padmanabh Bhatt, and Arash Raoufinia as inventors, was issued on July 20, 2010.

17. United States Patent Number 7,781,448 ("the '448 Patent"), entitled "Once Daily Dosage Forms Of Trospium," naming Argaw Kidane, Henry H. Flanner, Padmanabh Bhatt, and Arash Raoufinia as inventors, was issued on August 24, 2010.

18. United States Patent Number 7,763,635 ("the '635 Patent"), entitled "Once Daily Dosage Forms of Trospium," naming Argaw Kidane, Henry H. Flanner, Padmanabh Bhatt, and Arash Raoufinia as inventors, was issued on July 27, 2010.

19. The applications that matured into the '359, '448, '449, and '635 Patents are continuations of Application Number 10/980,818, which matured into the '978 Patent.

20. Supernus is the assignee of the '978, '359, '448, '449, and '635 Patents ("the patents-in-suit"). Allergan and Endo hold licensing, development, and commercialization rights to the patents-in-suit.

21. The patents-in-suit are listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") at the FDA in connection with SANCTURA XR®.

22. SANCTURA XR® is a commercial version of trospium and is available in the United States.

23. Allergan markets SANCTURA XR®, which is covered by at least one asserted claim of each of the patents-in-suit.

24. SANCTURA XR® is a 60 mg once-daily trospium extended-release formulation capsule for the treatment of OAB, and is comprised of both extended release ("XR1") and delayed release ("DR2") pellets.

25. The XR1 pellets are coated with release controlling ethylcellulose polymer to provide for a slow and steady release and the DR2 pellets are coated with Eudragit FS30D, enteric polymer designed to release at a pH 7.0, such that it will release in the colon and the lower gastrointestinal ("GI") tract.

26. Dissolution data in SANCTURA XR®'s New Drug Application ("NDA") and blood level data from clinical trials reported in the patents-in-suit are consistent with release in the lower GI tract.

27. The SANCTURA XR® label contains single dose pharmacokinetic data obtained from NDA study IP631-020 and the corresponding steady state C_{min} blood level is 418.6 pg/ml and steady state C_{max} blood level is 1873 pg/ml, which occurs at a T_{max} of 4.796 hours. These blood levels are within the range of approximately 0.5 ng/ml to about 6.0 ng/ml, with a C_{min} above about 0.5 ng/ml and a C_{max} below about 6.0 ng/ml, and a C_{max} below 24000 ng/ml.

28. SANCTURA XR® has comparable efficacy to SANCTURA®, the twice-a-day immediate release 20 mg trospium product, but has a better "safety profile," including a reduction in "dry mouth." The incidence of dry mouth reported on the SANCTURA XR® label is 10.7%, which is about half that of the immediate release trospium product SANCTURA®.

1. The Asserted Claims

29. The plaintiffs are asserting claims 1, 2, 4, 18, 19, and 20 of the '978 Patent against all defendants.

30. The plaintiffs are asserting claims 1, 10, and 16 of the '448 Patent against all defendants.

31. The plaintiffs are asserting claims 1, 10, and 18 of the '449 Patent against all defendants.

32. The plaintiffs are asserting claim 1 of the '359 Patent against all defendants.

33. The plaintiffs assert that the claims of the '978 and '448 Patents are directed to pharmaceutical compositions, which the defendants directly infringe.

34. The plaintiffs assert that the claims of the '359 and '449 Patents are method claims, which the defendants infringe by inducement.

ii. *'978 Patent, Claim 1*

35. Claim 1 of the '978 Patent reads:

> A pharmaceutical composition suitable for once-a-day administration of trospium chloride comprising controlled release solid, trospium chloride-bearing particulates, at least a portion of which releases trospium chloride in the lower gastrointestinal (GI) tract, such that once-a-day administration of said pharmaceutical composition provides steady state blood levels of trospium that are comparable to steady state blood levels of trospium achieved with twice daily administration of 20 mg immediate release trospium chloride tablets, said particulates comprising at least one polymer selected from enteric polymers, release controlling polymers, or combinations thereof.

iii. *'978 Patent, Claim 2*

36. Claim 2 of the '978 Patent reads: The composition of claim 1, in which once-a-day administration of said controlled release pharmaceutical composition provides steady state blood levels of trospium in the range of about 0.5 ng/ml to about 6.0 ng/ml.

iv. *'978 Patent, Claim 4*

37. Claim 3 of the '978 Patent reads: The composition of claim 2, in which once-a-day administration of said controlled release pharmaceutical composition provides steady state blood C_{max} levels of trospium in the range of about 2.5 ng/ml to about 4.5 ng/ml and C_{min} levels of trospium in the range of aout 0.5 ng/ml to about 1.5 ng/ml.

v. *'978 Patent, Claim 18*

38. Claim 18 of the '978 Patent reads: A pharmaceutical composition comprising trospium chloride as at least one active pharmaceutical ingredient in which at least a portion of said trospium chloride is contained in a delayed release formulation, which releases trospium chloride in the lower GI tract, said delayed release formulation comprising at least one enteric polymer.

vi. *'978 Patent, Claim 19*

39. Claim 19 of the '978 Patent reads: The composition of claim 1 or claim 18, wherein said lower GI tract is the colon.

vii. *'978 Patent, Claim 20*

40. Claim 20 of the '978 Patent reads:

> A pharmaceutical composition suitable for a once-a-day administration of trospium chloride comprising controlled release solid, trospium chloride-bearing particulates, at least a portion of which releases trospium chloride in the ileum, colon or both, such that once-a-day administration of said pharmaceutical composition provides steady state blood levels of trospium in the range of about 0.5 ng/ml to about 6.0 ng/ml, said particulates comprising at least one polymer selected from enteric polymers, release controlling polymers, or combinations thereof.

viii. *'448 Patent, Claim 1*

41. Claim 1 of the '448 Patent reads:

> An oral pharmaceutical composition suitable for once-a-day administration of trospium, comprising first trospium containing component comprising at least one component selected from the group consisting of an extended release (XR) component and a delayed release (DR) component and a second trospium containing component comprising at least one component selected from the group consisting of an extended release (XR) component, a delayed release (DR) component, and an immediate release component, wherein the first and second trospium containing components are different from each other, and wherein said composition at once-a-day administration provides steady state blood levels of trospium of a minimum of about 0.5 ng/ml and a maximum of about 6.0 ng/ml; comprises from 25 to 80 mg of trospium chloride and at least one polymer selected from the enteric polymers, release controlling polymers, or combinations thereof, and wherein at least a portion of which releases trospium in the lower gastrointestinal (GI) tract.

ix. *'448 Patent, Claim 10*

42. Claim 10 of the '448 Patent reads: The composition of claim 1, which is a combination of an XR trospium component and a DR trospium component.

x. *'448 Patent, Claim 16*

43. Claim 16 of the '448 Patent reads: The composition of claim 1, wherein said DR component releases trospium at a pH of about 7.0.

xi. *'449 Patent, Claim 1*

44. Claim 1 of the '449 Patent reads:

> A method of treating a bladder dysfunction in a mammal comprising an oral administration to said mammal of a once-a-day dose of a pharmaceutical composition comprising 25 to 80 mg of trospium chloride for at least a time sufficient to ameliorate said dysfunction, wherein at least part of the trospium chloride is contained in an extended release (XR) component or in a delayed release (DR) component, wherein said composition comprises at least one polymer selected from enteric polymers, release controlling polymers, or combinations thereof, wherein at least a portion of said composition releases trospium chloride in the lower gastrointestinal (GI) tract, wherein said administration provides steady state blood levels of trospium of a minimum of about 0.5 ng/ml and a maximum of about 6.0 ng/ml, and results in minimizing the occurrence of side effects as compared to twice daily administration of 20 mg of immediate release trospium chloride tablets; and wherein said bladder dysfunction is selected from the group consisting of urinary frequency, urgency, nocturia, and urge-incontinence due to detrusor instability, urge syndrome, and detrusor hyperreflexia.

xii. *'449 Patent, Claim 10*

45. Claim 10 of the '449 Patent reads: The method of claim 1, wherein said composition is a combination of an XR trospium chloride component and a DR trospium chloride component.

xiii. *'449 Patent, Claim 18*

46. Claim 18 of the '449 Patent reads: The method of claim 1, wherein said side effects are selected from a group consisting of dry mouth, headache, constipation, dyspepsia, abdominal pain, and a combination thereof.

xiv. *'359 Patent, Claim 1*

47. Claim 1 of the '359 Patent reads:

> A method for treating a bladder dysfunction in a patient comprising orally administering to a patient suffering from a bladder dysfunction a once-a-day dosage formulation of a pharmaceutically acceptable salt of trospium (Tr^+) comprising at least one component selected from the group consisting of an extended release (XR) and a delayed release (DR) component;
>
> wherein at least a portion of said formulation releases trospium chloride in the lower gastrointestinal (GI) tract;
>
> which formulation provides an average C_{max} at steady state of less than 2400 pg/ml of Tr^+ at a T_{max} of less than 6 hours; and

wherein the bladder dysfunction is selected from the group consisting of urinary frequency, urgency, nocturina, urge-in-continence associated with detrusor instability, urge syndrome, and detrusor hyperreflexia.

2. The Accused Products

i. *ANDA No. 91-289 Submitted by Watson*

48. Watson submitted an Abbreviated Drug Application ("ANDA") No. 91-289 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, or sale of trospium extended-release capsules, 60 mg ("the Watson Product"), prior to the expiration of the '978 Patent.

49. The Watson Product is an extended release capsule that contains two populations of extended release pellets, with each capsule containing 60 mg of trospium. Trospium is the active pharmaceutical ingredient in the Watson Product. The first population of pellets in the Watson Product ("Pellets-1") has an ethylcellulose coating that modifies release of the active ingredient. The second population of pellets in the Watson Product ("Pellets-2") has an Eudragit FS30D coating designed to modify release of the active ingredient.

50. Pellets-1 are trospium-bearing pellets coated with a release controlling polymer and Pellets-2 are trospium-bearing pellets coated with three different coating suspensions. The first is a polymeric film including Eudragit FS30D, the second is a talc suspension, and the third is a talc-Opadry II clear coating suspension.

51. Watson submitted the results from two *in vivo* bioavailability studies to the FDA to demonstrate bioequivalence between the Watson Product and SANCTURA XR®. Based on the results of its bioequivalence studies, Watson concluded that its proposed generic capsules are bioequivalent to SANCTURA XR® under both fasted and fed conditions.

52. The proposed product label for the Watson Product states that the capsules are indicated for "the treatment of [OAB] with symptoms of urge urinary incontinence, urgency, and urinary frequency." The proposed label for the Watson Product also states that the recommended dosage is one 60 mg capsule daily in the morning. The proposed label further states that it should be dosed with water on an empty stomach, at least one hour before a meal.

53. In sum, ANDA No. 91-289 seeks approval to market trospium extended release capsules for the treatment of overactive bladder with symptoms of urge incontinence, urgency, and urinary frequency.

54. On June 1, 2009, Watson sent the plaintiffs a letter, as a paragraph IV notice, stating that it had submitted its ANDA No. 910289 to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Watson Product prior to the expiration of the '978 Patent. Watson's letter also stated that the '978 Patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Watson Product.

55. The plaintiffs brought suit against Watson alleging infringement of the '978 Patent under 35 U.S.C. § 100 *et seq*, including §§ 271(e)(2) and 271(b), and 28 U.S.C. §§ 2201 and 2202 on July 13, 2009, within forty-five days of receipt of Watson's paragraph IV letter.

56. On August 24, 2009, Watson filed counterclaims for declaratory judgment of non-infringement and invalidity of the '978 Patent. On July 23, 2010, Watson asserted an additional counterclaim for declaratory judgment of unenforceability of the '978 Patent.

57. Watson sent the plaintiffs a letter dated August 17, 2010, stating that Watson had submitted an amendment to ANDA No. 91-289 to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Watson product prior to the expiration of the '359 and '635 Patents. This letter also stated that the '659 and '635 Patents are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Watson Product.

58. Watson sent the plaintiffs another letter on September 10, 2010, stating that it had submitted an amendment to its ANDA to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Watson Product prior to the expiration of the '448 and '449 Patents, and that these patents were invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Watson Product.

59. The plaintiffs brought suit against Watson alleging infringement of the '448 and '449 Patents under 35 U.S.C. § 100 *et seq*, including §§ 271(e)(2) and 271(a), and 28 U.S.C. §§ 2201 and 2202 on October 5, 2010, within forty-five days of receipt of Watson's paragraph IV letter.

60. On October 27, 2010, Watson filed counterclaims for declaratory judgment of non-infringement and invalidity of the '359, '448, '449, and '635 Patents.

61. On December 27, 2010, the plaintiffs filed counterclaims for declaratory judgment of infringement of the '359 Patent under 35 U.S.C. § 100 *et seq*, including §§ 271(e)(2) and 271(a), and 28 U.S.C. §§ 2201 and 2202.

ii. *ANDA No. 91-635 Submitted by Sandoz*

62. Sandoz submitted an ANDA to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j). The ANDA seeks FDA approval for the commercial manufacture, use, and sale of generic trospium extended-release capsules, containing 60 mg of trospium ("the Sandoz Product"). ANDA No. 91-635 specifically seeks FDA approval to market the Sandoz Product before the expiration of the '978 Patent.

63. According to its ANDA, the Sandoz Product is a trospium extended release capsule containing two types of extended release pellets ("ER pellets") and two types of delayed release pellets ("DR pellets"). The active pharmaceutical ingredient is Sandoz's proposed trospium extended release capsules is trospium.

64. Sandoz's ANDA states that its generic "Trospium Chloride ER Capsules 60 mg have been designed as a combination of two delayed release pellets and two extended release pellets mixed in a specific ratio to produce a release profile that mimics the RLD [SANCTURA XR®] product."

65. In Sandoz's Product, both of the ER pellets are trospium-bearing pellets coated with a Surelease E7-19010 coating. Surelease E7-19010 is an aqueous dispersion of ethylcellulose. One of the ER pellets ("ER1") has a 15% Surelease E7-19010 coating and the other ER pellet ("ER2") has a 24% Surelease E7-19010 coating. According to Sandoz's ANDA, the extended release pellets are designed to create a pH independent drug release covering the extent of the GI tract.

66. The DR pellets are trospium-bearing pellets that both contain Eudragit FS30D in their enteric coating. One of the two types of DR pellets ("DR2") is coated only with Eudragit FS30D enteric coating, at a coating level of about 26%. The other type of DR pellet ("DR1") is coated with an enteric composition of Eudragit L30D-55 and Eudragit FS30D, at a coating level of about 1.2% and 24%, respectively.

67. Sandoz's ANDA states that "[t]he Sandoz product was designed with components to obtain similar release rates compared to the RLD. Dissolution testing of the RLD demonstrated that the product released at different rates in different media and the chosen ratio of pellets in the Sandoz product matched the RLD." The ANDA further states that "[t]he Enteric 1 pellets have virtually no release in the stomach (pH 1-5) and target a slow drug release throughout the small intestine (pH 5.5 to < 7) pulsing the remaining drug substance at the beginning of the large intestine (pH > 7). The Enteric 2 Pellets have virtually no release of the drug substance in the stomach, a slight release throughout the small intestine and immediate release of drug substance at the beginning of the large intestine."

68. Sandoz's ANDA states that "[e]ach ER pellet formulation is very similar exception one has a 15% Surelease E7-19010 (aqueous ethylcellulose) coating whereas the other ER pellet has a 25% coating. The combination of ER pellets produces a specific pH independent drug release throughout the [GI] tract."

69. Sandoz's ANDA states that "[w]hen used alone (Enteric 2), Eudragit FS30D has little to no permeability of the coating up to about pH of 7.0 and then the coating dissolves rapidly releasing the drug substance."

70. Sandoz submitted the results from two *in vivo* bioavailability studies to the FDA to prove that its proposed generic capsules are bioequivalent to SANCTURA XR®. Based on the results of its bioequivalence studies, Sandoz concluded that its proposed generic capsules are bioequivalent to SANCTURA XR® under both fasted and fed conditions.

71. Sandoz's proposed label states that its capsules are indicated for "the treatment of [OAB] with symptoms of urge urinary incontinence, urgency, and urinary frequency." Sandoz's proposed label states that the recommended adult dose for most patients is one 60 mg capsule once a day, dosed with water on an empty stomach.

72. The Sandoz Product has the same dosage form, route of administration, dosing regimen, and indication as SANCTURA XR®.

73. ANDA No. 91-635 seeks approval to market trospium extended release capsules for the treatment of OAB with symptoms of urge incontinence, urgency, and urinary frequency.

74. On or about November 4, 2009, the plaintiffs received a letter stating that Sandoz had submitted its ANDA No. 91-635 to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j), seeking to market the Sandoz Product prior to the expiration of the '978 Patent. Sandoz's paragraph IV letter stated that the '978 Patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described in its ANDA.

75. Plaintiffs brought suit against Sandoz alleging infringement of the '978 Patent under 35 U.S.C. § 100 *et seq*, including §§ 271(e)(2) and 271(a), and 28 U.S.C. §§ 2201 and 2202 on November 19, 2009, within forty-five days of receipt of Sandoz's paragraph IV letter.

76. On or about November 24, 2010, the plaintiffs received a letter, dated November 23, 2010, stating that Sandoz had submitted an amendment to its ANDA to the FDA with a paragraph IV certification seeking FDA approval for the commercial manufacture, use, and sale of the Sandoz product prior to the expiration of the '359, '448, and '449 Patents. Sandoz's paragraph IV letter stated that these additional patents were invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Sandoz Product.

77. The plaintiffs brought suit against Sandoz alleging infringement of the '359, '448, and '449 Patents under 35 U.S.C. § 100 *et seq*, including §§ 271(e)(2) and 271(a), and 28 U.S.C. §§ 2201 and 2202 on January 22, 2011, within forty-five days of receipt of Sandoz's paragraph IV letter.

iii. *ANDA No. 20-1291 Submitted by Paddock*

78. Paddock submitted ANDA No. 20-1291 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking FDA approval for the commercial manufacture, use, or sale in the United States of generic trospium extended release capsules, containing 60 mg of trospium ("the Paddock Product") prior to the expiration of the '978 Patent.

79. ANDA No. 20-1291 states that the Paddock Product is a trospium extended-release capsule that contains three small tablets, with each capsule containing 60 mg strength of trospium and that trospium is the active pharmaceutical ingredient.

80. According to Paddock's ANDA, trospium and excipient, including magnesium aluminum silicate, stearic acid, and talc, are formed into granules using a binding solution of povidone and sodium chloride in purified water. The granules are dried, blended and sifted with talc, stearic acid, colloidal silicon dioxide, and magnesium stearate, and then compressed into tablets. Two-thirds of the tablets are coated with Eudragit L30D55.

81. Paddock submitted the results from two *in vivo* bioequivalence studies to the FDA to prove that its proposed generic capsules are bioequivalent to SANCTURA XR®. Based on the results of its bioequivalence studies, Paddock concluded that its proposed generic capsules are bioequivalent to SANCTURA XR® under both fasted and fed conditions.

82. Paddock's proposed label states that its capsules are indicated for "the treatment of [OAB] with symptoms of urge urinary incontinence, urgency, and urinary frequency," and that the recommended dose for most patients is one 60 mg capsule once a day, dosed with water on an empty stomach, at least one hour before a meal.

83. In sum, ANDA No. 20-1291 seeks approval to market trospium extended-release capsules in the United States for treatment of OAB with symptoms of urge incontinence, urgency, and urinary frequency.

84. On or about April 27, 2010, the plaintiffs received a letter dated April 26, 2010, stating that Paddock submitted ANDA No. 20-1291 to the FDA seeking approval for the commercial manufacture, use, or sale of a generic trospium extended release product prior to the expiration of the '978 Patent. Paddocks' paragraph IV letter stated that the '978 Patent was invalid and/or will not be infringed by the commercial manufacture, use, or sale of the Paddock Product.

85. The plaintiffs brought suit against Paddock alleging infringement of the '978 Patent under 35 U.S.C. § 100 *et seq*, including §§ 271(e)(2) and 271(b), and 28 U.S.C. §§ 2201 and 2202 on June 9, 2010, within forty-five days of receipt of Paddocks' paragraph IV letter.

86. On July 7, 2010, Paddock filed counterclaims for declaratory judgment of non-infringement and invalidity on the '978 Patents.

87. On or about August 19, 2010, the plaintiffs received a letter, dated August 18, 2010, stating that Paddock submitted an amendment to its ANDA to the FDA with a paragraph IV certification seeking FDA approval for the commercial manufacture, use, or sale of the Paddock Product prior to the expiration of the '359 and '635 Patents. Paddock's paragraph IV letter also stated that the '359 and '635 Patents were invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Paddock Product.

88. On or about September 14, 2010, the plaintiffs received another letter, dated September 13, 2010, stating that Paddock had submitted an amendment to its ANDA to the FDA with a paragraph IV certification seeking FDA approval for the commercial manufacture, use, or sale of its Paddock Product in the United States prior to the expiration of the '448 and '449 Patents. Paddock's paragraph IV letter also stated that the '448 and '449 Patents were invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Paddock Product.

89. The plaintiffs brought suit against Paddock alleging infringement of the '448 and '449 Patents under 35 U.S.C. § 100 *et seq*, including §§ 271(e)(2) and 271(b), and 28 U.S.C. §§ 2201 and 2202 on October 5, 2010, within forty-five days of receipt of Paddocks' paragraph IV letter.

90. On October 28, 2010, Paddock filed counterclaims for declaratory judgment of non-infringement and invalidity on the '978, '359, '635, '448, and '449 Patents, and on November 2, 2010, filed counterclaims for declaratory judgment of non-infringement and invalidity on the '359, '635, '448, and '449 Patents.

91. The plaintiffs filed counterclaims against Paddock alleging infringement of the '359 Patent under 35 U.S.C. § 271(a), (b), (e)(2), and (g), and 28 U.S.C. §§ 2201 and 2202 on December 27, 2010.

92. The plaintiffs do not assert that Paddock infringes any claim of the '635 Patent.

D. Procedural History

93. The plaintiffs filed their Complaint for patent infringement against Watson Pharmaceuticals Inc., Watson Laboratories Inc.—Florida, and Watson Pharma, Inc. (collectively, "Watson") on July 13, 2009, in what was labeled the 09-cv-511 action.

94. In separately-captioned actions, the plaintiffs filed complaints for patent infringement against Sandoz, 09-cv-882, and Paddock, 10-cv-501, on November 19, 2009 and June 9, 2010, respectively.

95. The plaintiffs' action against Watson was consolidated with the Sandoz action on March 22, 2010 and consolidated with the Paddock action on September 21, 2010.

96. The plaintiffs filed an Amended Complaint for patent infringement against Paddock in the consolidated action on October 14, 2010. (D.I. 75.)

97. The court held a seven-day bench trial in this matter on May 2 through May 10, 2011 (D.I. 204-210).

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that: (1) all asserted claims of the patents-in-suit are invalid due to obviousness; (2) the asserted claims of the patents-in-suit are not invalid due to anticipation; (3) claim 1 of the '978 Patent and claim 1 of the '449 Patent are not invalid due to indefiniteness; (4) claim 1 of the '359 Patent is not invalid due to written

description; (5) the defendants' proposed products infringe the asserted claims of the patents-in-suit; and (6) each of the parties' Rule 52(c) motions are granted in part and denied in part. The court's reasoning follows.

A. Obviousness

The defendants challenge the validity of each of the asserted claims as obvious in light of the prior art. The court finds, for the reasons that follow, that the defendants have established by clear and convincing evidence that the patents-in-suit are, in fact, obvious.

1. The Legal Standard

35 U.S.C. § 103(a) provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence"[2] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the

[2] "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

use of hindsight is not permitted. *See KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See KSR*, 550 U.S. at 415. The *KSR* Court acknowledged, however, the importance of identifying "'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *KRS*, 550 U.S. at 418).

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

2. <u>The Level of Ordinary Skill in the Art</u>

A person of ordinary skill in the art with respect to the patents-in-suit would have: (1) a Ph.D. in pharmaceutics, pharmacy, chemistry, or a related field, several years of experience

formulating and evaluating dosage forms, and would have participated as a member of a development team, though "[e]xtensive practical experience could be substituted for the relevant degrees"[3]; or (2) a B.S. in pharmacy or a similar field with several years of formulation experience or a Ph.D. with a few years of experience and, at least one year of experience working with controlled release dosage forms.[4] The court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.

3. The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

As an outset consideration, it is important to identify what the asserted claims of the patents-in-suit cover and what they do not. The court notes that the claims do not cover a new drug, a new method of treatment, or novel ways of formulating trospium. In fact, Madaus, a German company, had been selling trospium in an immediate release form in Europe since 1967.[5] Interneuron, now called Indevus, acquired the U.S. rights to trospium in 1999 and began selling an immediate release, twice-daily dosage trospium in the United States under the name SANCTURA®. Here, the claims cover an invention that "is directed to pharmaceutical compositions that allow for once daily dosage forms of trospium." *See generally* '978 Patent. The patent states that a once-a-day administration of trospium is "advantageous over the twice-a-day

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[3] The plaintiffs' identification of a person of ordinary skill in the art is derived from Drs. Weiner, Davis, and Kibbe's testimony and, in its entirety, would require:

> [A] Ph.D. degree in pharmaceuticals, pharmacy, chemistry, or some related field, and would have at least several years' experience in formulation or evaluation of oral dosage forms. The person would likely be a member of a development team that may include other individuals skilled in relevant areas, such as, for example, persons skilled in running or assessing clinical trials. Extensive practical experience could be substituted for the relevant degrees. The experience could have been obtained in either industry, government, or academia.

(D.I. 203 at 27 (quoting Tr. at 532:25-533:15 (Weiner); *id.* at 610:18-19 (Davis); *id.* at 856:23-857:3 (Kibbe).)

[4] The defendants' description of a person of ordinary skill in the art is derived from Dr. Kibbe's testimony. (D.I. 202 at 2 (citing Tr. at 856:11-857:10 (Kibbe); WDX 126).)

[5] Trospium chloride was introduced into the market as a spasmolytic agent in 1967 under German patent 1 194 422. *See* '978 Patent, col. 1:36-38.

administration in terms of both patient compliance and reduced adverse events, thus providing better treatment" of OAB. *Id.* at col. 1:66-2:2.

Both at trial and in their post-trial briefings, the plaintiffs focus their non-obviousness arguments on the fact that trospium is a quaternary ammonium, which renders the compound positively charged and, as a result, leads to negligible colonic absorption. Specifically, the plaintiffs assert that, for the defendants to meet their burden of demonstrating, by clear and convincing evidence, that the patents-in-suit are obvious, they must show that "each of the limitations can be found in the prior art and that there was a reason to combine the prior art to make the claimed inventions with a reasonable expectation of success." (D.I. 203 at 26.) The plaintiffs contend that the defendants cannot make this showing because trospium's lack of colonic absorption and challenging attributes made use of the molecule in a once-a-day formulation non-obvious to a person of ordinary skill in the art. This issue dominated the parties' invalidity arguments at trial. Consequently, although the court concludes that the prior art renders every element of the asserted claims obvious,[6] it will focus its discussion on how trospium was viewed as a potential candidate for once-a-day formulation by a person of ordinary skill in the art in 2002 based on its quaternary ammonium properties.

As noted, unlike Ditropan and Detrol, the two mainstay OAB drugs available in 2002, SANCTURA XR® utilized trospium, a quaternary ammonium. The plaintiffs assert that the following trospium attributes make it a challenging molecule to use in a once-a-day formulation[7]: (1) permanent positive charge; (2) negligible colonic absorption, particularly in view of the thirty-

[6] The court has examined each asserted claim of the patents-in-suit and concludes that the defendants have established obviousness for each. The court is persuaded by Drs. Kibbe and Mayersohn's testimony.

[7] In addition to these challenging attributes, the plaintiffs also assert that trospium: low bioavailability, low partition coefficient, high solubility, hydrophilicity, poor permeability, flip-flop pharmacokinetics, motility effects, and lack of IVIVC. (D.I. 203 at 28 (citing Tr. at 1401:25-1402:22, 1403:19-1404:8, 1404:11-18, 1405:1-16, 1406:8-21 (Davis); *id.* at 952:1-11 (Derendorf); *id.* 1012:4-13 (Kibbe)).)

percent colonic absorption "threshold" required for a successful once-a-day formulation[8]; (3) paracellular absorption[9]; (4) wide range of variable half-life values; and (5) binding to mucus and feces. (D.I. 203 at 28.) During the years preceding the filing of these applications, however, a number of prior art references appeared disclosing, among other things: multiparticulate formulations using extended, delayed, and immediate release pellets; multiparticulate formulations designed to target the lower GI tract; properties of trospium that made it a good candidate for once-a-day formulation, such as its relatively long half-life; and the market drive to formulate once-daily formulations. A number of these references suggested that trospium could be used in a once-a-day formulation. The court discusses each of the prior art references presented at trial below.

a. Prior Art Addressing Multiparticulate Formulations to Target Drug Delivery Along the GI Tract & Prolong Release

Multiparticulate formulations designed to target release in the lower GI tract were standard technology in the prior art in 2002. As explained by Dr. Kibbe, Watson's expert, multiparticulate formulation refers to a type of dosage form in which there can be different kinds of release within the same capsule. Tr. at 870:4-18 (Kibbe). For instance, a formulator can have "an immediate release segment, an extended release segment, a delayed release segment, and extended release with a delayed release coating." *Id.* Dr. Kibbe testified that, as of 2002, those of ordinary skill in the art: (1) were familiar with the materials and methods used to make multiparticulate formulations, including excipients to control release; (2) could examine

[8] The plaintiffs maintain that, "[i]t was well recognized in 2003 that poor colonic absorption meant low expectation of success" and that "formulators were aware of a rule of thumb that molecules which exhibited colonic absorption of 30% or less, were 'very difficult and probably impossible' to formulate as an extended release product." (D.I. 203 at 28 (quoting Tr. at 1428:13-1429:15 (Davis); PTX-647; PTX-635).)

[9] Dr. Kidane testified that trospium's absorption is paracellular, rather than transcellular. Dr. Kidane defined paracellular absorption as absorption "between the cells" rather than "through the cells," which the plaintiffs argue "pose[s] yet another challenge since the junctions between cells in the lower gastrointestinal tract are especially tight." (*Id.* at 4 (citing Tr. at 307:21-309:5; 321:22-25 (Kidane)).)

numerous prior art publications that described particulates with active ingredients coated with enteric polymers, release controlling polymers, or combinations thereof; and (3) would be aware that the prior art taught methods to target the lower GI tract by utilizing release controlling polymers. *Id.* at 871:9-872:2; 1034:9-1035:7. Notably, even the plaintiffs' expert, Dr. Davis, stated that formulations using extended and delayed release pellets were "well-known systems that had been described in the literature and in patents," and that a person of skill in the art could effectively select and combine polymers to target drug release in the GI tract. *See id.* at 1472:7-11, 1475:12-1476:14, 1520:8-14 (Davis).

One such prior art reference is the 1975 edition of Remington's *Science and Practice of Pharmacy*,[10] which lists more than thirty long-acting multiparticulate dosage forms. Dr. Kibbe testified that multiparticulate dosages have been used since the 1950s and that the long-acting products listed in Remington are "long-acting because they contain coated or slow release beads." *Id.* at 867:9-21 (Kibbe). Dr. Kibbe also identified two FDA-approved prior art products having multiparticulate dosage forms, Shire's Carbatrol® and Adderall XR®. (D.I. 202 at 3.) Both products employed Shire's "Microtol platform," which is the same platform Shire used in developing once-a-day trospium. Tr. at 375:13-376:3 (Kidane); *see also id.* at 1349:25-1350:16 (Bhatt).

Specifically, Carbatrol®, developed by Shire in 1997, combines immediate, extended, and delayed release pellets in a single capsule and, per its Orange Book U.S. Patent No. 5,326,570 (the "'570 Patent") specification, the extended release pellets can be coated with ethylcellulose and hydroxypropyl methylcellulose. *See* DTX-2075 at 3; '570 Patent at col. 6:21-27, 6:34-40; Tr. at 872:3-13, 875:8-21 (Kibbe). The '570 Patent also reveals that the delayed release pellets can be coated with polymers such as methyl methacrylate, which is often referred to as Eudragit. *See*

[10] *See* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 15th ed., at 1618-1643 (1975).

'570 Patent at col. 7:16-25, 7:30-36; *see also* Tr. at 876:2-9 (Kibbe). Dr. Kibbe testified that a person of ordinary skill in the art would have known that this polymer blend can be adjusted to control the release of the drug. Tr. at 875:22-876:1 (Kibbe). Finally, the '570 Patent also teaches that a combination of immediate, extended, and delayed release pellets releases carbamazepine for approximately twelve hours, which allows it to be administered twice-a-day rather than four times a day. *See* DTX-1014 at Fig. 1. In light of Dr. Davis' testimony regarding transit times of pellets through the GI tract in the fasted state,[11] a person of ordinary skill in the art could conclude that Carbatrol® would be expected to release the drug in the ileum and the colon.

In response to this reference, the plaintiffs assert that Carbatrol® and the '570 Patent do not teach that a once-a-day trospium product could prove successful because Cabatrol® is a tertiary amine that is only available in a twice-daily extended release dosage form and Shire was not able to make a once-daily formulation. DTX-1158; DTX-2075; Tr. at 872:14-17, 1071:23-1072:3, 869:16-17, 1072:4-1073:8 (Kibbe). The plaintiffs also note that Dr. Kibbe acknowledged on cross-examination that Carbatrol® "wouldn't meet a lot of the claims" of the patents-in-suit "for a lot of reasons, one of which is that it's a completely different drug . . . [and that] you have to take into account the nature of the drug before you can make a decision that you can move it to a once daily." (D.I. 203 at 33 (quoting Tr. at 1073:15-24 (Kibbe)).)

The plaintiffs did not, however, establish that the difference in chemical structure between Cabatrol® and trospium would preclude use of multiparticulate dosage forms in developing a once-a-daily formulation, or challenge that substituting trospium for carbamazepinein in this formulation resulted in the claimed invention at issue here. Thus, while the court agrees with the plaintiffs that Carbatrol® would not meet several of the claims of the patents-in-suit because it is not a once-a-day drug, the court does not agree with the plaintiffs' conclusion that the

[11] *See infra* Section III.E.2; *see also* Tr. at 613:17-615:12 (Davis).

"Carbatrol® art teaches nothing about once-daily trospium." (*Id.*) Instead, the court concludes that, despite the patents-in-suit and Cabratrol® being different formulations, the Carbatrol® art, including the '570 Patent, does teach that multiparticulate formulations can be employed to target release in the lower GI tract by adjusting the polymer blend used to control release of the drug.

Other references that disclosed the use of multiparticulate dosage formulations include two Canadian patent applications, the 2,035,155 application ("the CA '155") and the 2,403,670 application ("the CA '670"). The CA '155 discloses that using extended release and delayed release pellets in a multiparticulate formulation can target the ileum and the colon. *See* DTX-1021 at Abstract, page 8:3-25; Tr. at 878:15-880:11 (Kibbe). Specifically, the Abstract to CA '155 states:

> The invention provides pharmaceutical compositions with the property of targeted controlled release of active principles which act pharmacologically within the intestine and in particular within the colon and the terminal portion of the ileum. To attain this object the active principle is prepared in multiparticle multidose form and is covered with at least two membranes, one of pH-dependent solubility and the other insoluble but permeable to the intestinal fluids.
>
> While the covered active principle remains in the stomach and in the initial intestinal portion, ie while the pH is less than 5.5, it is not released.
>
> Only when it reaches an environment of higher pH (small intestine or colon) does the pH-dependent membrane dissolve to commence release of the active principle.
>
> From this moment the second membrane, which is pH-independent but impermeable to the intestinal fluids, acts to slow down and control the dissolution of the medicament within the small intestine-colon tract.

DTX-1021 at Abstract. The CA '670 also discloses the use of two different polymer-coated pellets to target release along the GI tract, including the lower intestine, and combining pellets with enteric coatings of different pH sensitivities to target different regions, including the colon. DTX-2029 at Abstract, page 10:1-18; *see also* Tr. at 880:12-882:12 (Kibbe).

The court rejects the plaintiffs' assertion that CA '155 does not teach that multiparticulate formulations can be used to target the lower GI tract simply because that application "describes

delivery of drug to the lower GI for local, topical action" rather than delivery for absorption. (D.I. 203 at 33.) Specifically, and as the defendants make clear, while CA '155 does not teach absorption in the lower GI tract, it does teach that multiparticulate dosage forms can be used, in combination with coating selections, to target when a drug is released in the lower GI tract. Moreover, the court finds unavailing the plaintiffs' argument that CA '670 "teaches that [its inventors] did not consider trospium to be one of the many molecules that would lend to once a day extended release formulation" because it was not included in a four page list of possible active ingredients. (*Id.* at 33-34.)

Similar to the court's finding with respect to CA '155, the court concludes that a person of ordinary skill in the art would find CA '670 highly relevant to the subject matter of the patents-in-suit because it teaches that polymer-coated pellets can be used to target release in the lower GI tract. Contrary to the plaintiffs' arguments in connection with these Canadian applications,[12] the court notes that each prior art reference is not required to teach each claim of the patents-in-suit for those patents to be deemed obvious. Consequently, because these applications are relevant in revealing how a skill artisan can target pellet release, the court concludes that these references teach to the multiparticulate claims of the patents-in-suit.

Similarly, another prior art reference, U.S. Patent No. 6,322,819 ("the '819 Patent"), also describes a multiparticulate system for pulsed delivery of a drug throughout the GI tract. *See* DTX-1016 at Abstract; *see also* Tr. at 1215:8-1216:15 (Mayersohn). This patent, which is assigned to Shire Laboratories, describes the same "Microtrol platform" that was ultimately employed in the once-a-day trospium formulation. Tr. at 1216:9-15 (Mayersohn); *id.* at 367:8-11

[12] Specifically, the plaintiffs argue, in connection with CA '155, that this application is not relevant to the defendants' obviousness defense because the "CA '155 patent does not teach that there is a likelihood of success of formulating once-daily trospium as it teaches nothing about trospium, extended release products, once-daily dosage forms or formulating drugs with low colonic absorption." (D.I. 203 at 33-34.)

(Kidane). Moreover, it discloses enteric polymers, including Eudragit, for targeting delivery to the colon by delayed release for a period of time or until the pellets reached a particular pH level. *See* '819 Patent at col. 2:5-14, 3:57-4:4. Here, again, the court rejects the plaintiffs' argument that, because the '819 Patent covers amphetamine salts, it "does not teach that there is a reasonable likelihood of success of developing once-daily trospium product as it does not disclose trospium, quaternary ammonium compounds, or any blood levels." (D.I. 203 at 34.) For the reasons stated above, the court finds that a person of ordinary skill in the art would find this reference relevant to the claimed invention because it discloses targeting the release of multiparticulate formulations in the lower GI tract through the use of enteric polymers.

Finally, the defendants also introduced European Patent Application Nos. 1101490 and 1125586 (collectively, "the Ishibashi Patents"), which were published in 2001. (D.I. 202 at 4; D.I. 203 at 33.) The Ishibashi Patents describe a multiparticulate system for targeting drug release throughout the ileum and the colon, residence time in the GI tract, and disclose how release can be targeted through the use of pH enteric polymers. DTX-1022 at 7:15-17, 2:16-31, 4:35-39; DTX-1023 at 4:21-25; Tr. at 876:10-878:14 (Kibbe); *id.* at 1215:18-1216:8 (Mayersohn). In addition, the Ishibashi Patents include a list of various possible active ingredients for controlled release formulas and includes trospium among them. Tr. at 877:2-878:14, 1077:20-1078:19 (Kibbe); *id.* at 1265:1-14 (Mayersohn).

In response, the plaintiffs argue that the Ishibashi Patents are not relevant to the obviousness analysis because they do not discuss "trospium's unique characteristics, challenges, or any blood levels" and none of the other quaternary ammonium molecules included on the list have been "made into an extended release form." (D.I. 203 at 33.) With respect to the plaintiffs' former argument, again, the court finds this reference relevant because it discloses

multiparticulate formulation targeted release in the lower GI tract. Regarding the plaintiffs' latter argument, the court does not find this assertion persuasive because the fact that the other quaternary ammonium molecules listed were not developed into extended release formulations is irrelevant to how a person of skill in the art in 2002 would view the Ishibashi Patents' disclosures and teachings.

In light of the references examined above, the court finds that the use of multiparticulate dosage forms, including enteric-coated polymers, to target the lower GI tract was obvious in 2002. Notably, even the plaintiffs' expert Dr. Davis agreed on cross-examination that a person of ordinary skill in the art in 2002 would have an "extensive toolkit" of technologies available for formulating controlled release dosage forms. Tr. at 1470:14-1471:2 (Davis). Dr. Davis also acknowledged that one of skill in the art would be able to use this toolkit to develop dosage forms designed to release a drug in the lower GI tract, specifically the ileum and the colon, and that this artisan would know that a once-a-day formulation would need to be delivered throughout the GI tract. *Id.* at 1472:7-11, 1520:8-14, 1384:18-1386:8. The court agrees.

In view of the foregoing, the court concludes that: (1) the asserted claims of the patents-in-suit are obvious as they relate to the administration of trospium through a controlled release solid, trospium-bearing particulates; (2) the asserted claims of the patents-in-suit are obvious as they relate to using multiparticulate formulations to target the lower GI tract[13]; (3) claims 1 and 20 of the '978 Patent, claims 1, 10, and 16 of the '448 Patent, claims 1 and 10 of the '449 Patent, and claim 1 of the '359 Patent, are obvious as they relate to multiparticulate formulations[14]; and (4)

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[13]*See also* Tr. at 1035:8-20 (Kibbe); *id.* at 1040:22-1042:2, 1042:8-1043:7 (concluding that releasing at least a portion of trospium in the lower GI tract is obvious "to get levels of the drug spread out over the longer time period").

[14]*See also id.* at 1048:12-1050:11 (concluding that the element of comprising trospium containing extended, delayed, and immediate release components "is exactly the same kind of blending" as Carbatrol® and the '570 Patent); *id.* at 1050:12-1053:5 (noting that claims 10 and 16 of the '448 Patent would also be obvious, for similar reasons, because the combination of extended and delayed release components "is one of the possible combinations

claims 1, 18, and 20 of the '978 Patent, claim 1 of the '448 Patent, and claim 1 of the '449 Patent, as they relate to using a delayed release formulation comprising at least one enteric polymer to target the lower GI tract, are obvious in light of the references discussed.[15]

b. Prior Art Addressing Trospium's Attributes That Rendered It a Viable Candidate for Once-a-Day Formulation

In addition to the foregoing, the prior art in 2002 also taught that trospium was a candidate for once-a-day formulation. The testimony of both sides' experts makes clear that a person of ordinary skill in the art would weigh and consider all known attributes of a molecule before determining whether it is a candidate for a once-a-day formula. *See, e.g.*, Tr. at 1026:21-1027:22, 1073:13-24, 1074:3-13 (Kibbe); *id.* at 1400:4-24 (Davis). As Dr. Davis explained:

> The first thing they would want to do is find out about the drug molecule. What are the properties of the molecule? I referred to this in the past as understand the personality of the molecule. What is its stability? What is its solubility, its partition coefficient? Then what do we know about its pharmacokinetic properties?
>
> So the person that is going to start formulation really start looking at the literature, try to find out as much as possible about the molecule and any deficiencies or any concerns. Is this going to be easy, mediocre, or difficult? To start thinking about the challenge you are going to face.

Id. at 1400:9-24. In light of this testimony[16], the court concludes that prior art references related to trospium's characteristics, aside from what the plaintiffs argue is its negligible colonic absorption, are relevant in determining whether trospium would be perceived by one of skill in the art as a once-a-day formulation candidate in 2002. The court further concludes that these references, discussed below, not only showed trospium to be a candidate for once-a-day

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we could get at to get the release patterns . . . and then the absorption pattern we need," and an enteric coating that releases at a pH of about 7.0 would release in the colon).

[15] *See id.* at 1034:9-1035:7; *see also id.* at 1048:12-1050:11 (stating that the elements related to selecting one component from a group consisting of an extended release component and a delayed release component, such as that required by '449, claim 1, along with an immediate release component would be obvious in light of Carbatrol® and the '570 Patent, among other references).

[16] The court notes that Dr. Kibbe also testified that one of skill in the art would consider and need to understand both trospium's positive and negative attributes to determine whether it can be developed into a once-a-day formulation. Tr. at 1026:21-1027:22 (Kibbe)

formulation, but also suggested how formulators could identify steady state blood levels, develop a formulation utilizing known half-life data, and address trospium's low colonic absorption.

By 2002, there were three references available that identified trospium's pharmacokinetic parameters, as observed from its long use as an immediate release product: G. Frohlich[17] (DTX-1031), Fusgen[18] (DTX-1033), and Zerres[19] (DTX-1169). Specifically, Frohlich and Fusgen disclosed that trospium is known to have a C_{max} of 3-5 ng/ml with a T_{max} of about five hours. DTX 1031 at 295; DTX-1031 at 225; *see also* Tr. at 1010:3-11 (Kibbe). Zerres also disclosed that trospium had a steady state C_{min} of about 0.6 ng/ml, steady state C_{max} of about 1.9 ng/ml, and an area under the curve (an "AUC") of 30 ng/ml per hour. Tr. at 1206:25-1207:18 (Mayersohn); *id.* at 1469:4-16 (Davis). Drs. Kibbe, Mayersohn, and Kidane all testified that a person of ordinary skill in the art would have used these pharmacokinetic parameters, known from immediate release trospium, to establish target blood levels for a once-a-day formulation. *Id.* at 1038:22-1039:21 (Kibbe); *id.* at 1207:19-1208:2 (Mayersohn); *id.* at 296:3-9, 302:5-13 (Kidane).

Specifically, Dr. Kibbe testified that a person of skill in the art seeking to develop a controlled release dosage form would start with the "goal of having a lower C_{max} and slightly higher C_{min}" than the immediate release formulation and would "establish [concentration] ranges based on the immediate release drug." *Id.* at 1035:21-1036:12, 1038:22-1039:21 (Kibbe). Namely, the objective in controlled release formulations, as Dr. Kibbe explained, is to slow absorption such that the "peak shifts to the right," i.e., the T_{max} occurs later and the minimum effective concentration is maintained. *Id.* at 860:5-18. Dr. Kibbe testified that, because trospium

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[17] G. Frohlich, M. Bulitta, & W. Strosser, *Trospium Chloride in Patients with Detrusor Overactivity*, 40 INT'L J. OF CLINICAL PHARMACOLOGY & THERAPEUTICS, no. 7, 2002 at 295-303.

[18] I. Fusgen & D. Hauri, *Trospium Chloride: An Effective Option for Medical Treatment of Bladder Overactivity*, 38 INT'L J. OF CLINICAL PHARMACOLOGY & THERAPEUTICS, no. 5, 2000 at 223-234.

[19] KATHRIN ZERRES, BESTIMMUNG DES PHARMAKOKINETISCHEN PROFILS VON TROSPIUM CHLORID NACHEINMAL UND MERHRFACHGABE BEI GESUNDEN, ALTEREN PROBANDEN (2000).

has a "relatively long T_{max}, five hours, and a relatively long half-life, 12 to 14 hours," shifting the peak requires:

> only . . . a little bit. . . . We don't have to move it to where the C_{max} comes in at 12 hours or 14 hours, because we know that the half-life is 14 hours. So if we could just move it some, and perhaps move it six hours, we would get levels in the body that would then, because of the long half-life, still stay above the minimum concentrations as we moved it out.

Id. at 1014:4-1016:5. The Fusgen and Zerres references each teach that trospium has a half-life of five to seventeen hours, which is a range considered favorable for a once-a-day formulation because only a small increase in the effective half-life is needed to provide twenty-four hour therapeutic effect. DTX-1033 at 225; DTX-1169; *see also* Tr. at 1206:25-1208:9, 1215:3-7, 1281:19-1283:15, 1294:11-24 (Mayersohn); *id.* at 1469:17-22 (Davis).

The plaintiffs maintain that the Frohlich, Fusgen, and Zerres references do not disclose "a once-daily trospium product, releasing trospium in the lower GI tract or that once-daily form of trospium could produce blood levels comparable to the twice-a-day product." (D.I. 203 at 31.) Specifically, the plaintiffs contend that: (1) the Frohlich reference, a review paper, "noted the low bioavailability of trospium [] and differentiated trospium from the two tertiary amine OAB products"; (2) Zerres was "similarly discouraging" in that it reported trospium's half-life to be in the range of 6.18 hours to 16.76 hours, "evidenc[ing] the difficulty in formulating once daily trospium and the low expectation of success a person of skill would have had in 2003"; and (3) Fusgen reported on trospium's "low bioavailability, differences from tertiary amines, side effects and observed maximum concentrations for twice a day administration." (*Id.*) The plaintiffs also note that Dr. Davis testified that trospium's reported half-life was a "wide range" that "could be problematic." Tr. at 1400:25-1401:18 (Davis).

Dr. Mayersohn, however, explained that formulators routinely deal with this level of variability. *Id.* at 1208:3-9, 1292:25-1294:24 (Mayersohn). In response to Dr. Mayersohn's comments that trospium's half-life was in a "normal range," Dr. Davis stated that he was "not sure that they're normal, but [he had] not checked the literature." *Id.* at 1401:8-18 (Davis). Notably, Dr. Kidane, a member of the Shire development team, also found the half-life of trospium encouraging, stating:

> Due to its rather long elimination half-life, this drug would benefit from a slight extension on the absorption phase without significantly compromising its bioavailability. By extending its absorption phase by 4-8 hours, it is possible to achieve an extended release preparation that could be used as a once a day rather than the current twice a day treatment.

JTX-039 at Background. Based on these conclusions, the court disagrees with the plaintiffs' argument that a person of skill in the art would have found Zerres' findings as to trospium's half-life discouraging.

The court notes that the plaintiffs' arguments, in the main, focus exclusively on how trospium's "negative" attributes are disclosed in these references, rather than on the "positive" attributes and/or useful information also disclosed. For example, in arguing that the Frohlich paper would have been "discouraging" to one of skill in the art because it disclosed trospium's low bioavailability, the plaintiffs neglect to detail that the Frohlich reference also taught trospium's C_{max} values, which would be useful to a skilled artisan seeking to establish blood levels based on the immediate release pharmacokinetic parameters. *See* DTX-1031 at 295. As noted, experts on both sides testified that a person of ordinary skill in the art would have considered both the positive and negative attributes of a molecule before determining whether it could be developed into a once-a-day formulation. The court finds this testimony persuasive and concludes that these references and, specifically, the data disclosed as to trospium's steady state

blood levels, C_{max} and C_{min} figures, and half-life range, would be viewed as relevant to a person of skill in the art seeking to develop a once-a-day trospium formulation.

Another reference detailing trospium's pharmacokinetic parameters was the Langguth study[20], which disclosed that trospium's limited absorption resulted from binding to mucus in the GI tract particularly at neutral pH levels and, further, that this limited absorption could be overcome by saturating the binding sites. *See* DTX-1035 at 269. Specifically, Langguth taught that "[t]he binding is saturable, since at higher trospium concentrations the percentage of mucus-bound trospium decreases. . . . The mucus binding of trospium could be partially inhibited by the addition of excess cationic hexamethonium bromide [i.e., quaternary ammonium] to the incubation solution." *Id.* Dr. Kibbe testified that this approach would allow the "residual trospium that was available . . . the opportunity to be absorbed." Tr. at 1029:10-1030:9 (Kibbe). In addition, the Breuel paper[21] demonstrated that high doses of trospium were tolerable, such that increasing the amount of trospium to promote absorption would not risk patient safety. *See* DTX-1028 at 463; *see also* Tr. at 271:8-218:13 (Sandage); *id.* at 1233:17-1234:5 (Mayersohn). Finally, U.S. Patent No. 2,899,357 (the "'357 Patent") also taught the use of a therapeutically inactive material to possibly reduce mucin binding and enhance absorption. *See* Tr. at 1030:24-1031:3, 1101:11-1102:3 (Kibbe).

In response, the plaintiffs assert that Langguth discouraged development of the claimed invention because it disclosed that "permeability of trospium was low and could not be improved by microemulsion or cyclodextrin complex formulations." (D.I. 203 at 34 (citing Tr. at 1098:14-25; 1100:11-1101:2 (Kibbe)).) The plaintiffs argue that Langguth demonstrated that the

[20] Peter Langguth & AlfonsKubis, et al., *Intestinal Absorption of the Quaternary Trospium Chloride: Permeability-Lowering Factors and Bioavailabilities for Oral Dosage Forms*, 43 EURO. J. OF PHARMACEUTICS & BIOPHARMACEUTICS, 1997, at 265-272 .

[21] H.-P. Breuel, G. Murtz, S. Bondy, J. Horkulak & B.M. Gianetti, *Safety and Tolerance of Trospium Chloride in the High Dose Range*, *in* ARZNEIMITTEL FORSCHUNG DRUG RESEARCH: SPECIAL SECTION BIOTECHNOLOGY IN DRUG RESEARCH, at 461 (1993).

absorption mechanism of trospium across the intestinal epithelum is "rather complex," "bioavailability of quaternary parasympatholytics (trospium) is low and variable, and intestinal permeability is low due to positive charge." (*Id.* (citing JTX-12 at 75607; Tr. at 1246:6-1248:3 (Mayersohn)).) Moreover, the plaintiffs assert that Langguth's suggestion to encourage absorption by adding excess hexamethonium bromide does not teach to the asserted claims because it suggested a compound other than trospium. (*Id.* at 35.) The plaintiffs cite Langguth's "Conclusion" as evidence that it taught away from the claimed invention:

> Trospium chloride undergoes a complex absorption mechanism in the intestine involving intestinal secretion and reversible mucus binding. Its overall permeability across the intestinal epithelium is low and could not be significantly improved by microemulsion and cyclodextrin complex formulations, thus providing a mechanistic explanation for its low bioavailability in man.

JTX-012 at 75613. As noted, however, persons of skill in the art would evaluate a drug's positive and negative attributes in assessing whether it can be developed into a once-a-day formulation. To this end, a formulator would not focus exclusively on trospium's low bioavailability, but, rather, would consider this attribute in combination with its other pharmacokinetic parameters as well as references suggesting ways to remedy negative attributes. Consequently, in light of the evidence before it, the court finds the plaintiffs' argument that this study would discourage use of trospium unavailing.

The court also rejects by the plaintiffs' argument that a person of skill in the art would not find this reference or the '357 Patent relevant because they do not suggest the use of excess trospium, for three reasons. First, the Langguth reference suggests the use of a quaternary ammonium and, therefore, the fact that it does not suggest trospium itself is inconsequential. Second, the court finds that the '357 Patent's suggestion of using therapeutically inactive material to reduce mucin binding and absorption would be considered relevant, despite not mentioning the

addition of trospium, as it taught a method of enhancing absorption applicable to the claimed invention. Third, Shire's internal emails undermine the plaintiffs' argument as to Langguth's relevance. Specifically, an internal email from October 29, 2002 noted that:

> Recent transport study results as well as literature search revealed that the low bioavailability of Trospium is at least partially due to its binding to mucin (negatively charged for the most part). Blocking the binding of trospium to mucin by incorporating other quaternary ammonium compounds resulted in permeability enhancement. With this in mind, one avenue of enhancing 'bioavailability' is to increase the dose in the DR portion. This is basically to use trospium itself to saturate the binding sites (mucin) hence what comes beyond the saturation point will be absorbed.

DTX-2175; *see also* Tr. at 398:11-403:17 (Kidane); *id.* at 1028:17-1033:4 (Kibbe). This statement, coupled with a September 12, 2002 Shire email citing the Langguth study by name and highlighting its findings, makes clear to this court that the Langguth reference would be considered both relevant and instructive to a person of ordinary skill in the art pursuing the subject matter of the claimed inventions because it taught how to overcome trospium's low colonic absorption. *See* DTX-2174 at 2.

In light of these references, the court concludes that: (1) claims 1, 2, 4, and 20 of the '978 Patent, claims 1 and 16 of the '448 Patent, claim 1 of the '449 Patent, and claim 1 of the '359 Patent, as they relate to seeking steady state blood levels comparable to the immediate release formulation blood levels, are obvious based on the Frohlich, Fusgen, and Zerres references[22]; and (2) claims 1, 18, 19, and 20 of the '978 Patent, claim 1 of the '448 Patent, claim 1 of the '449 Patent, and claim 1 of the '359 Patent, as they relate to releasing trospium in the colon and lower

[22]*See also* Tr. at 1035:21-1036:12, 1036:21-1037:8 (Kibbe) (concluding that the prior art disclosed using information on the immediate release product to set "the boundaries of the target that you are trying to develop", here, "having a lower C_{max} and slightly higher C_{min} on the sustained release"); *id.* at 1038:24-1039:21 (noting that claims 2 and 4 of the '978 Patent are obvious because "it would be obvious to establish ranges based on the immediate release drug and then to go ahead and meet those ranges"); *id.* at 1045:7-1048:11 (concluding that claim 1 of the '359 Patent is obvious because "[t]he average C_{max} can be arrived at by looking at the immediate release," and "we know that the T_{max} for the immediate release is between three and five" and, because you "want to push it later," "you could establish a time frame that you would be aiming for, and it could be less than six hours"); *see also id.* at 1206:25-1207:18 (Mayersohn) (discussing how Zerres taught the steady state C_{max} of immediate release trospium).

GI tract, would be obvious in light of the prior art in general and the Langguth reference in particular.[23]

c. The Motivation to Develop Once-a-Day Trospium

By 2002, Distropan and Detrol had been reformulated to once-a-day dosage forms. Rover,[24] a review article on once-daily extended release formulations for OAB treatment, concluded that once-a-day formulations "can be expected to maximize convenience and thereby improve compliance," and that the pharmacokinetic profiles of extended release formulations "should lessen the 'peak and trough, serum concentrations seen following multiple daily dosing with immediate release formulations," such that "peak drug levels may be associated with a reduction in dose-related adverse effects" like dry mouth. DTX-2049 at 8; *see also* Tr. at 863:7-866:3 (Kibbe); *id.* at 1208:10-19 (Mayersohn). Rover also indicated that the C_{min} and C_{max} of the extended release tolterodine formulation used in Detrol fell within the corresponding limits of the immediate release Detrol, and the AUC of the extended and immediate release tolterodine formulations were equivalent for the same total daily dosage. DTX-2049 at 10. To this end, Rovner taught: (1) that the OAB market was moving toward once-a-day formulations; and (2) that an extended release formulation should have a lower C_{max} and higher C_{min} than its corresponding immediate release formulation. *Id.*

Dr. Kibbe testified that the Rovner reference disclosed that lowering the C_{max} for an extended release formulation would improve patient compliance and tolerability because it results in lower occurrence of side effects, such as dry mouth. Tr. at 1046:24-1048:11, 1067:21-1068:2

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[23] *See also id.* at 1035:8-20 (Kibbe) (concluding that the claim element "releases trospium chloride in the lower gastrointestinal (GI) tract" was suggested in the prior art, and because trospium had limited absorption in the lower GI tract, targeting release there to obtain a once-a-day formulation would be "a natural consequence of that"); *id.* at 1040:22-1042:2, 1042:8-1043:7 (describing the '978 Patent's method of releasing trospium in the colon "to get levels of drug spread out over the longer time period" as "conventional wisdom" based on the prior art).

[24] Rovner, E.S. & A.J. Wein, *Once-Daily, Extended Release Formulations of Antimuscarinic Agents in the Treatment of Overactive Bladder: A Review*, 41 EUR. UROL., 2002, 6-14.

(Kibbe). Dr. Kibbe also testified that this conclusion was consistent with what was seen "all the time across the board with side effects" of other drugs, because lowering C_{max} "can avoid some of the side effects associated with peak heights." *Id.*; *see also id.* at 865:8-18.

The plaintiffs' cross-examination of Dr. Kibbe was limited to establishing that Rovner reviewed oxybutynin and tolterodine, which are not quaternary ammoniums. *Id.* at 1063:14-1064:23, 1066:8-11. Dr. Davis' testimony regarding Rovner likewise focused on the distinction that trospium is a quaternary ammonium. *Id.* at 1413:19-1414:5 (Davis). The plaintiffs did not, however, counter Rovner's findings that the market was moving toward once-a-day formulations by 2002 or that having a lower C_{max} and higher C_{min} in an extended release formulation, as compared to that formulation's immediate release counterpart, results in a reduction of side effects and increases patient compliance. To this end, the plaintiffs did not, aside from highlighting that Rovner did not address trospium, otherwise dispute that there would have been a motivation for those of skill in the art in 2002 to develop a once-a-day trospium formulation. Consequently, in consideration of the Rovner reference's findings, Dr. Kibbe's credible testimony,[25] and the claimed invention, the court finds the plaintiffs' argument unconvincing and concludes that Rovner would have been relevant to a person of skill in the art in 2002, particularly in light of the other information known about trospium at that time.

In view of the foregoing, the court concludes that: (1) all of the asserted claims of the patents-in-suit and, in particular, claim 1 of the '978 Patent, as it relates to the development of a once-a-day trospium formulation, are obvious based on the Rovner reference; and (2) claims 1,

[25]*See also* Tr. at 1033:21-1034:3, 1034:4-8 (Kibbe) (concluding that claim 1 of the '978 Patent is obvious in light of the Rovner reference, which discussed the demand for once-a-day formulations in the OAB market).

10, and 18 of the '449 Patent, as they relate to "minimizing the occurrence of side effects", would have been obvious in light of Rovner's findings.[26]

d. Reasonable Expectation of Success

The plaintiffs argue that a person of skill in the art in 2002 would not have a reasonable expectation of success that a once-a-day trospium formulation could be developed. Aside from the arguments already addressed, the plaintiffs assert this proposition, in the main, in connection with their contentions that: (1) the Fuhr/Schroder Poster disclosed that trospium, because of its quaternary ammonium structure, has low colonic absorption; and (2) that this low absorption, coupled with trospium's other negative attributes, would lead those of skill in the art to believe that a once-a-day trospium formulation would prove unsuccessful. (D.I. 203 at 27.) With respect to their first argument, the plaintiffs assert that the Fuhr/Schroder Poster taught away from the claimed invention. The court, therefore, addresses the Fuhr/Schroder Poster's conclusions separately in connection with the plaintiffs' "teaching away" argument,[27] but focuses here on how skilled artisans viewed trospium's low colonic absorption in 2002. For the reasons stated below the court concludes that a person of skill in the art in 2002 would, in fact, have a reasonable expectation of success.

In support of their argument that formulators would have a low expectation of success, the plaintiffs cite to the testimony of Drs. Davis, Derendorf, Mayersohn, and Kibbe, who all noted, to

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[26] *See also id.* at 1053:7-1054:21, 1054:22-1055:15 (finding that these claims would be obvious because, based on the prior art, "minimizing the occurrence of side effects" is a "direct result of us attempting to get a C_{max} of this product lower than the C_{max} of the immediate release product because we already said there is a direct relationship between at least dry mouth and the levels of drug in the body").

[27] Though discussed more fully in connection with the plaintiffs' "teaching away" argument in Section III.A.d.4, the court notes as relevant to this examination that persons of skill in the art would have found the Fuhr/Schroder Poster's disclosures regarding enteric-coated tablets encouraging. Specifically, these findings demonstrated that an enteric tablet could be released and absorbed in the small intestine, resulted in a later T_{max} and flatter concentration curve, and showed the trospium was absorbed in the lower GI tract. *See infra* Section III.A.d.4. Thus, the plaintiffs' argument that the Fuhr/Schroder Poster findings would cause a skilled artisan to predict a low expectation of success is unavailing based on this finding.

varying degrees, that trospium presented challenges. This testimony included: (1) Dr. Davis' prediction that once-a-day trospium would be difficult to develop (Tr. at 1389:5-8); (2) Dr. Derendorf's assessment that trospium is a "very unusual compound" and a "very, very poorly absorbed drug" (*id.* at 1005:5-6); (3) Dr. Mayersohn's conclusion that, on a scale of easy to extremely difficult, development of once-a-day trospium would be characterized as "to the right of medium" (*id.* at 1291:5-14); and (4) Dr. Kibbe's assessment that such development, while not impossible, would be challenging and that these challenges, though not insurmountable, would be difficult (*id.* at 1022:15-17, 1062:7-22, 1027:18-19, 1062:23-1063:20).

The plaintiffs also state that, as of 2002, persons of skill in the art knew that low colonic absorption, specifically, absorption under the thirty-percent—which was viewed as the threshold for once-a-day formulation success—would make once-daily formulation "very difficult and probably impossible." (D.I. 203 at 28 (citing Tr. at 1428:13-1429:15 (Davis)).) The plaintiffs cite to an article edited by Dr. Park, a Watson expert who did not testify, that described molecules with low colonic absorption as presenting "significant risk for development" and concluded that controlled release "development [was] not recommended." Tr. at 1426:16-1428:2 (Davis); *see also* PTX-647. The plaintiffs also refer to the *in silico* modeling that Dr. Arash Raoufinia, a member of Shire's development team, conducted during formulation of the claimed invention and calculated tropsium's absorption at twenty-five percent. Tr. at 1518:18-19, 22-23 (Davis); *id.* at 475:8-19 (Raoufinia). Dr. Kidane explained that this *in silico* modeling confirmed that development of once-daily trospium would be difficult. *Id.* at 334:10-17 (Kidane). Finally, the plaintiffs detail the perceptions of the Shire development team as representative of this low expectation of success: Dr. Bobby Sandage, the Chief Scientific Officer at Interneuron who acquired the trospium rights from Madaus, believed that trospium once-daily formulation would

be a "risky" project (*id.* at 169:3-4); and Dr. Kidane testified that it was the "most difficult" project on which he had ever worked (*id.* at 295:13-22).

The court, however, disagrees with the plaintiffs' conclusion that recognition of trospium's challenges equated to a low expectation of success. Rather, while trospium's low colonic absorption rendered its development of a once-a-day formulation more challenging than other molecules due to its quaternary ammonium structure, the prior art discussed above makes clear that persons of skill in the art had numerous references available that addressed trospium's positive attributes as well as how to remedy trospium's negative attributes.[28] Specifically, the prior art taught that: (1) multiparticulate formulations combining extended, delayed, and immediate release pellets could be used to target the lower GI tract; (2) formulators should strive to have a lower C_{max} and slightly higher C_{min} than the immediate release trospium formulation to reduce side effects; (3) trospium had a relatively long half-life, which was desirable for once-a-day formulations; and (4) trospium's mucus binding could be at least partially inhibited by the addition of excess quaternary ammonium cations.

In light of these prior art references, and accepting as credible Drs. Davis and Kibbe's testimony that a person of skill in the art would evaluate a molecule's positive and negative attributes in determining whether to attempt a once-a-day formulation, the court finds the plaintiffs' argument that a person of skill in the art would not have a reasonable expectation of success unpersuasive. This argument, which focuses primarily on trospium's low colonic absorption, fails to sufficiently weigh trospium's positive attributes that would have been known to skilled artisans or the prior art teachings that disclosed how to overcome recognized absorption challenges.

[28] *See supra* note 7 and accompanying text.

Notably, and as noted, even Dr. Davis acknowledged that a person of skill in the art in 2002 had an "extensive toolkit" of technologies available for formulating controlled release products and that these technologies could be employed to develop dosage forms to release in the lower GI tract. *Id.* at 1470:14-1471:2, 1472:7-11, 1520:8-14 (Davis). Dr. Davis further testified that, although he was aware that some references not included in the prior art[29] stated that once-daily dosage forms were "not recommended" for drugs with poor colonic absorption, he was unsure as to what "not recommended" would mean, other than that a formulator would need to think carefully about how to make the formulation.[30] *Id.* at 1427:21-1428:8. Dr. Davis nonetheless concluded that he did not equate "not recommended" with the message "don't do it." *Id.* at 1381:1-3, 1427:25-1428:2. Characterizing trospium's difficulty as "just right of medium," Dr. Davis stated that these references may be interpreted to support the use of other molecules. *Id.*

The court also notes that Shire's development team was not dissuaded by trospium's challenges and developed the trospium once-a-day formulation in a short period of time. Specifically, Dr. Sandage testified that, in September 2001, Indevus was "very optimistic that we could eventually make a once-a-day" formulation due, at least in part, to trospium's relatively long half-life. *Id.* at 149:10-151:5, 256:4-257:4 (Sandage). Indevus also told prospective partners that trospium could "easily" be converted into a once-a-day because of this long half-life.[31] DTX-

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[29] *See* PTX-647; PTX-635.

[30] With respect to the non-prior art reference concluding that drugs with poor colonic absorption are "not recommended" for once-a-day formulations, Dr. Davis testified:

> Q: If we look here what the implications are then for this poor colonic absorption, that is expected, what does it say about whether one should or should not try to develop a controlled release product?
>
> A: Well, it says that "controlled release with development not recommended." I don't think they said don't do it. But they don't recommend it. I am not sure quite what they mean by recommend. Perhaps they are saying there are better things to do, maybe go for another molecule rather than the one you are looking at.

Tr. at 1427:21-1428:8 (Davis).

[31] Specifically, Interneuron stated, in a September 2001 Non-Confidential Summary that "the relatively long half-life of 12 to 18 hours allows the opportunity for effective b.i.d. dosing with trospium, which may be easily converted into a once-a-day treatment." DTX-1046 at 3.

1046 at 3. In fact, the Shire development team developed numerous formulations that the applicants told the PTO embodied the claimed inventions only two months after first receiving trospium. *See* JTX-002 at SANCXR_AGN0005638-48; JTX-032 at SANCXR_SUP00152163; JTX-038 at SANCXR_END_01516563; *see also* Tr. at 351:17-374:11 (Kidane); *id.* at 1229:12-1230:11 (Mayersohn).

For the reasons stated above, the court concludes that a person of skill in the art in 2002 would have a reasonable expectation of success that, by combining the teachings and disclosures known in the prior art, once-a-day trospium formulation development was possible.

4. Secondary Considerations

The evidence in the record on several relevant secondary considerations does not weigh for or against a finding of obviousness and, consequently, does not undermine the court's finding that the patents-in-suit are obvious in light of the prior art. Under relevant law, once a *prima facie* case of obviousness has been established, the burden then shifts to the applicant to present evidence of secondary considerations of non-obviousness to overcome this *prima facie* showing. *See, e.g.*, *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). The Supreme Court has made clear that secondary considerations can include evidence of: commercial success; long felt but unsolved needs; and/or the failure of others. *See Graham*, 383 U.S. at 17-18. A plaintiff may also rebut obviousness by demonstrating that there were: unexpected results created by the claimed invention; unexpected properties of the claimed invention; licenses showing industry respect for the invention; and/or skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). However, "[e]vidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and

the commercial success." *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

Here, the plaintiffs contend that the defendants failed to establish a *prima facie* case of obviousness in light of the evidence adduced at trial. The plaintiffs also argue, in the alternative, that should the court determine, as it has, that the defendants established a *prima facie* case on this issue, the secondary considerations of copying, teaching away, failure of others, licensing, and unexpected results/skepticism sufficiently rebut this *prima facie* case. (D.I. 202 at 137); *see also Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1373 n.9 (Fed. Cir. 2004). The court addresses each secondary condition the plaintiffs raise in turn.

c. Copying

The plaintiffs assert that Watson and Sandoz's proposed products are copies of the patented invention. (D.I. 202 at 137.) Specifically, the plaintiffs contend that, like SANCTURA XR®, Watson and Sandoz's proposed products are capsules containing extended release and delayed release pellets. Moreover, the plaintiffs assert that Paddock's proposed product also copies the patented invention, in that it is a capsule that contains extended release and delayed release components intended to release in the lower GI tract and, as Paddock stated to the FDA, was designed to "match" SANCTURA XR®. *See* PTX-131; Tr. at 644:25-645:14 (Davis). In view of relevant law, however, the court does not agree that the defendants' alleged "copying" rebuts the *prima facie* case of obviousness.

Specifically, and as several courts have recognized, demonstration that a defendant has copied a patented invention is not compelling evidence of non-obviousness in the Hatch-Waxman context due to the unique nature of the ANDA process. *See, e.g., Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc.*, 642 F. Supp. 2d 329, 373-74 (D. Del. 2009) ("[A] showing of

copying, which Plaintiffs have provided here, is not compelling evidence of non-obviousness in the Hatch-Waxman context."); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001) ("[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective."). Consequently, even assuming that the defendants engaged in copying, such conduct is not strong objective evidence of non-obviousness in this action.

d. Teaching Away

The plaintiffs cite the Fuhr/Schroder Poster as teaching away from the claimed invention because it discourages the use of once-daily trospium.[32] Specifically, the plaintiffs maintain that the Poster teaches that Madaus, via Dr. Fuhr, was exploring the feasibility of developing a modified release formulation and that development of a modified release formulation of trospium would not succeed because absorption in the colon was negligible. (D.I. 203 at 30.) As the plaintiffs detail, Fuhr and Schroder initiated their study to "investigate the influence of intestinal site of administration on absorption of trospium chloride as the basis for the development of modified release preparations." *See* JTX-0014. The study utilized a methodology wherein eight individuals "received single 20 mg doses of trospium chloride orally as a tablet (reference), as an

[32] In addition to making this argument at trial and in their briefing, the applicants of the claimed invention also maintained this assertion to the PTO in its November 4, 2004 Amendment and Response Under 37 CFR § 1.111. Specifically, the applicants noted that Fuhr/Schroder study observed that "trospium chloride 'was mainly absorbed in the upper small intestine' and that absorption 'declined rapidly upon administration into more distal regions of the gastrointestinal tract.'" DTX-4019 at 14-15. To this end, the applicants argued that:

> [O]ne of ordinary skill in the art in 2003 would have believed: (i) that trospium chloride is absorbed predominately in the upper part of the small intestine; (ii) that very little trospium chloride is absorbed, if any, in the lower part of the small intestine and colon; (iii) that while modified release formulations of trospium chloride would have been desirable, there was little, if any reasonable expectation that a once-a-day formation would work because little or no absorption of trospium chloride would obtain after 8-12 hours when the formation would reach the colon.

Id. at 15.

Eudragit coated tablet dissolving at pH 6.0 (local administration into the small intestine), and rectally via mini enema (corresponding to local administration into the large intestine)." *Id.*

The study ultimately concluded that absorption of trospium from rectal administration, which "can be used as a model of colonic absorption," was only two-percent, far below the thirty-percent colonic absorption threshold generally recommended for successful extended release formulations. (D.I. 203 at 30 (citing JTX-0014 at Table 2).) The plaintiffs assert that these results taught away from the claimed invention because, as stated in the Poster's conclusions, there were "very low concentrations of trospium chloride found after rectal administration," "colonic absorption [was] almost negligible," and, as a result, "modified release preparations of the study drug using conventional technology are not expected to improve trospium chloride bioavailability." (*Id.* at 30-31 (citing JTX-0014).)

Based on the evidence presented at trial, however, the court concludes that the Fuhr/Schroder Poster does not teach away from the claimed invention. First, the reference itself and the methodology employed both indicate that the study was directed toward improving trospium bioavailability, rather than attempting to target trospium in the lower GI tract through the use of an extended release formulation.[33] Tr. at 1491:3-17 (Davis). Specifically, and as the

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[33] On this point, the plaintiff's expert, Dr. Davis, noted that:

> A: But the Schroder poster says nothing about once-a-day product. It's trying to improve the bioavailability. You could look at that poster and believe what they are trying to do is to improve the bioavailability of the drug by delivering it to the colon as an immediate release formulation. My groups have done that many times. Not interested in once a day. We just want to improve the bioavailability of different drugs . . . .
>
> . . . .
>
> Q: Let's go back to Schroder and what a person, if they looked at it, would take away from it. The person of ordinary skill in the art would not look at Schroder and say "I couldn't use the colon." Correct?
>
> A: Well, certainly, if somebody skilled in the art working for me looked at that and said, oh, I can use the colon, I would say, look, it is exactly what you would have expected from reading the literature. This expert, Fuhr, in looking at regional drug absorption, has said it's two percent of what you get in the upper GI tract, but it doesn't specifically say don't use the colon for once a day because it doesn't seem to be addressing that.

Tr. at 1491:3-17 (Davis); *see also id.* at 1491:18-149:4.

court examines further in connection with Paddock's anticipation argument, the Fuhr/Schroder study did not: (1) teach a formulation suitable for once-daily administration of trospium; (2) disclose steady state blood levels; or (3) present a formulation design aimed at targeting the lower GI tract. JTX-0014; *see also* D.I. 203 at 25. As a result, the court concludes that the study's finding that trospium, when placed in the rectum, exhibits poor colonic absorption, would have limited, if any, effect in teaching away from the claimed invention.

Second, this conclusion is further supported by testimony at trial indicating that the Fuhr/Schroder findings were viewed as speculative, inconclusive, and inconsistent with the known therapeutic effectiveness of trospium suppositories. In particular, this testimony detailed that the scope and methodology of the study limited the validity of its results. The study included a small sample of eight males and placed only five milliliters, the equivalent of one teaspoon, of trospium in the rectum. Drs. Kibbe, Mayersohn, and Flanner, in testimony the court finds credible, questioned the legitimacy of implementing the methodology employed based on the conclusion reached. *See* Tr. at 1010:17-1011:16, 1020:10-1027:22 (Kibbe); *id.* at 1210:4-22, 1259:20-1260:20, 1272:9-16 (Mayersohn); *id.* at 1335:12-1336:9 (Flanner); *id.* at 1457:5-1462:2, 1462:24-1465:4 (Davis).

Notably, even the plaintiffs' expert, Dr. Davis, stated at trial that: (1) it would be "unlikely" for a five millimeter mini-enema to physically make it from the rectum to the colon (*id.* at 1462:7-15); (2) he had never employed an enema to evaluate colonic absorption (*id.* at 1463:12-20); (3) the Fuhr/Schroder Poster was not published in a peer reviewed, scientific journal (*id.* at 1463:12-20); and (4) the prior art did not demonstrate a correlation between rectal and colonic absorption (*id.* at 1458:10-1465:4). Drs. Kibbe and Mayersohn concurred with Dr. Davis' assessment that while absorption in the rectum can indicate a drug will be absorbed in the colon,

poor absorption in the rectum does not allow a conclusion regarding colonic absorption. *Id.* at 1023:20-1024:10 (Kibbe); *id.* at 1259:20-1260:20 (Mayersohn). In addition, various references on trospium suppositories demonstrated that trospium was particularly effective for nocturnal enuresis in children and Dr. Mayersohn testified that this effectiveness "suggests colonic absorption following rectal administration" at least for that test group.[34] *Id.* at 1210:4-12, 1259:13-16 (Mayersohn). Dr. Davis also testified that he believed that a person of ordinary skill in the art would have largely ignored the Fuhr/Schroder Poster and would have given it no more than a minute's thought.[35] *Id.* at 1490:8-1492:19 (Davis).

Finally, the court agrees with the defendants' contention that a person of ordinary skill in the art interested in developing once-daily trospium would have found the Fuhr/Schroder Poster encouraging with respect to its disclosures regarding enteric-coated tablets. Specifically, and as Drs. Kibbe and Kidane explained, the enteric tablet demonstrated that trospium could be released and absorbed in the lower small intestine. *Id.* at 1025:3-1026:20 (Kibbe); *id.* at 392:20-394:3, 397:2-7 (Kidane). The results with the coated tablet showed a later T_{max} and a flatter concentration-time curve, which are both desired in a once-daily formulation. *Id.* at 1216:23-1217:24 (Mayersohn). In fact, Dr. Kidane stated that the results from the enteric-coated tablet

[34] The plaintiffs dispute the trospium suppository study findings because: (1) they do not teach to the development of a once-a-day trospium formulation; (2) the studies are focused on children with night-time bed wetting problems who received six suppositories per day; (3) a conclusion that trospium absorbs in an adult's colon could not be drawn from the conclusion that children demonstrate some trospium absorption; and (4) the references did not include any information about blood levels or take into account placebo effects. (D.I. 203 at 35-36 (citing Tr. at 1275:15-24 (Mayersohn); *id.* at 1089:12-14 (Kibbe); DTX-2025).) While the court does not draw a conclusion as to whether the suppository references can be applied to adults, it does find that these references, despite not addressing the development of every element of the claimed invention, nevertheless would not have discouraged a person of skill in the art from attempting to develop a trospium once-a-day formulation.

[35] Specifically, Dr. Davis stated:

> My view is [a person of ordinary skill in the art] would have probably ignored the Schroder poster. That's what I would have expected. There has been a lot of attention to the Schroder poster. I think the skilled person would say, Hmm, two percent. Okay, it's rectum. One could say there was information on the poor colonic absorption. . . . You could look at the poster and believe that what they are trying to do is to improve the bioavailability of the drug by delivering it into the colon as an immediate release formulation.

Tr. at 1490:5-1491:10.

showed trospium was absorbed in the lower GI tract. *Id.* at 392:20-394:3, 397:2-7 (Kidane). This conclusion is also confirmed by his Invention Disclosure:

> Although it has been reported that the drug exhibits an absorption window in the upper duodenum, there is also evidence of its absorption in the lower gastro-intestinal tract. An enterically coated trospium with a polymer that starts to dissolve at pH 6.0 resulted in bioavailability that is only 15% lower than the non-enteric tablet.

See JTX-038.

In view of the foregoing, the court concludes that the Fuhr/Schroder Poster did not teach away from the asserted claims. Specifically, the plaintiffs' argument that the Fuhr/Schroder study demonstrated negligible trospium absorption in the colon and, therefore, would have discouraged the invention of once-daily trospium, is not grounded in the evidence. Rather, the trial testimony made clear that the study's correlation of rectal to colon absorption, methodology, and conclusions would have been questioned by skilled artisans in 2002. Consequently, the plaintiffs' teaching away argument does not rebut the finding of obviousness.

e. Long Felt Need and Failure of Others

The plaintiffs further contend that, by 2002, no other inventor or company had successfully formulated trospium into a once-daily dosage, despite the fact that trospium had been marketed in Europe for several decades and there was a motivation to do so. (D.I. 203 at 37.) In support of this argument, the plaintiffs state that: (1) Dr. Kibbe, recognized that there had always been a motivation to develop a once-a-day extended release formulation; (2) Madaus unsuccessfully attempted to develop a modified release trospium formulation; (3) Paddock failed "both pilot and pivotal biostudies before its third formulation attempt," which was the basis for its ANDA; and (4) Mr. Bhalani, a member of Paddock's development team, acknowledged that the project took approximately twenty months longer than expected and was his "most challenging in

[his] 30 years of product development experience." (*Id.*) Based on the evidence presented at trial, however, the court concludes that the plaintiffs' assertions do not undermine its obviousness finding.

First, the plaintiffs have failed to demonstrate that the development of the patents-in-suit met a long felt but unmet need. The plaintiffs cite to the testimony of the defendants' expert, Dr. Kibbe, who stated that the "motivation" to turn the twice-daily dosage to a once-daily formulation "ha[d] been with us for a long time based on the benefits to the patient." Tr. at 1070:2021 (Kibbe). The plaintiffs also note that Dr. Kibbe agreed that trospium, though available in Europe since 1967, had not been formulated into a once-daily dosage as of 2002. *Id.* at 1068:7-21. The plaintiffs failed to demonstrate, however, that the need was long felt. Specifically, Dr. Kibbe also testified that, although there was some motivation to develop a once-daily formulation, he could not testify as to "why the German company [Madamus] wasn't motivated to try to do something," and agreed with the statement that "[t]he technology to do that as far as making an extended release once-a-day product was certainly there." *See id.* at 1070:2-25. Moreover, Drs. Sandage and Kidane's statements that once-a-day formulations were where the "market [was] headed" by 2002 similarly fail to make this showing. *See id.* at 226:6-15, 229:2-11, 272:9-274:4 (Sandage); *id.* at 320:1-321:7 (Kidane). Instead, their testimonies demonstrate that the need for once-daily OAB formulations was generated by market development and demand in the early 2000s, just prior to formulation of the claimed invention. *See* DTX-2049 at 6-7; PTX-471.

Second, the plaintiffs' argument that others had attempted to create a once-daily trospium formulation and failed does not rebut the *prima facie* case of obviousness. In support of this argument, the plaintiffs state that: (1) "Madaus unsuccessfully attempted to develop a modified release trospium chloride formulation"; (2) Paddock twice failed in their pilot and pivotal

biostudies before creating the ANDA at issue here; and (3) Mr. Bhalani noted that the project took much longer than expected and was his "most challenging." Tr. at 1140:9-10, 1141:5-14 (Bhalani). With respect the plaintiffs' first contention that Madaus attempted to develop a once-a-day formulation, this evidence, as stated, is not sufficiently established in the record. Specifically, Dr. Sandage's testimony regarding Madaus' work with trospium related not to its attempt to develop a once-daily formulation, but instead to its effort to reduce trospium dosing by doubling the immediate release dosage in a single 80 mg tablet. *Id.* at 152:11-15 (Sandage). Notably, Madaus' effort to simply double the immediate release dosage is not the claimed invention and does not demonstrate "failure of others" to develop a once-a-day extended release trospium formulation.

Further, and with respect to Paddock's failures during its development of its ANDA, the plaintiffs cite to Mr. Bhalani's testimony that "[o]n the first formulation we did not meet the bioequivalent set out by the FDA," and that, on the second attempt, Paddock "failed again . . . although we got fairly close." *See id.* at 1140:9-10, 1141:5-14 (Bhalani). The plaintiffs join these statements with Mr. Bhalani's testimony that development of the Paddock product was difficult and took longer than anticipated. While Mr. Bhalani did testify that the project was lengthy and difficult, the plaintiffs do not reference his explanation that the difficulty and length of the project did not rest exclusively trospium's challenges, but also on the fact that: creating a "bioequivalent product is difficult" and the "unusual formulation [of the drug] required [him] to modify [the] equipment design." *See id.* at 1196:13-1198:15. Consequently, though Mr. Bhalani did testify that the development of Paddock's ANDA was difficult, took longer than expected, and proved successful on the development team's third try, the court does not agree that this evidence demonstrate "failure of others" sufficient to undermine the *prima facie* case of obviousness.

f. Licensing

The plaintiffs assert, without developed argument, that Indevus' granting of licenses to Allergan and Madaus to market its once-a-day technology, constitutes a relevant secondary consideration. *Id.* at 190:1-17; 208:12-209:7 (Sandage); *see also* PTX-239; JTX0024A. The Federal Circuit has directed that licensing can be taken into account in evaluating secondary considerations, particularly with respect to whether the patentee has received substantial industry recognition or acceptance. *See, e.g.*, *EWP Corp. v. Reliance Universal*, 755 F.2d 898, 907-08 (Fed. Cir. 1985); *see also Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 436 (D. Del. 2010). The plaintiffs, however, did not introduce evidence at trial as to revenue generated from the licenses or that Allergan and Madaus licenses were granted because these entities were interested in competing in the patented area and could not do so without infringing the patents-in-suit. Rather, the plaintiffs demonstrated that the licenses were granted so that the licensees could market trospium in their respective territories. Consequently, because there is no evidence that any license was granted by the patent owner to a potential infringer who wanted to compete in the market but was impeded from doing so, and the plaintiffs have not otherwise established evidence of substantial industry recognition, the court concludes that the licensing in this case does not undermine the *prima facie* case of obviousness.

g. Skepticism/Unexpected Results

The plaintiffs maintain that a person of "skill [in the art] would not have expected to be able to make a successful once-daily modified release trospium dosage form." (D.I. 203 at 38.) The plaintiffs cite the following as evidence supporting this contention: (1) the skepticism of leading pharmaceutical companies, Bayer and Madaus; (2) "the conventional wisdom taught by the Fuhr/Schroder Poster and others that trospium absorption in the colon was negligible"; and (3)

Drs. Kibbe, Derendorf, and Mayersohn's "admissions that trospium is a challenging, complex drug." (*Id.*) Because the court has already addressed the plaintiffs' arguments with respect to the Fuhr/Schroder Poster and testimony that trospium presented formulation challenges, it does not reexamine these arguments here. In light of the evidence before it, the court finds Bayer and Madaus' alleged skepticism similarly unavailing in rebutting obviousness.

In support of their skepticism argument, the plaintiffs presented testimony of Drs. Sandage and Bhatt that Bayer decided not to partner with Indevus due to a "high degree of skepticism as to the likelihood of success in developing a once per day XR dosage form." *See* PTX-398; *see also* Tr. at 187:1-5, 189:1-9 (Sandage). The plaintiffs also entered into evidence an email from Dr. Woody Bryan, Shire's Vice President of Business Development in 2003, wherein he stated that Bayer was not interested in partnering with Shire and explained that, "[a]pparently the limited absorption in the colon [was] the main reason for their skepticism." *See* PTX-398. Drs. Sandage and Bhatt also recalled "a general sense of skepticism from [Bayer] regarding the chances of success in developing a once-a-day controlled release product of trospium." Tr. at 187:1-5, 189:1-9 (Sandage); *id.* at 1347:21-25 (Bhatt). However, this testimony refers only to out-of-court statements of unnamed Bayer employees, no Bayer employees testified at trial, and no written or published statements of skepticism from Bayer were introduced into evidence to support Bayer's alleged rationale. Thus, though Drs. Sandage, Bhatt, and Bryan may have accurately relayed their impressions as to why Bayer was not interested in partnering on the development of once-a-day trospium formulation, the court does not find this evidence persuasive enough to rebut or undermine the *prima facie* case of obviousness already established.

With regard to Madaus' decision not to partner with Indevus, Dr. Sandage testified that Madaus was skeptical as to whether trospium could be developed into a once-a-day formulation

based on Dr. Fuhr's findings reported in the Fuhr/Schroder Poster. *Id.* at 157:2-21, 158:17-162:4 (Sandage); *see also* PTX287; JTX-31. Dr. Sandage testified that he personally met with Dr. Fuhr in Germany and that Dr. Fuhr told him that "he [Fuhr] didn't think there was a chance to make a once-a-day," that "since you don't have colonic absorption, we are never going to be able to do that," and that Indevus "should abandon the program because we weren't able to do it." Tr. at 164:6-166:5 (Sandage). As discussed above in connection with the plaintiffs' "teaching away" argument, however, the court does not find the Fuhr/Schroder Poster's conclusions to be reflective of how persons of ordinary skill in the art viewed trospium or the correlation between rectal and colonic absorption in 2002. Consequently, the court concludes that Dr. Fuhr and/or Madaus' skepticism, based on the Fuhr/Schroder findings, fails to establish that those of skill in the art were generally skeptical as to whether a once-a-day trospium formulation was possible. Moreover, the court notes that Dr. Fuhr did not testify at trial and the plaintiffs did not depose Dr. Fuhr in connection with this litigation, despite Dr. Fuhr current position as a Madaus' consultant.

The court also concludes, for the reasons outlined in the obviousness analysis above, that the development of once-a-day trospium did not yield unexpected results. While some persons of ordinary skill in the art believed it would be challenging to develop a once-a-day trospium formulation, the plaintiffs have not demonstrated that there was a widespread belief that the claimed invention was impossible or that the challenges of trospium were insurmountable, such that development of the claimed invention was unexpected. In light of this finding, the court concludes that these arguments do not rebut the defendants' *prima facie* case of obviousness.

B. Anticipation

"[I]nvalidity by anticipation requires that the four corners of a single[] prior art document describe every element of the claimed invention, either expressly or inherently, such that a person

of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1271, 1282 (Fed. Cir. 2000). The Federal Circuit recently discussed the standards for inherent disclosure in *Verizon Services Corp. v. Cox Fibernet Virginia, Inc.*, 602 F.3d 1325 (Fed. Cir. 2010):

> "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." However, a patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." "The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112." It is well-settled that utility or efficacy need not be demonstrated for a reference to serve as anticipatory prior art under section 102.

Id. at 1337 (internal citations omitted). Whether a prior art reference anticipates a patent claim is a question of fact. *Advanced Display Sys.*, 212 F.3d at 1281.

The plaintiffs argue that the Fuhr/Schroder Poster does not anticipate the asserted claims of the patents-in-suit because all elements of these claims are not included within the four corners of the Poster. (D.I. 203 at 25.) Specifically, the plaintiffs note that the Poster does not disclose: (1) a formulation suitable for once-daily administration of trospium; (2) steady state blood levels; (3) any ingredients of the formation; and (4) a formulation designed to release in the lower GI tract. (*Id.* (citing JTX-0014; Tr. at 1407:1-6; 1407:11-18 (Davis)).)

In light of the evidence presented and in consideration of the relevant law, the court agrees with the plaintiffs that the Fuhr/Schroder Poster does not anticipate the asserted claims. As noted, the law governing anticipation narrowly confines the court's analysis to the "four corners" of the specific prior art reference in question. *See Adv. Display Sys.*, 212 F.3d at 1282. Here, the Fuhr/Schroder Poster summarizes a study that measured tropsium concentration in eight subjects after administration of: (1) an immediate release tablet; (2) an enteric-coated delayed release

tablet; and (3) a mini-enemato put trospium into the rectum. *See* JTX-0014. Based on the findings of this experiment, the authors concluded that trospium evidenced poor colonic absorption. While the court examines the implications of this Poster and its findings in connection with the obviousness discussion separately, relevant here is whether a person of ordinary skill in the art would consider every element of the claimed invention expressly or inherently described in this reference.

Review of the Fuhr/Schroder Poster makes clear that it does not disclose a formulation suitable for once-a-day trospium administration or a formulation designed for release in the lower GI tract. To the contrary, the Poster describes how an Eudragit coated immediate release tablet dissolves at pH 6.0 for "local administration to the small intestine." (*Id.*) Conversely, the asserted claims in the patents-in-suit at issue here: disclose a once-a-day trospium formulation designed to release in the lower GI; employ multiparticulate formulations to target the lower GI tract; and seek to establish steady state blood levels comparable to those of the twice-daily dosage trospium formulation. Thus, while the Fuhr/Schroder study showed that trospium could be released and absorbed lower in the small intestine and in the lower GI tract[36] and, therefore, presents findings relevant to obviousness, the court concludes, based on the differences highlighted, that the Fuhr/Schroder Poster does not expressly or impliedly anticipate every element of the claimed invention.

C. Indefiniteness

At trial, Watson[37] asserted that two claims of the patents-in-suit are invalid due to indefiniteness—claim 1 of the '978 Patent and claim 1 of the '449 Patent. A patent claim satisfies

[36] *See supra* Section III.A.4.d.

[37] Sandoz did not present 35 U.S.C. § 112 defenses at trial and Paddock's § 112 defense consisted of a written description argument. *See infra* Section III.D. Consequently, neither Sandoz nor Paddock joined Watson in its indefiniteness defense.

the definiteness requirement of 35 U.S.C. § 112 if a person of ordinary skill in the art would understand the bounds of the claim when read in light of the specification. *See Personalized Media v. ITC*, 161 F.3d 696, 705 (Fed. Cir. 1998). Section 112, paragraph 2, requires that the claims of a patent "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112. To this end, a "claim is considered indefinite if it does not reasonably apprise those skilled in the art of its scope." *Microprocessor Enhancement Corp. v. Texas Instruments, Inc.*, 520 F.3d 1367, 1374 (Fed. Cir. 2008) (quoting *IPXL Holdings, L.L.C. v. Amazon.com, Inc.*, 430 F.3d 1377, 1383-84 (Fed.Cir. 2005)). Where a claim is incapable of construction or fails to give adequate notice of the boundaries between infringing and non-infringing activities it is invalid. *See Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1581 (Fed. Cir. 1996) (citing *Rengo Co. v. Molins Mach. Co.*, 657 F.2d 535, 551 (3d Cir. 1981)).

Importantly, however, a claim term is not necessarily rendered indefinite because the term's construction defines it without reference to precise measurements. *See Enzo Biochem v. Applera*, 599 F.3d 1325, 1335 (Fed. Cir. 2010) (citing *In re Marosi*, 710 F.2d 799, 803 (Fed. Cir. 1983)). To determine whether those skilled in the art "would understand what is claimed," courts are instructed to apply general principles of claim construction, considering such intrinsic evidence as the claim language, the specification, and the prosecution history. *See id.* at 1332 (citing *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007)). Thus, where a court finds that the intrinsic evidence provides "a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine [the scope of the claims]," the claim is not indefinite. *See id.* at 1335 (citing *Young*, 492 F.3d at 346); *see also Seattle Box Co., Inc. v. Indus. Crating & Packaging, Inc.*, 731 F.2d 818, 826 (Fed. Cir. 1984) (noting that when a "word of

degree" is used, the court must determine whether the patent provides "some standard of measuring that degree").

1. Claim 1 of the '978 Patent—"Comparable to"

Watson first asserts that claim 1 of the '978 Patent is indefinite because the specification does not define "comparable to" or provide guidance as to the term's scope. (D.I. 202 at 22.) Watson supports this contention with the fact that Dr. Weiner, plaintiffs' expert who testified that a person of ordinary skill in the art would understand the meaning of "comparable to" as recited, nevertheless defined the meaning of this term differently in his March 2011 deposition. (*Id.* (citing Tr. at 597:23-599:22 (Weiner)).) This inconsistent testimony, Watson argues, is consistent with Dr. Davis' testimony that the claims reciting this term do not "define what it means by those blood levels or how they are actually measured." (*Id.* (citing Tr. at 724:5-21 (Weiner)).) In addition, Watson notes that "comparable to" is recited in an independent claim in the '978 Patent, "and a dependent claim adds the 0.5-.60 ng/ml limitation", while "the '448 and '449 [P]atents recite the 0.5-6.0 ng/ml limitation in an independent claim, and a dependent claims adds the 'comparable to' limitation." (*Id.* at 22-23.) Based on the placement of this term, Watson contends that a person of ordinary skill in the art would not know "from the language of the claims, specification, and prosecution history how the steady state blood levels obtained with a once-a-day formulation should be compared [to] meet the claim limitation" because there is no explanation as to how this term could be both broad and narrow, how the comparison should be made, or what is required to satisfy it. (*Id.* at 23.)

In response, the plaintiffs assert that the specification provides general guidelines and examples sufficient to enable a person of ordinary skill in the art to determine the scope of "comparable to" as used in claim 1 of the '978 Patent. (D.I. 203 at 39.) Specifically, the

plaintiffs argue that, per Dr. Davis' testimony, a person of ordinary skill in the art would understand that the term "comparable to" refers to steady state blood levels of trospium that are compared to those levels achieved in the immediate release twice-daily administration trospium. *Id.*; *see also* Tr. at 1436:19-1437:21 (Davis). In particular, Dr. Davis testified that the term "comparable to" means that "you should make a comparison of the steady state blood levels that you achieve with a twice-a-day with that that you may achieve with the invention. So you look at the steady state plasma levels that you get with the invention with the once-a-day and compare it to the steady state levels that you have achieved with a twice-a-day formulation and are they comparable." Tr. at 1437:15-21 (Davis). Dr. Davis also noted that this term is used in other patents, such as Shire's patent for its drug, Carbatrol®, to denote that steady state blood levels resulting from a once-daily formulation should be similar to the steady state blood levels that result from a twice-daily dosage of the same formula. *Id.* at 1437:22-1438:9; DTX-2075.

Moreover, the plaintiffs note that the patent itself provides numerous guidelines and examples to define this term's scope. Specifically, the plaintiffs note that the '978 Patent identifies the following as acceptable metrics of comparability: a steady state blood level range of 0.5 to 6.0 ng/ml; average C_{max} and average C_{min} between 80 and 120 percent of the values for the twice daily formulation; and relative bioavailability in the range of 80 to 120 percent of corresponding twice a day formulation. *See* '978 Patent at col. 4:24-34, 21:1-35; *see also* Tr. at 537:5-538:17 (Weiner).

The court finds Dr. Davis' testimony credible and agrees with the plaintiffs that the intrinsic evidence—namely, the '978 Patent's claims and specification—provides general guidelines and examples sufficient for a person of ordinary skill in the art to understand the meaning of "comparable to." Specifically, and as the plaintiffs correctly note, the '978 Patent's

specification recites the acceptable ranges of comparability and serves as a general guideline informing construction of the term. *See* '978 Patent at col. 4:24-34. The fact that "comparable to" is included in an independent claim in the '978 Patent and in dependent claims in the '448 and '449 Patents, does not undermine this conclusion in light of the court's findings. Moreover, the court is not persuaded by the defendants' argument that: (1) Dr. Weiner's inconsistent testimony as to the meaning of "comparable to" demonstrates the indefiniteness of this term; or (2) Dr. Davis' statement that claim 1 of the '978 Patent does not define "what it means by those blood levels or how they are actually measured" renders the term indefinite.

With respect to Dr. Weiner's statements, Dr. Weiner clarified in his trial testimony that his initial deposition testimony was incorrect because he "was confused by the hypotheticals" Watson presented, due at least in part to his belief that the product described in the hypothetical could not be created.[38] Thus, the court does not find Dr. Weiner's inconsistent statement to undermine this court's conclusion with respect to the "comparable to" term. Moreover, the court reaches a similar conclusion regarding Dr. Davis' testimony. Contrary to the defendants' assertion that this statement demonstrates the indefiniteness of this term, the court reaches the opposite conclusion. While it is clear from a simple reading of claim 1 of the '978 Patent that the blood levels and how

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[38] Specifically, Dr. Weiner explained in his trial testimony that:

Q: Now, was it your testimony here today that for that parameter to be comparable, you have to both have a C_{max} that's 80 to 120 percent of the C_{max} of the IR product administered twice a day, and then also a C_{min} that's 80 to 120 percent of the IR product administered twice a day?

A: That's correct.

. . . .

Q: I want to ask, were you asked this question and did you give this answer:

"Question: So if—if an extended release product produced a C_{min} that was in the range set forth there in Column 4 but had a C_{max} that was ten times the C_{max} of the immediate release product, it would still be comparable to the immediate release product in your view because it satisfied the one C_{min} parameter. Is that correct?

A: I did state that at the time. But in thinking about that later, that really isn't accurate. . . . You know, if I could explain, yes, at the time I did, but we were dealing with—frankly, I got confused by the hypotheticals and I was thinking about the hypotheticals and whether they could even occur. And in thinking about it later I just sort of got sidetracked.

Tr. at 598:1-599:18 (Weiner).

they are measured are not defined, this explicit definition within the claim is not required. Rather, the court concludes that the parameters and requirements of claim 1 are defined by the general guidelines and examples included in the specification, such that a person of ordinary skill in the art could identify the claim's scope. Consequently, in light of the '978 Patent's intrinsic evidence, the court finds that Dr. Davis' statement does not support a conclusion of indefiniteness.

In view of the foregoing, the court finds that the defendants have not established by clear and convincing evidence that the "comparable to" limitation is indefinite. *See Enzo Biochem, Inc.*, 599 F.3d at 1335. Consequently, the court concludes that the claims reciting the term "comparable to" are not invalid under Section 112.

2. Claim 1 of the '449 Patent—"Minimizing the Occurrence"

The court is not persuaded by the defendants' remaining indefiniteness arguments. (D.I. 202 at 23-24.) The defendants assert that the term "minimizing the occurrence," included in claim 1 of the '449 Patent, is indefinite. (*Id.*) The court disagrees, and finds that this term can be construed to have a definite meaning that would be readily understood by a person of ordinary skill in the art. Specifically, the court agrees with the plaintiffs that Dr. Davis' testimony is credible and negates the defendants' argument that the term is indefinite because it does not disclose "how high trospium blood levels or spikes in those levels must be to cause side effects" or "how low they must be to reduce side effects." (*Id.* at 23-24; D.I. 203 at 39-40.)

Dr. Davis testified that one of ordinary skill in the art would have "no problem in understanding what the patentees meant" in using the term "minimizing the occurrence of side effects." Tr. at 683:4-8 (Davis). Specifically, Dr. Davis testified that this term is informed by the '978 Patent's specification, which details in at least three places that the purpose of the invention

is to reduce the side effects associated with the spikes that typically occur in plasma concentration.[39] Tr. at 684:2-17 (Davis); *see also* '978 Patent, col.13:21-24; 4:64-5:5, 12:64-13:7. Dr. Davis further explained that, as one of skill in the art, he does not discern a difference between the term "minimize" and the term "reduce," such that the patent specification's use of the term "reduce" when detailing the objective of "reducing side effects" is consistent with the meaning of the disputed term.[40] The defendants' expert, Dr. Kibbe, likewise used the term "minimizing side effects" to mean "reduce side effects" in his expert report. Tr. at 1090:15-1091:18 (Kibbe). In light of the specification and relevant testimony, the court concludes that the construction of this term does not need to define "how high trospium blood levels or spikes in those levels . . . cause side effects" or "how low they must be to reduce side effects" to be definite. (D.I. 202 at 23.) Rather, the court finds that this term, read in light of the specification and in conjunction with the other claims, is not directed to defining the relevant blood levels needed to minimize side effects, but, instead, to defining what an infringing product must do with respect to the side effects associated with twice-daily trospium. Consequently, the defendants' argument is unavailing.

In addition to these arguments, the defendants also maintain that "minimizing the occurrence" is indefinite because the '449 Patent does not disclose which side effect(s) must be minimized to meet the "minimizing the occurrence of side effects" limitation in claim 1 of the '449 Patent. (D.I. 202 at 23.) The defendants assert that Dr. Davis' only response to Dr. Kibbe's conclusion that "minimizing" is indefinite was that "minimizing" means "reducing incidences of dry mouth" only. (*Id.* at 24 (quoting Tr. at 840:8-14 (Davis)).) The court disagrees with this

[39] Specifically, Dr. Davis testified that "if one looks to the specification, it does talk about reducing side effects associated with the spikes in the plasma concentration as one example." Tr. at 1438:19-23 (Davis).

[40] Dr. Davis stated, in response to the question, "[A]s one of skill in the art, do you see a difference between reducing side effects and minimizing side effects?": "Not in the way it is described in the patent. I must admit having been involved in this case, when people in conversation use the word 'minimize,' I go, oh, no, no, no. You don't mean 'minimize,' you mean 'reduce.'" *Id.* at 1439:17-24.

assertion. Dr. Davis clarified in his testimony that one of ordinary skill in the art would understand the side effects to which the applicants were referring. Specifically, Dr. Davis noted that, for instance, column 1 of the '978 Patent states that the side effects associated with the "use of twice daily trospium chloride regimen" includes "dry mouth, headache, constipation, dyspepsia" and result from "high blood concentration of trospium chloride." '978 Patent, col. 1:57-62. The applicants also state in the '978 Patent that a once-daily administration of trospium is advantageous over twice-a-day because it lends to increased patient compliance and reduction in adverse side effects. *Id.* at col. 1:58-2:3.

Finally, the court notes that the '449 Patent itself describes the goal of "minimiz[ing]" or "reduc[ing]" the side effects associated with twice-daily trospium and the general way in which the patented formulation does so. Specifically, the '449 Patent states:

> In order to provide for an effective once-a-day form of trospium, there is a need for unique formulation approaches that provide the desired therapeutic effects while minimizing, if not eliminating, the undesired side effects mentioned above. This means that the minimum blood trospium concentration (C_{min}) at steady state should be above the minimum therapeutically effective blood concentration (C_{max}) also at steady state should be below the maximum toxic blood concentration over the treatment period.

'449 Patent, col. 2:9-18. In view of the foregoing, the court finds that the defendants have not established by clear and convincing evidence that the "minimizing the occurrence" is indefinite. *See Enzo Biochem, Inc.*, 599 F.3d at 1335. Consequently, the court concludes that the claims reciting the term "minimizing the occurrence" are not invalid under Section 112.

D. Written Description

Paddock argues that the C_{max} element of the '359 Patent's claim 1, is invalid because it does not meet the written description requirement.[41] (D.I. 203 at 38.) To satisfy the written

[41] The court notes that Paddock does not raise its written description defense in its proposed findings of fact and conclusions of law submission. (*See* D.I. 201.) However, the defendants' jointly submitted proposed findings of

description requirement, the application must show that, as of the filing date, the applicants were in possession of the invention in question. *See Santarus,* 720 F. Supp. 2d at 436 (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 2000)). To show that one is "in possession," the applicant must clearly describe the invention in the four corners of the specification, but "does not have to describe exactly the subject matter claimed." *Vas-Cath Inc.*, 935 F.2d at 1563; *see also Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Specifically, a person of ordinary skill in the art "must immediately discern the limitation at issue in the claims." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Thus, "while the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement." *Ariad Pharms.*, 598 F.3d at 1352 (internal citations omitted). To this end, support in the written description must be based on what actually is disclosed, and not on an obvious variant of what is disclosed. *See Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997). Whether the written description requirement is met is a question of fact. *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1369-70 (Fed. Cir. 2009) (citation omitted). The party challenging the sufficiency of a written description must establish by clear and convincing evidence that the claim is invalid or not entitled to an asserted filing date. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1329-30 (Fed. Cir. 2008).

Here, Paddock asserts that the "average C_{max} at steady state of less than 2400 pg/ml of Tr^{+}" limitation in the '359 Patent is invalid for lack of written description because: (1) the specification repeatedly states that the average C_{max} at steady state should be between 2.0-6.0

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fact and conclusions of law reference the written description argument that Paddock sought to establish through Dr. Derendorf's testimony. (D.I. 202 at 24-25.) Consequently, the court refers to the defendants' joint submission in connection with this argument.

ng/ml (2000-6000 pg/ml), or 2.5-4.5 ng/ml (2500-4500 pg/ml), which does not include the claimed range[42]; and (2) none of the disclosed ranges for C_{max} in the specification require that the average C_{max} at steady state be less than 2400 pg/ml.[43] Paddock also notes that Dr. Davis agreed in his testimony that nothing in Table 6 states that the average C_{max} should be from 0-2400 pg/ml, and that Formulations A and B have an average C_{max} greater than 2400 pg/ml. *See* '359 Patent at Table 6; Tr. at 1500:20-24, 1502:11-13 (Davis). Moreover, Paddock also highlights that nothing in the specification indicates that Formulation D, the formulation with a C_{max} less than 2400 pg/ml, is preferred over Formulations A or B and, further, that even if the specification did indicate that Formulation D is preferred, this Formulation describes only a "single point (2398 pg/ml), not a claimed range." (D.I. 202 at 25.) In support of these assertions, Paddock presented Dr. Derendorf who testified that he could not "deduce from [Table 6] that the 2.4 should be in the claim" because "there are so many numbers, so many products . . . there is nothing to indicate that any of these is special or the preferred teachings, so it could be any of the C_{max}'s between 1.9 and 3.2 that may be relevant here." Tr. at 949:25-950:6 (Derendorf).

Conversely, the plaintiffs maintain that claim 1 of the '359 Patent is not invalid because Formulations C and D in Table 6 demonstrate that the C_{max} range is adequately described. *See Id.* at 347:24-348:15 (Kidane); *id.* at 1440:15-1441:10 (Davis). Specifically, the plaintiffs assert that where, as here, a claim includes a specific range limitation, that limitation need not correspond exactly to ranges found in the disclosure. (D.I. 203 at 40 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985).) Instead, the disclosure must only provide "guidance to one skilled in the art that the range limitation is an aspect of the invention." (*Id.* (citing *In re Ruschig*, 379 F.2d 990, 994-95 (C.C.P.A. 1967).)

[42]*See* '359 Patent at col. 2:35-39; 5:13-16; 12:41-45.
[43]*See* Tr. at 949:11-19 (Derendorf); *id.* at 1500:6-11 (Davis).

The plaintiffs argue that the disclosure here provides the necessary guidance. In particular, the plaintiffs note that the patent emphasizes the importance of lowering C_{max} to reduce side effects. *See* '978 Patent at col. 1:60-61, 5:2-5. In addition, Example 7 and Table 6 in the '978 Patent provides results from the steady state human study reported in the patent. Of the four extended release formulations tested in that study, two have C_{max} values less than 2400 pg/ml at T_{max} less than six hours. (*Id.* at Table 6 (Formulations C & D).) The plaintiffs maintain that this data confirms that the applicants recognized the importance of a low C_{max}, "conveyed knowledge in their examples, and appropriately claimed that parameter." (D.I. 203 at 40 (citing Tr. at 1529:19-23; 1529:3-12 (Davis)); *see also* '978 Patent at col. 8:50-52. Thus, because the specification emphasizes the importance of a low C_{max} and reports data from the steady state human trial showing two of the four extended release formulations tested with a C_{max} of less than 2400, as shown in Table 6, the specification shows that the inventors identified a low C_{max} as an aspect of the invention and that they were in possession of it.

In light of Drs. Kidane and Davis' testimony and the evidence before it, the court concludes that claim 1 of the '359 Patent is not invalid for lack of written description. As the plaintiffs correctly note, to challenge the sufficiency of a patent's written description the defendants must prove by clear and convincing evidence that the claim is invalid or not entitled to an asserted filing date. *See Tech. Licensing Corp.*, 545 F.3d at 1329-30. Here, the defendants have failed to do so. While Dr. Derendorf's testimony was limited primarily to identifying that the specification mentions ranges other than that required by claim 1, Drs. Kidane and Davis, discussed the meaning of claim 1's C_{max} limitation in the context of the specification's asserted objective of minimizing side effects and in comparison to the other C_{max} ranges identified in the specification. Specifically, Dr. Kidane testified that, as a formulator, claim 1's requirement that

the formulation provide an average C_{max} at steady state of less than 2400 pg/ml of trospium at a T_{max} of less than six hours, is a "significant" limitation because it results in the "side effects [being] reduced while having an effective product." *Id.* at 347:12-25 (Kidane). Dr. Davis also testified that he had no "trouble, as one of skill in the art, in finding where in the patent levels of below 2400 picograms per milliliter were . . . disclosed." *Id.* at 1141:1-10 (Davis). In particular, Dr. Davis stated that the values in Table 6 "led" him to the 2400 pg/ml limitation and that a person of skill in the art could have determined, based on the specification, "what the patentee intended." *Id.* In view of this persuasive testimony and the '359 Patent's specification, the court concludes that the disclosure provides guidance to those skilled in the art that the low C_{max} range limitation is an aspect of the invention and the applicants were in possession of it.[44] *See Ralston Purina Co.*, 772 F.2d at 1575.; *In re Ruschig*, 379 F.2d at 1575.

E. Infringement[45]

As noted, the plaintiffs contend that the defendants directly infringe the asserted claims of the '978 and '448 Patents, which are directed to pharmaceutical compositions. (D.I. 203 at 7.) In addition, the plaintiffs allege that the defendants infringe the asserted claims of the '359 and '449 Patents, which are directed to method claims, by inducement. (*Id.*) Defendants Sandoz and Watson focus their infringement defenses on the assertion that the plaintiffs have failed to show that their proposed products meet the "release" element of the asserted claims because the plaintiffs offered *in vitro* as opposed to *in vivo* data at trial. (D.I. 202 at 25-27.) Because each of the asserted claims require that the defendants' ANDA products "release" a portion of trospium in the lower GI tract, Watson and Sandoz argue that the plaintiffs cannot meet their burden of

[44] *See* '978 Patent at Table 6 (Formulations C and D); *id.* at col. 1:60-61, 5:2-5; *see also* Tr. (Davis) 1529:19-23; 1529:3-12; JTX-1 at 8:50-52

[45] For the purposes of the infringement analysis, the court assumes *arguendo* that the patents-in-suit are valid.

proving infringement. In addition, Watson and Sandoz also maintain that the plaintiffs failed to establish: (1) infringement of claim 1 of the '359 Patent based on Dr. Weiner's assessment that their proposed products, as well as Paddock's product, do not possess the C_{max} steady state value required by that claim (*id.* at 26); (2) infringement of claims 1, 10, and 18 of the '449 Patent because they did not show that the proposed products meet the necessary "minimizing the occurrence of side effects" requirement (*id.*); and (3) that either defendant possessed the requisite level of knowledge and intent to induce infringement of the method claims (*id.* at 25-26). Conversely, the plaintiffs maintain that they established evidence sufficient to prove infringement by a preponderance of the evidence.

Notably, defendant Paddock presents two other infringement defenses, asserting that the plaintiffs failed to prove that its proposed product: (1) meets the steady state blood level and AUC limitations of the patents-in-suit; and (2) contains particulates comprising an enteric and/or release controlling polymer. (D.I. 201.) Because Paddock presents its own infringement defenses on these issues, the court will consider the defenses separately in its infringement analysis.

For the reasons that follow the court concludes that each of the defendants' proposed products infringe the asserted claims of the patents-in-suit.

1. The Legal Standard

The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused patent. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984) (citing

Hughes Aircraft Co. v. United States, 717 F.2d 1351, 1361 (Fed. Cir. 1983)). To this end, a patent owner does not have to produce "definite" proof of infringement, but must instead demonstrate that "infringement was more likely than not to have occurred." *See Warner-Lambert Co. v. Teva Pharms., USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005) (citing *Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001)). "Under [35 U.S.C.] § 271(e)(2)(a), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

Under Section 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To establish liability under this Section, a patent holder must prove that once the defendant knew of the patent, it "actively and *knowingly* aid[ed] and abett[ed] another's direct infringement." *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1305 (Fed. Cir. 2006) (citation omitted) (emphasis in original). The "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." *Id.* (citing *Warner-Lambert Co.*, 316 F.3d at 1364).

2. The "Release" Element of the Asserted Claims

As noted, each of the asserted claims require that the defendants' proposed products "release" trospium in the lower GI tract, which the court construed to mean the ileum and colon,[46] or in the colon. At trial, the plaintiffs presented evidence of this "release" via the defendants' ANDA data and *in vitro* dissolution data considered in combination with known information about GI transit times and *in vivo* data from SANCTURA XR®. (D.I. 203 at 7-8.) The plaintiffs presented *in vitro* rather than *in vivo* data because, per Drs. Weiner and Davis, testing defendants'

[46] *See* D.I. 144.

unapproved products in live human subjects is neither feasible nor ethical.[47] *See* Tr. at 606:10-15 (Weiner); *id.* at 623:6-626:2, 822:13-19. The plaintiffs assert that this *in vitro* data, coupled with consideration of the defendants' ANDAs and GI transit time data, suffices to prove, by a preponderance of the evidence, that the "release" element is met because this evidence links the *in vitro* and *in vivo* data. (D.I. 203 at 9 (citing *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1296 (Fed. Cir. 2006) (concluding that infringement can be found based on *in vitro* data where the evidence before the court demonstrates that the *in vitro* system adequately modeled the results that would be derived from *in vivo* conditions).

Conversely, the defendants assert that this *in vitro* data is unreliable because: (1) "there are variables that affect transit time through the GI tract and nothing replaces the human body to account for them" (*id.* at 8 (citing Tr. at 1058:15-24, 423:7-13 (Kidane)); (2) Dr. Davis' GI transit time calculations did not account for the fact that trospium "significantly slows the time it takes for a given dosage form to travel from the stomach or duodenum to the lower GI tract" and, therefore, has "no predictive value regarding site of release" (D.I. 201 at 3); (3) Indevus' statement to the FDA that there is a poor correlation between *in vitro* and *in vivo* data from SANCTURA XR® undermines the plaintiffs' argument (*id.* at 8-9); and (4) as, shown from the actual dissolution rate of SANCTURA XR®'s XR1 and the Shojaei applications, Dr. Davis' GI transit times calculations do not predict the location of release *in vivo* (*id.* at 4). In addition, Paddock also presented what it termed "affirmative evidence" that its proposed product releases its trospium rapidly in the upper, rather than the lower, GI tract, such that it cannot meet the "release" element of the asserted claims. (*Id.* at 5.)

[47] In particular, Dr. Davis testified that there are ethical concerns associated with taking blood samples from and exposing human subjects to radioactivity "when one can from *in vitro* data, and data already in the literature, on transit" determine infringement without such testing. Tr. at 623:6-23 (Davis).

In light of the evidence before it, the court concludes that the plaintiffs have met their burden of proving, by a preponderance of the evidence, that each of the defendants' proposed products meet the "release" element and, therefore, infringe the asserted claims of the patents-in-suit. The court examines Dr. Davis' findings and addresses each of the defendants' non-infringement arguments in turn below.

a. Dr. Davis' Methodology for Predicting Lower GI Tract "Release"

The defendants argue, in the main, that the plaintiffs have failed to show their products meet the "release" element of the asserted claims because Dr. Davis' *in vitro* data does not sufficiently model *in vivo* release. The defendants cite a number of propositions in support of this contention. First, all defendants assert that Dr. Davis' *in vitro* testing did not adequately reflect or take into account the actual *in vivo* conditions of the GI tract. Specifically, the defendants note that while the GI tract "contains many millions of charged particles in both the fasted and fed states," the *in vitro* dissolution data Dr. Davis used contained "relatively few charged particles—only those necessary to adjust the pH," and did not account for the fact that trospium slows pellet release. (*Id.* at 3 (citing Tr. at 899:21-900:4, 905:10-13, 906:17-24 (Derendorf); *id.* at 1150:7-13 (Bhalani); *id.* (citing Tr. at 795:7-21 (Davis); *id.* at 899:15-900:22 (Derendorf).) Second, the defendants assert that this argument is confirmed by the fact that the *in vivo* dissolution rates for SANCTURA XR®'s XR1 and the Shojaei applications do not tract Dr. Davis' *in vitro* dissolution data method. (*Id.* at 3-4.) In consideration of the totality of evidence presented, however, the court disagrees with the defendants' contention that the plaintiffs, via Dr. Davis' testimony, have failed to show that it is more likely than not that the defendants' proposed products release in the lower GI tract.

As noted, Dr. Davis' evaluation of the defendants' proposed products encompassed consideration of a number of factors, including: (1) the defendants' ANDA data; (2) *in vitro* dissolution data; (3) known data about GI transit times of dosage forms; and (4) *in vivo* data from SANCTURA XR®. (D.I. 203 at 7-8.) With regard to Dr. Davis' *in vitro* data assessment, Dr. Davis testified that, based on his decades of experience in transit times of dosage forms, known transit times for pellets to travel through the GI tract can be considered in combination with *in vitro* dissolution data to demonstrate *in vivo* release. Tr. at 610:20-617:16, 619:3-4 (Davis). Specifically, Dr. Davis testified that, through his work using gamma scintigraphy,[48] it has been established that mini-tablets and/or pellets: exit the fasted stomach in approximately twenty minutes; traverse the duodenum in another five to ten minutes (thirty minutes cumulative time); the jejunum in about one and a half hours (two hours cumulative time); reach the ileum in about an hour and a half (three and a half hours cumulative time); and arrive in the colon in about twelve to twenty-four hours (cumulative time fifteen and a half to twenty seven and a half hours). *Id.* at 614:9-615:12. Based on this data, Dr. Davis testified that, in the fasted state, ten to fifty percent of pellets and/or mini-tablets have arrived in the colon at two and a half to three and a half hours after ingestion. *Id.* at 617:1-16; *see also* PTX-671 at 28198T. These transit times, Dr. Davis noted, are recognized in the scientific community and have been published in a recognized treatise on *in vivo* transit of pellets and/or mini-tablets[49] as well as in other journals and books.

In conducting his analysis of the defendants' proposed products, Dr. Davis stated that he compared the dissolution data contained in their ANDAs to the known transit times outlined above. *Id.* at 621:15-622:3. In particular, Dr. Davis tracked the GI tract transit times on the x-

[48] Dr. Davis explained gamma scintigraphy is a technique wherein a tablet or pellet is labeled (i.e., labeled with radioactive material) so that it can be observed using a gamma camera as it travels through the GI tract. Dr. Davis stated that this technology has been used to measure and quantify the arrival of pellets in the small intestine and throughout the GI tract. Tr. at 616:1-9 (Davis).

[49] Dr. Davis testified that the GI tract transit times for pellets and/or mini-tablets were included in Professor Richwall's book and the GastroPlus model. *Id.* at 615:17-616:3.

axis of each dissolution profile to correspond roughly to where materials would be in the GI tract. *Id.* Dr. Davis concluded, based on this comparison, that each of the defendants' proposed products releases trospium in the lower GI tract because, per their dissolution data, each product continues to release trospium after two and a half hours (i.e., the ileum) and after three and a half hours (i.e., the colon). In particular: Watson's dissolution data in its ANDA shows trospium release after five hours, and transit times to the ileum and colon are about two and three and a half to five hours, respectively; Sandoz's dissolution profiles show that only twenty percent of the trospium is released at around two hours, when pellets would be arriving in the lower GI tract and ileum; and Paddock's dissolution data showed that after two hours, more than eighty percent of trospium was not yet released and, further, that more than fifty percent of trospium was not yet released after four hours. *Id.* at 635:1-18, 621:11-622:3, 613:17-617:16, 653:17-658:13.

In addition, Dr. Davis further explained that the *in vivo* data on SANCTURA XR® confirms that the defendants' *in vitro* dissolution data establishes this release. Specifically, Figure 10 of the '978 Patent charts the *in vivo* blood levels for various formulations. *Id.* at 1530:13-1531:4. Formulation B presents a delayed release formulation with Eudragit FS30D polymer coating that releases at around pH 7.0, which corresponds to the pH in the colon. Figure 10 shows that Formulation B did not produce measurable blood levels until about three hours later than the other formulations, which resulted in bioavailability of only five percent of the immediate release formulation, depicted in Formulation F. *Id.* at 1530:7-1531:4; *id.* at 346:3-11 (Kidane). Dr. Davis testified that the delayed onset of the blood levels and reduced bioavailability confirm that drug is released in the lower GI tract. *Id.* at 1530:7-1531:4 (Davis).

Finally, Dr. Davis also explained the pH levels present at various parts of the GI tract and compared this information to the defendants' ANDAs. Specifically, Dr. Davis testified that the

pH level is approximately 7 in the ileum and the colon, in addition to defining levels in other areas. *Id.* at 612:7-613:4. Dr. Davis explained that formulators seeking to target drug release at a particular part of the GI tract would use these known pH values to determine an appropriate pellet coating that would release at that pH level. *Id.* at 613:5-16. Dr. Davis then compared these values to the information contained in the defendants' ANDAs and considered the defendants' statements to the FDA to conclude that at least some portion of the trospium in the proposed products release in the lower GI tract.

For the Watson proposed product, Dr. Davis testified that its ANDA describes a 60 mg capsule containing extended release and delayed release pellets, wherein the extended release pellets are coated with ethylcellulose polymer and the delayed release pellets are coated with Eudragit FS30D, which has a pH sensitivity of 7.0. *Id.* at 617:17-618:25; *see also* PTX-162 at 12765; PTX-156 at 12762, 12764. Watson's ANDA also states that its product uses the polymers to mimic SANCTURA XR®'s drug release profile and, more specifically, that it intended to target colonic absorption and employed the polymers selected to delay release until the lower GI tract. Tr. at 1107:12-18 (Davis). In addition, Watson told the FDA that a "key excipient" for its product is Eudragit FS30D, which "dissolves by salt formation above pH 7.0" and "allows target colon delivery." *Id.* at 617:22-618:11; *see also* PTX-162 at 12770. In consideration of Watson's selected polymers and its statements to the FDA, Dr. Davis concluded that Watson's proposed product releases in the lower GI tract. Tr. at 1107:12-18 (Davis).

With regard to the Sandoz proposed product, Sandoz's ANDA states that is product was designed "as a combination of two delayed release pellets and two extended release pellets mixed in a specific ratio to produce a release profile that mimics [SANCTURA XR®]." *See* PTX-145 at 281; Tr. at 634:6-14 (Davis). To this end, Sandoz's proposed product is a 60 mg capsule that

contains two types of extended release and two types of delayed release pellets: ER1 and ER2 pellets coated with fifteen and twenty-four percent ethylcellulose polymer, respectively; and DR1 pellets coated with Eudragit FS30D polymer, with a pH sensitivity of 7.0, such that it is designed to release at that pH level. *See* PTX-147 at 433-34; PTX-145 at 269; Tr. at 633:3-634:5 (Davis). Dr. Davis also noted that Sandoz told the FDA in its ANDA that it intended to release trospium throughout the "extent of the GI tract," and that its product's enteric coated pellets have a "slight release throughout the small intestine and immediate release of drug substance at the beginning of the large intestine," which is the same as the colon. *See* Tr. at 635:19-636-16; PTX-145 at 273-74. In consideration of the pH sensitivity coating Sandoz selected as well as its representations to the FDA that it intended to release trospium in the lower GI tract, Dr. Davis concluded that Sandoz's proposed product meets the "release" limitation of the asserted claims. Tr. at 637:22-24.

Regarding Paddock's proposed product, Dr. Davis noted that Paddock's ANDA states that it is designed as a "multi mini-tablets system to match the pellets of [SANCTURA XR®] in terms of gastric transit nature under fasting conditions." *Id.* at 644:25-655:14; *see also* PTX-131 at 135. Dr. Davis concluded that this representation to the FDA, coupled with the product formulation discussed below in connection with Paddock's immediate release and "controlled release" non-infringement arguments, demonstrates that the Paddock proposed product releases in the lower GI tract. Tr. at 644:25-655:14 (Davis).

The court finds Dr. Davis' testimony and methodology for assessing the defendants' proposed products credible. This conclusion is not undermined by the defendants' non-infringement arguments outlined above. First, the court finds the defendants' assertion that Dr. Davis' consideration of *in vitro* dissolution data was improper to be unpersuasive in light of the

evidence adduced at trial. Specifically, while Dr. Davis agreed with Paddock on cross-examination that "GI tract fluid is more complicated than what is in a standard *in vitro* dissolution system," he also testified that the absence of such fluid components as bile acids, bile salts, and electrolytes, among others, is inconsequential because such components are "not going to be in the gastrointestinal tract in the fasted state." *Id.* at 772:15-774:11. Similarly, Dr. Davis stated that the presence of mucous in the GI tract in its fasted state would not impact the release from a pharmaceutical dosage form such that it would need to be included in an *in vitro* dissolution test. *Id.* at 775:6-10. Thus, while the inclusion of varying pH levels was needed—and was, in fact, included—in the *in vitro* dissolution test because pH sensitivity along the GI tract is relevant, Dr. Davis concluded, in what the court finds credible testimony, that the absence of other GI tract fluid components in the dissolution test does not impact the validity of his analysis.

Defendant Paddock also asserts that Dr. Davis acknowledged that trospium "significantly" slows transit time from the duodenum to the lower GI tract, but "did not account for this slowed transit at all, much less try to quantitatively apply it to his analysis as would be required to establish a reliable correlation between the *in vitro* dissolution data and *in vivo* release times." (D.I. 201 at 3.) The court notes, however, that Paddock did not develop the argument it presents in its cross-examination of Dr. Davis at trial. Notably, while Dr. Davis did agree that he has not conducted studies assessing pellet release of trospium, Paddock did not adduce testimony from Dr. Davis that he did not consider this fact[50] or that he found this slowing effect "significant." Paddock also did not establish the degree to which trospium would slow transit time. Moreover, Dr. Davis testified that he was familiar with the fact that trospium can slow transit time and

[50] The defendants asked Dr. Derendorf whether, based on Dr. Davis' testimony, he thought that Dr. Davis considered trospium's slowing affect in his assessment of the dissolution data. Tr. at 909:11-910:2 (Derendorf). While Dr. Derendorf testified that he did not think Dr. Davis considered this fact in his analysis, Paddock did not ask Dr. Davis this question during cross-examination. Consequently, the court finds that this fact was not established in the evidence and, therefore, does not undermine Dr. Davis' conclusions.

referenced the specific study that presented this conclusion. Tr. at 795:7-796:5 (Davis). Absent development of the degree to which tropsium slows GI transit time, the court finds that the defendants have failed to present evidence sufficient to undermine Dr. Davis' conclusion that *in vitro* dissolution data is properly used in assessing GI release.[51]

The court also finds Paddock's argument unavailing in light of its own representations to the FDA regarding its *in vitro* dissolution tests. Specifically, Sidmark Laboratories India ("Sidmark"), which developed Paddock's proposed product under the leadership of Mr. Bhalani, conducted "biorelevant" media testing to evaluate the release of tropsium from Paddock's formulation. *Id.* at 663:13-14; *see also* PTX-131 at 141, 144. Paddock developed these media "based on [the biorelevant media's] ability to detect the differences found in *in-vivo* studies," and "to account for the pH transition[s]" in the GI tract in order to have "relevance to the biological situation." Tr. at 1149:24-1150:1 (Bhalani); *id.* at 63:16-25 (Davis); *see also* PTX-888 at 20029. Importantly, these tests arrived at results similar to those reported in Paddock's FDA media. In particular, the data derived from these tests showed that: at two hours about eighty percent of trospium was not yet released; after four hours fifty percent was not yet released; after seven hours about thirty percent was not yet released; and at ten hours twenty percent was not yet released. PTX-132 at 733; Tr. at 1190:16-1191:19 (Bhalani). The court notes that Dr. Davis considered the results of these media in assessing Paddock's proposed product. Tr. at 663:13-14, 663:16-25 (Davis).

The defendants also argue that the *in vitro* dissolution data does not adequately predict *in vivo* release because "it is undisputed that there is no '*in vitro/in vivo* correlation,' or 'IVIVC' for trospium." (D.I. 201 at 2 (citing Tr. at 496:19-23 (Raoufinia); 770:18-25, 1404:19-24 (Davis);

[51] The court notes that the defendants did ask Dr. Derendorf to explain how trospium's properties "affects the general GI transit time," and Dr. Derendorf responded, "Well, it makes it longer." *Id.* The court does not find this testimony sufficient to undermine Dr. Davis' conclusion that the use of *in vitro* dissolution data is appropriate.

911:5-7 (Derendorf). Aside from expert testimony, the defendants support this contention with Indevus' statement to the FDA that:

> Given the high inter and intra-subject pharmacokinetic variability for Trospium Chloride and the fact that the drug is highly water soluble, the establishment of an *in-vivo/in-vitro* correlation is likely to be difficult at best. Therefore, we do not plan to undertake work to establish a correlation at this time, but may consider conducting investigations in the future.

DTX-1055. The defendants argue that without IVIVC, "one cannot draw any conclusions regarding the *in vivo* performance of Paddock's product from the *in vitro* dissolution tests." (D.I. 201 at 3 (citing Tr. at 910:7-16 (Derendorf).) However, while the experts agree that there is no IVIVC for trospium, such correlation is not required here. Namely, IVIVC relates *in vitro* dissolution data and *in vivo* pharmacokinetic parameters, not *in vivo* release. Tr. at 769:16-19 (Davis); *see also* DTX-1148. As noted, pharmacokinetic parameters are factors such as C_{max}, C_{min}, and AUC. Dr. Davis, however, offers *in vitro* dissolution data simply to support the finding that trospium is released, in any amount, in the lower GI tract and colon, rather than to prove the value of any particular pharmacokinetic parameter or performance.[52] To this end, the absence of an IVIVC does not change the court's analysis.

Finally, the defendants argue that Dr. Davis' correlation of dissolution data and GI tract transit times cannot be used to demonstrate release because his release projections are unreliable. In support of this assertion the defendants note that: (1) while the XR1 portion of SANCTURA XR® is designed to release *in vivo* in the upper GI tract in two and a half hours, this formulation

[52] The court notes that the instant case is distinguishable from the facts of *Alza Corporation v. Mylan Laboratories*, a Federal Circuit case which addressed the correlation between *in vitro* and *in vivo* dissolution data. *See Alza Corp.*, 464 F.3d at 1296. In *Alza Corp.*, the Federal Circuit concluded that the *in vitro* or "indirect" dissolution evidence did not adequately model *in vivo* behavior, such that the court did not accept its *in vitro* derived rates of release. *Id.* Here, however, Dr. Davis analyzed the defendants' *in vitro* dissolution data to simply show release, rather than to establish a pharmacokinetic parameter such as rate of release. Dr. Davis also coupled his *in vitro* data findings with consideration of additional evidence, such as the defendants' ANDAs and SANCTURA XR® *in vivo* data. Consequently, the court concludes that while the *in vitro* data provided in *Alza Corp.* was insufficient to prove a pharmacokinetic parameter, the data and evidence Dr. Davis considered here sufficiently establishes the "release" element.

took ten to twelve hours to dissolve in an *in vitro* dissolution test; and (2) the patent applicants represented to the PTO that all of the Shojaei applications release their trospium in the upper duodenum, although the formulations were not fully dissolved for six to twelve hours *in vitro*. (D.I. 201 at 4 (citing Tr. at 497:5-9 (Raoufinia); *id.* at 817:25-819:2 (Davis); *id.* at 1351:13-1352:4 (Bhatt); *id.* at 419:22-25 (Kidane); DTX-1093 at 1; PTX-210 at SANCXR_AGN00000359-60).) In consideration of the testimony presented regarding these two examples, the court concludes that they do not undermine Dr. Davis' methodology and findings.

With regard to the SANCTURA XR® XR1 dissolution time, Dr. Bhatt, a member of the Shire development team, testified that, based on the model developed, XR1 would release in the stomach and continue to release in the upper part of the GI tract at two and a half hours. Tr. at 1351:19-25 (Bhatt). Dr. Bhatt qualified in his testimony, however, that this *in vivo* release prediction was part of an initial model and that that model was changed throughout the development process. *Id.* at 1352:15-1353:9. In particular, Dr. Bhatt noted that models are built on "assumptions that have to be made because you don't know everything that you are trying to achieve" and or the "exact performance." *Id.* at 1351:5-12. To this end, Dr. Bhatt described the use and development of models as an "iterative exercise where you build something with assumptions, you project the next phase, you bring that actual data . . . back into the model" and then "you predict into the unknown again for the next phase." *Id.* at 1353:1-6.

In light of this testimony, the court finds the defendants' argument unpersuasive in undermining the use of *in vitro* dissolution data. Specifically, it is clear from Dr. Bhatt's testimony that while the XR1 was designed to release in the stomach and continue releasing in the upper GI tract at two and a half hours, this timeframe was a projection made in a model, rather than a figure based on *in vivo* data. Thus, while a difference in *in vivo* versus *in vitro* dissolution

times may be probative as evidence that a correlation does not exist between the two, the court finds that the difference between actual *in vitro* dissolution and predicted *in vivo* release of XR1 does not alter its conclusion in this case. Moreover, the court notes that its findings regarding the "release" element of the asserted claims do not rest exclusively on Dr. Davis' comparison of *in vitro* dissolution to GI transit times, but also includes consideration of other factors such as the defendants' ANDA statements and SANCTURA XR®'s *in vivo* data.

With respect to the defendants' second example, Dr. Kidane testified that the dissolution time of the Shojaei applications cannot be used to discredit the use of *in vitro* dissolution data because the Shojaei formulation pellets are "irregularly shaped" and, by design, "entrapped in what's called Microvelai of the upper part of the small intestine" such that they are "retained there." Tr. at 421:7-15 (Kidane). As a result, the pellets are "stuck in that location" and "their release could take however long." *Id.* Dr. Davis likewise agreed that the dissolution time of the Shojaei applications was a direct result of the formulation the inventors developed. *Id.* at 809:3-9 (Davis). Consequently, the court is not persuaded that the Shojaei applications demonstrate that *in vitro* dissolution data and *in vivo* release data cannot be credibly compared.

In view of the foregoing, the court finds Dr. Davis' testimony and conclusions—including his comparison of *in vitro* dissolution data to known GI tract transit times, analysis of SANCTURA XR®'s *in vivo* data, and the defendants' ANDA representations—to be credible and well supported. Thus, in the court's view, the plaintiffs have shown, by a preponderance of the evidence, that the defendants' proposed products meet the "release" element of all the asserted claims.[53]

[53] The court notes that in reaching this conclusion it also finds that, contrary to the defendants' assertions, the plaintiffs did not need to present gamma scintigraphy testing to prove the release element. (D.I. 201 at 1.) Specifically, the defendants argued that the *in vivo* data gamma scintigraphy provides the only reliable evidence of "release" in the lower GI tract because the movement of pellets can be observed using a gamma camera. (*Id.*)

b. Paddock's Immediate Release Argument

As noted, Paddock presents a separate non-infringement argument that the plaintiffs cannot show that "at least a portion of the formulation 'releases trospium [] in the lower GI tract" because its formulation actually releases all trospium rapidly in the upper GI. For the reasons noted above and those that follow, the court finds this argument unavailing.

In support of its argument, Paddock explains that its formulation utilizes a Eudragit L30D55 coating polymer on two of its three mini-tablets that dissolves as the pH level corresponding to release in the upper GI tract. *Id.* at 1142:7-21, 1162:9-19 (Bhalani). Paddock states that its third mini-tablet does not have a coating to delay release. *Id.* at 893:14-894:17 (Derendorf). Paddock also describes that its mini-tablets are contained in a clay matrix, such that when the capsule is ingested, the trospium and clay interact with the charged particles in the GI tract by an ion exchange mechanism wherein trospium is rapidly released from the clay matrix. *Id.* at 903:20-906:11; DTX-4068 at 2-4.

The evidence presented at trial, however, does not support this conclusion. First, Mr. Bhalani, the lead developer of the Paddock proposed product testified that his goal was to have a formulation with "[a]n extended release and an enteric release component" and agreed that he "decided to design [his] formulation to have no immediate release." Tr. at 1159:23-1160:8 (Bhalani). Mr. Bhalani also stated that he studied SANCTURA XR® and determined that it released trospium in the lower GI tract. *Id.* at 1135:5-12, 1136:10-15, 1136:20-1137:14. Moreover, and in addition to Paddock's ANDA statements referenced in the preceding section, the plaintiffs presented a Paddock development document stating that the uncoated extended

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However, for the reasons articulated above, the court concludes that Dr. Davis' assessment of the defendants' products is sufficient to demonstrate that the "release" limitation is met by the defendants' proposed products.

release mini-tablet "releases drug in a pH independent manner throughout the gastrointestinal tract (GIT)." PTX-880 at 18827.

The court also finds persuasive Dr. Davis' testimony that: (1) Paddock asserts that the gastric transit and dissolution profile of its formulation is essentially the same as SANCTURA XR® and gives no indication that the GI transits are different (Tr. at 644:25-655:14 (Davis); PTX-131 at 135); (2) if Paddock's proposed product released all of its trospium in stomach and duodenum there would be a "huge peak" in the blood plasma levels due to a "serious problem of dose dumping" (*id.* at 652:24-654:2); and (3) Paddock's ANDA describes its matrix as "hydrophobic," or "water-hating," which slows dissolution.[54] (*id.* at 671:1-8; PTX-131 at 104). While the court examines Paddock's proposed product formulation in more detail in connection with the "controlled release" element of the assert claims, the court finds that, for the reasons discussed in that section and here, Paddock has not established evidence sufficient to show that its product releases all of its trospium in the upper GI tract and, therefore, does not meet the lower GI "release" limitation. Consequently, the court concludes that Paddock's proposed product infringes all asserted claims of the patents-in-suit.[55]

3. The "Steady-State" Pharmacokinetic Parameters Element of the Asserted Claims

[54] The court finds Paddock's response, via Mr. Bhalani, that the matrix is not "hydrophobic" and that inclusion of that term in Paddock's ANDA "may have been a poor choice of words" is unavailing in light of the evidence presented at trial. Tr. at 1145:24-1146:1 (Bhalani).

[55] The court finds that the defendants' products infringe claim 1 and, similarly, claims 2, 18, and 20 of the '978 Patent. *Id.* at 629:3-14, 629:24-630:20, 632:17-633:2, 637:22-24, 637:25-638:11, 639:2-17, 640:21-641:18 (Davis); *id.* at 541:250542:11-16 (Weiner). In addition, because the defendants' products release trospium in the colon, they also infringe claim 19 of the '978 Patent. The court also finds that, because each of the defendants' proposed products are comprised of extended and delayed release pellets that release at a particular pH level, they also infringe claim 10 of the '449 Patent, and claims 10 and 16 of the '448 Patent. *Id.* at 685:22-686.2 (Davis). The court also notes that none of the defendants contest that their proposed products are pharmaceutical compositions suitable for once-a-day administration as required by asserted claims 1, 2, 4, and 20 of the '978 Patent; claim 1 of the '448 Patent; and claim 1 of the '449 Patent. The court agrees with Drs. Davis and Weiner that the defendants' proposed products infringe, either directly or by inducement, each element of the asserted claims of the patents-in-suit.

All of the asserted claims, except claims 18 and 19 of the '978 Patent, require one or more steady-state pharmacokinetic parameters. These parameters include: steady state blood levels (claims 1, 2, and 20 of the '978 Patent); steady state C_{max} and C_{min} (claim 1 of the '359 Patent, claims 1, 10, and 18 of the '448 Patent, and claims 1, 10, and 18 of the '449 Patent); and steady state AUCs (claim 4 of the '978 Patent). With respect to these steady state pharmacokinetic parameters, all three defendants contend that their proposed products do not infringe claim 1 of the '359 Patent because, per Dr. Weiner's testimony, their products do not have a steady state C_{max} of less than 2400 pg/ml as required by that claim. Tr. at 545:10-546:2 (Weiner); *see also* PDX-611; PDX-612; PDX-613. Watson and Sandoz do not dispute, however, that their proposed products meet the other steady state pharmacokinetic parameter limitations of the patents-in-suit.[56] (D.I. 203 at 26.) The court addresses infringement of the asserted claims of the '978, '448, '449 Patents first, and examines the defendants' alleged infringement of claim 1 of the '359 Patent separately.

As noted, Paddock presents separate defenses with respect to the steady state pharmacokinetic parameters. Specifically, Paddock maintains that the plaintiffs failed to show infringement based on the steady state claims because: (1) Paddock's proposed product does not include information related to steady state blood levels or AUC on its label and the plaintiffs did not test what the steady state levels would be "following administration of [the Paddock] product according to the proposed label"; and (2) the plaintiffs' use of Paddock's bioequivalence study to extrapolate single dose data was improper and, thus, was not probative, because (a) the bioequivalence study was designed to assess the relative differences between the two products,

[56] The defendants' jointly submitted Proposed Findings of Fact and Conclusions of Law challenges whether the defendants' proposed products meet the steady state C_{max} limitation of claim 1 of the '359 Patent, but does not dispute that these products meet the other steady state pharmacokinetic parameters. (D.I. 203 at 26.)

not actual values, and (b) the study was not administered amongst the U.S. population and was instead conducted in India.[57] (D.I. 201 at 8-10.)

In addition, Paddock also presented "affirmative evidence" via Dr. Derendorf, who testified that he conducted a study wherein, using Paddock's bioequivalence data, he assessed the relative difference between steady state blood levels and AUC for SANCTURA XR® and the Paddock product, and then applied the difference to the actual steady state blood levels for SANCTURA XR® in the applicants' 020 study[58]. (*Id.* at 10.) Dr. Derendorf concluded that Paddock's steady state blood levels and AUC values do not meet the claim limitations the patents-in-suit require.[59] (*Id.* (citing Tr. at 932:18-935:14 (Derendorf); PTX-130).) Specifically, whereas the patents-in-suit require steady state blood levels in the range of about 0.5 ng/ml to about 6.0 ng/ml and steady state AUC in the range of about 30 to about 60 ng/ml*hr, Dr. Derendorf calculated these values as 0.37 ng/ml and 17.52 ng/ml*hr, respectively. (*Id.* (citing Tr. 932:18-935:14 (Derendorf); *id.* at 593:11-24, 595:8-25 (Weiner); PTX-130).) Paddock further notes that the plaintiffs' expert, Dr. Weiner: confirmed the accuracy of Dr. Derendorf's calculations; and acknowledged that he did not take into account differences in the U.S. and Indian populations

[57] Paddock argues that the plaintiffs erred in assuming that "the blood levels and AUC from Paddock's [bioequivalence] study will directly correlate to the blood levels and AUC that would be obtained from administration of Paddock's product to a U.S. population according to the instructions on the label." (D.I. 201 at 9.) Specifically, Dr. Derendorf, Paddock's expert, testified that Paddock's bioequivalence study reported the C_{max} and AUC for SANCTURA XR® at rates two to three times higher than the C_{max} and AUC for SANCTURA XR® in thes 020 study. (*Id.* (citing Tr. at 591:7-592:3 (Weiner); *id.* at 923:14-924:14 (Derendorf); PTX-054A; PTX-130).) Dr. Derendorf testified that "this large discrepancy could result from (1) cultural, body weight, or genetic differences between the study subjects, and (2) the four hour fast after dosing in the Paddock [bioequivalence] study versus the one hour fast required after dosing in the 020 study, which implicated the well[-]known food effects of trospium." (*Id.* (citing Tr. at 924:15-925:6 (Derendorf).)

[58] The 020 study refers to a study in which SANCTURA XR® was administered in accordance with the instructions on its label to a U.S. population and steady state pharmacokinetic result levels were reported. *See* PTX-054A at SANCXR_END_01396395-97, 01396434.

[59] Specifically, Dr. Derendorf testified that Paddock's product would have a steady state C_{min} of 0.37 ng/ml and an AUC of 17.52 ng/ml*hr, values that do not meet the claim limitations. *See* Tr. at 594:12-18, 596:1-3 (Weiner); 934:13-935:2 (Derendorf).

when formulating his own calculations. (*Id.* (citing Tr. at 593:15-596:3, 587:1-7, 581:18-582:6, 582:16-22, 583:9-25 (Weiner).)

Conversely, the plaintiffs argue that, per Dr. Weiner's testimony, the linear superposition technique it employed to calculate the defendants' mean steady state pharmacokinetic values was appropriate and demonstrates infringement. (D.I. 203 at 10.) In support of this argument, the plaintiffs maintain that Dr. Weiner's calculation method is more credible than Dr. Derendorf's calculations because the Derendorf model seeks first to compare the steady state blood levels measured for SANCTURA XR® and for the Paddock's Indian bioequivalence study, to determine a blood level ratio between the two. (*Id.* at 21 (citing Tr. at 932:19-934:13 (Derendorf).) Once this ratio, estimated at roughly 1.5, is established, the Derendorf model then calculates the steady state blood levels by multiplying this ratio by the steady state blood levels determined for SANCTURA XR® in clinical trials. (*Id.*)

The plaintiffs contend that Dr. Derendorf's method[60] of calculating Paddock's steady state blood levels and AUC values is improper because the ratios calculated from Paddock's

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[60] Specifically, Dr. Derendorf explained his methodology on direct examination:

Q: So I think you said you looked at the numbers for the Paddock product versus the SANCTURA product in the same patient. From the Paddock bioequivalence study, what did you find with respect to the relationship of those numbers?

A: Yes. As we have seen looking at the actual numbers, the Paddock product has a slightly lower C_{max} and AUC. One can use the linear superposition to calculate out what the respective numbers are at steady state. Then also at steady state, one would have a Cmin. In a superposition, one doesn't have a C_{min}, but when you extrapolate multiple doses, you do. Then when you compare the two products, we can see that the Paddock product has a 14 percent lower C_{min} and a 15 percent lower AUC. So slightly lower [pharmacokinetic] parameters. . . . So now that we've established the relationship between the products, now we can go back to the intended population and take advantage of the actual study that was done by plaintiff as part of the NDA. There is a multiple dose steady state study. . . . This is actually measurement in the intended population in the label country.

. . . .

Q: So how did you figure out what the expected steady state blood levels for Paddock's product in a U.S. population according to the label, what that would be?

A: Well, no it's fairly straightforward. We just have to put one and one together. That is available. Secondly, we know that the Paddock product is . . . much lower, 14 to 15 percent. So we can project what we would expect in the Paddock product under label conditions.

Tr. at 932:19-934:13 (Derendorf).

bioequivalence study were not fixed and the values were not based on their patient data. (*Id.* (citing Tr. at 605:22-606:4 (Weiner).) Specifically, Dr. Weiner testified that:

> [T]here is no reason to believe that the ratio is fixed. In other words, if you repeated the studies that ratio would vary. And that's consistent with the concept when you do bioequivalence that the ratio could vary between 80 to 125 percent. In addition, I don't agree with Dr. Derendorf's whole approach to doing this fraction of the data to begin with, because that suggests that for whatever reason, defendant does not feel that the data in their own label is consistent with the data that they collected from their ANDA study. I would have taken the data directly, as I did, from the patients that they studied and predicted their steady state results, which I did.

Tr. at 605:22-606:4 (Weiner).

Based on this assessment, Dr. Weiner engaged a different linear superposition methodology. Because the defendants' ANDAs contain only single-dose, rather than steady state, pharmacokinetic values for their proposed products, Dr. Weiner employed linear superposition, which allows steady state values to be predicted from a single dose. Unlike Dr. Derendorf's model, however, Dr. Weiner explained that this analysis involved: ensuring he had the "exact same data that was reported in the [defendants'] ANDAs"; taking that "data and for each individual, for each study, [] computing the C_{max}, T_{max}, AUC, et cetera, . . . comput[ing] the mean values, and compar[ing] those to the mean results that were reported in the ANDA"; "perform[ing] the superposition analysis for each subject for each study in order to estimate the replacement concentrations at steady state"; and evaluating the "degree of accumulation for each individual," averaging the accumulation, and "compar[ing the average ratios] to the SANCTURA XR® data." *Id.* at 526:16-527:9, 528:18-529:4.

From this analysis, Dr. Weiner calculated the mean steady state pharmacokinetic values for the defendants' proposed products as:

Mean Parameter	***Defendant Watson***	***Defendant Sandoz***	***Defendant Paddock***
C_{max} (ng/ml)	3.56	3.89	5.58
C_{min} (ng/ml)	0.77	0.88	1.45
AUC (ng/ml*hr)	37.05	38.41	63.66
Blood Level Range (ng/ml)	0.77-3.25	0.88-3.55	1.46-4.91

Notably, Dr. Derendorf testified that he agreed with the linear superposition methodology Dr. Weiner used as well as his calculation results, and stated that linear superposition is the "standard way to" project out single dose to steady state values. *Id.* at 954:5-13 (Derendorf). Dr. Derendorf disagreed, however, "with the data [Dr. Weiner] used and conclusion he came up with." *Id.* at 954:14-20. Specifically, Dr. Derendorf stated that: "The method was fine. The math was fine. But [Dr. Weiner] used the results from the study in India to say this is what will happen, compare these numbers with the limitations of the patent, and that is not proper." *Id.*

The court disagrees with Dr. Derendorf's assessment. In consideration of the expert testimony presented at trial, the court finds Dr. Weiner's methodology and results credible. The court notes that in reaching this finding it rejects Paddock's arguments, enumerated above, that the plaintiffs erred in not testing Paddock's steady state levels "following administration . . . according to the proposed label" and in using Paddock's bioequivalence study[61]. Moreover, the

[61] As noted, Paddock also argued that the discrepancy between the C_{max} and AUC for SANCTURA XR® in its bioequivalent study could be at least partially attributed to the fact that the four hour fast required after dosing in the bioequivalent study versus the one hour period required in the 020 study, resulted in food effect on trospium. Tr. at 924:15-935:6 (Derendorf). Paddock further argued that Dr. Weiner's calculations failed to take this factor into account and, therefore, were questionable. (D.I. 201 at 9-10.) The court finds this argument unavailing in light of the evidence before it. Specifically, the testimony and exhibits adduced at trial make clear that trospium is intended for administration to a fasted, not fed, patient. Tr. at 522:20-524:16 (Weiner); *see also* PTX-129 at 79; PTX-585. Moreover, even Dr. Derendorf conceded that the four hour lag in Paddock's bioequivalence study is provided for by FDA guidance and was followed. Tr. at 925:2-15 (Derendorf). This delay was implemented to reduce trospium's food effects. *Id.* at 967:18-970:6. Further, the court finds Dr. Weiner's testimony that there would be no difference

court finds Paddock's argument regarding the use of data obtained from participants in India similarly unavailing.[62]

In light of these findings, the court concludes that Paddock infringes the asserted claims referenced above that include the steady state pharmacokinetic parameters element.[63] As noted, Dr. Weiner determined that the steady state pharmacokinetic values for Paddock are: C_{max} of 5.58 ng/ml; Cmin of 1.45 ng/ml; AUC of 63.66 ng/ml*hr; and a blood level range of 1.46 to 4.91 ng/ml. Tr. at 529:23-25, 531:9-12 (Weiner). Because blood level ranges between about 0.5 ng/ml and about 6.0 ng/ml are comparable to those achieved by twice-daily administration of trospium, the court finds that Paddock meets this limitation. *See id.* at 540:6-11; *id.* at 666:2-17 (Davis); PTX180C. Moreover, using these steady state blood levels, the court concludes that these values fall within the blood level limitations of claim 2 and 20 of the '978 Patent. Tr. at 531:9-16, 533:19-534:8, 535:10-536:5, 540:2-19, 542:5-21, 544:9-545:9 (Weiner). Further, and with respect to claim 4 of the '978 Patent, Paddock's AUC value of 63.66 ng/ml*hr falls within the claimed range of about 30 to about 60 ng/ml*hr, because 63.66 ng/ml*hr is "about" or "approximately" 60 ng/ml*hr as defined by the patent specification. *Id.* at 543:25-545:9; *see also* '978 Patent at col. 4:46-47. With regard to this finding, the '978 Patent applicants stated in the specification that, "with respect to blood levels, 'about' means within FDA acceptable guidelines." '978 Patent at col. 4:46-47. Because FDA guidelines allow for "plus or minus 20

"in bioavailability between the one hour and four hour fast" after an overnight fast credible. *Id.* at 525:12-526:12 (Weiner).

[62] The court finds that Paddock has failed to present evidence sufficient to show that conducting a bioequivalence study in India is significant. Specifically, and as the plaintiffs correctly note, the FDA recommends that bioequivalence studies "be conducted in individuals representative of the general population, taking into account age, sex, and race." *See* PTX-892 at 7. There is no evidence that Paddock told the FDA that its studies, which they now assert should be distinguished from testing in the United States, were not conducted in accordance with FDA guidance. Tr. at 605:1-5; PTX-679; PTX-892. Moreover, Dr. Weiner testified that there are no known differences between an Indian population and a U.S. population with respect to trospium's pharmacokinetic parameters and Dr. Derendorf did not rebut this conclusion. Tr. at 581:18-24 (Weiner); *id.* at 924:15-23; 964:14-22 (Derendorf).

[63] Specifically, the court finds that Paddock infringes: claims 1, 2, and 20 of the '978 Patent; claims 1, 10, and 18 of the '448 Patent; claims 1, 10, and 18 of the '449 Patent; and claim 4 of the '978 Patent. As noted, the court addresses infringement of claim 1 of the '359 Patent separately.

percent," it is clear that this figure falls within the range limitation specified in claim 4. Tr. at 544:15-545:2, 563:20-565:2 (Weiner).

The court further concludes that Watson and Sandoz likewise infringe these asserted claims, as the values Dr. Weiner calculated for their proposed products fall within the limitations stated in the patents-in-suit. Consequently, the court concludes that all three defendants infringe claims 1, 2, and 20 of the '978 Patent, claims 1, 10, and 18 of the '448 Patent, claims 1, 10, and 18 of the '449 Patent, and claim 4 of the '978 Patent.

The court next addresses whether the defendants infringe claim 1 of the '359 Patent. As noted, the defendants assert that they do not infringe this claim because, based on Dr. Weiner's modeling which the court accepts as credible, their proposed products do not have a C_{max} at steady state of less than 2400 pg/ml[64], as required by this claim limitation. (D.I. 203 at 26 (citing Tr. 545:10-546:2).) Specifically, Dr. Weiner's modeling assessed the defendants' C_{max} values as greater than 2.4: 3.56 for Watson; 3.89 for Sandoz; and 5.58 for Paddock. Tr. at 529:14-25, 530:25-531:12 (Weiner). In response, the plaintiffs argue that the defendants do, in fact, infringe claim 1 of the '359 Patent based on the information they provided on their proposed product labels. (D.I. 203 at 24.) Specifically, the plaintiffs assert that because the defendants choose to report pharmacokinetic data from the SANCTURA XR® label, instead of their own data, the court should rely on the label data—specifically SANCTURA XR®'s 1873 pg/ml C_{max} figure—in determining whether the defendants infringe this claim. The plaintiffs further argue that relevant case law supports this comparison. Specifically, the plaintiffs note that the Federal Circuit has instructed that trial courts can, where appropriate, compare a bioequivalent ANDA product to branded product to show infringement. *See Adams Resp. Therapeutics v. Perrigo Co.*, 616 F.3d

[64] The court notes that, for comparison purposes, this 2400 pg/ml figure coverts to 2.4 nanograms. *Id.* at 545:21-24 (Weiner).

1283, 1288-89 (Fed. Cir. 2010) (concluding that "[o]ur cases law does not contain a blanket prohibition against comparing the accused product to a commercial embodiment" in assessing infringement where that commercial embodiment meets all of claim limitations of the patent at issue).

The court concludes that such comparison is appropriate in this case. Namely, and as detailed above, the defendants decided to include SANCTURA XR®'s pharmacokinetic data on their labels, rather than file a petition with the FDA to put their own single-dose data on their labels instead.[65] Tr. at 959:3-13, 960:3-13 (Derendorf); *see also* PTX-913. In so doing, the court concludes that the defendants can be held to their published steady state C_{max} value, which fall within claim 1 of the '359 Patent. *See Adams Resp. Therapeutics*, 616 F.3d at 1288-89. The court notes that this finding is not undermined by the fact that the court finds Dr. Weiner's modeling of steady state pharmacokinetic parameters to be credible and used these figures in assessing infringement of the '978, '448, and '449 Patents. Similarly, Dr. Weiner's statement on cross-examination that using the defendants' actual data is a reliable method and preferable to using the single dose SANCTURA XR® data, does not negate this finding.[66] While the court

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[65] The defendants argued, via the testimony of various witnesses at trial, that they were "required" to copy SANCTURA XR®'s label. However, the court notes that Dr. Derendorf conceded in his testimony that the defendants, in fact, could have filed a petition with the FDA to use their own pharmacokinetic parameter values. Tr. at 959:3-13, 960:3-13 (Derendorf); *see also* PTX-913. Thus, the court finds that the defendants elected to list the SANCTURA XR® data on their labels, rather than report their own data. This finding is not undermined by the fact that it is "common" for generic companies to list the data from the patented product onto the proposed ANDA label, because, as was made clear through the testimony presented, the ANDA filers have a choice to report either. Tr. at 958:18-963:10.

[66] Specifically, Dr. Weiner testified as follows:

> Q: And you chose instead to use the label approach just for the one patent and one claim. Correct?
>
> A: Well, as I stated earlier, since defendants had single dose data available, I did use that. But since, with respect to the '359 patent, since they also included other pharmacokinetic data in their label, which I assume the defendants believed has some relevance, I used that for the purposes of the '359 claim.
>
> Q: Right. Now, my question is a little bit beyond that. That question is, did you choose to use the actual data relating to the defendants' products that you had available to you for the '978, the '448, and the '449 patents because you thought the superposition analysis using the actual data was a preferable approach?
>
> A: Yes.

agrees that Dr. Weiner's steady state values, as derived from the defendants' actual data, are credible and properly considered in the infringement analysis, this determination does not preclude the court from considering in this instance the data the defendants selected for their proposed labels. *See Adams Resp. Therapeutics*, 616 F.3d at 1288-89.

Consequently, because the defendants' label C_{max} values fall within the range limitation covered by claim 1 of the '359 Patent, the court concludes that the defendants infringe this claim. The court also notes that the defendants, in electing to copy the SANCTURA XR® data on their labels, would have known that persons using their ANDA products were likely to infringe any patent rights associated with the data or were "willfully blind" to this fact.[67] *See Global-Tech Appl., Inc. v. SEB S.A.*, No. 106-, 2011 WL 2119109, at *10 (May 31, 2011). As a result, the defendants also infringe claim 1 of the '359 Patent by inducement. *Id.*; *see also DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1305-06 (Fed. Cir. 2006) (*en banc*).

4. The "Particulates Comprising an Enteric and/or Release Controlling Polymer" Elements of the Asserted Claims

Claims 1, 2, 4, and 20 of the '978 Patent require that the claimed composition have trospium-bearing particulates comprising enteric polymers, release controlling polymers, or combinations thereof. *See* '978 Patent. Watson and Sandoz do not dispute that their proposed products infringe the asserted claims requiring these elements. Paddock, however, asserts that: (1) pursuant to the court's claim construction, the mini-tablets in its proposed product are not particulates or equivalent to particulates; and (2) its proposed product contains "granules" and that the "magnesium aluminum silicate (Veegum) and povidone in those granules are [not] 'release controlling polymers.'" (D.I. 201 at 11.) For the reasons that follow, the court concludes that

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Id. at 577:13-578:2 (Weiner).

[67] It is clear to the court, based on the evidence before it, that the defendants were each aware of the SANCTURA XR® product and its associated patents. As noted, the defendants each stated in their ANDAs that their generic was developed to mimic SANCTURA XR®.

Paddock's proposed product infringes the asserted claims requiring these elements. For the purpose of clarity, the court will address the "polymer selected from enteric or release controlling polymers" element separately from the "controlled release" element examined below.

a. The "At Least One Polymer Selected from Enteric or Release Controlling Polymers" Element

Paddock asserts that Veegum is not a polymer. Tr. at 941:2-19 (Derendorf). Specifically, Dr. Derendorf offered this opinion based on a manual published by the Environmental Protection Agency under the Toxic Substances and Control Act. *See id.*; DTX-4080. That Manual describes a polymer as a carbon-based compound that has covalent bonds. DTX-4080 at 7; Tr. at 941:2-19 (Derendorf). Because Veegum is inorganic clay that does not contain covalent bonds and controls release via ion exchange, Paddock's argues that its proposed product does not meet this limitation of the asserted claims. Tr. at 940:20-941:1, 941:20-22, 907:5-909:10 (Derendorf).

The court disagrees. As the plaintiffs correctly note and Dr. Davis testified, veegum is recognized by the Handbook of Pharmaceutical Sciences as a polymeric complex made of magnesium, aluminum, and silicon. PTX-609; Tr. at 667:6-668:18 (Davis). The International Journal of Pharmaceutics similarly recognizes veegum by this characterization. PTX-897; Tr. at 668:19-669:9 (Davis). While Paddock argues that polymer and "polymeric complex" cannot be construed to have the same meaning and does not mean that "'polymeric' is necessarily a polymer," this argument is unsupported by the evidence. In particular, the Environmental Protection Agency Manual explicitly states that "the definitions provided herein are those used in the new polymer exemption rule, and that these terms may not necessarily have the same meaning as commonly used in an academic or industrial setting." DTX-4080 at 7; Tr. at 982:21-984:8 (Derendorf). Moreover, Paddock's granules also comprise povidone, which is a polymer that controls trospium's release as a known binder in pharmaceutical formulations. Tr. at 669:16-

670:21 (Davis); PTX-604; PTX-595. Because the court agrees, based on Dr. Davis' testimony regarding the manuals presented, that veegum is appropriately characterized as a polymer and disagrees with Dr. Derendorf's assessment on this issue, the court concludes that Paddock's proposed product infringes claims 1, 2, 4, 18, 19, and 20 of the '978 Patent.

b. The "Controlled Release Solid, Trospium-Bearing Particulates" Element

With respect to the "controlled release solid, tropsium-bearing particulates" element of the asserted claims, Paddock contends that the plaintiffs have failed to prove this limitation by a preponderance of the evidence because: (1) Paddock's proposed product are not "particulates" as construed by the court in its claim construction and are not equivalent to particulates because they are much larger and function in a different manner; (2) povidone, even if it is capable of controlling release when used as a coating, does not do so in the Paddock product because it acts as a binder instead of a release controlling agent; and (3) this limitation has been construed to require that povidone "actually function to control the rate of release" of tropsium, and it does not do so. (D.I. 201 at 6-8.)

Conversely, the plaintiffs assert that Paddock's proposed product meets this limitation. (D.I. 203 at 14-17.) For the reasons that follow, the court agrees. First, as is clear from Paddock's ANDA, the proposed product is made using a wet granulation process, wherein trospium, veegum, stearic acid, talc, povidone, and sodium chloride are processed together as granules and subsequently compressed to form extended release mini-tablets. PTX-131 at 150; Tr. at 646:6-647:16 (Davis). As admitted by Paddock's expert, Dr. Derendorf, these mini-tablets are, in fact, "solid, tropsium-bearing particulates" within the meaning of claim 1 of the '978 Patent.[68] Tr. at 981:7-20 (Derendorf). Dr. Davis likewise agreed with this characterization of

[68] Specifically, Dr. Derendorf testified as follows on cross-examination:

Paddock's mini-tablets. *Id.* at 649:4-19 (Davis). Based on this testimony, the court finds that the mini-tablets in the Paddock product are particulates within the meaning of claims 1 and 20 of the '978 Patent and, thus, that Paddock infringes this limitation.

Second, the court also finds that the Paddock proposed product meets the "controlled release" limitation of the asserted claims. Specifically, Paddock's ANDA describes veegum as a "controlled release agent" and a "hydrophobic matrix former" and identifies stearic acid and talc as "hydrophobic matrix formers." PTX-131 at 131, 132, 144, 145, 148; *see also* Tr. at 664:1-22 (Davis); *id.* at 1181:25-1182:17 (Bhalani). As noted above, Dr. Davis testified that "hydrophobic" is defined as "water-hating" and, because of this property, acts to slow the release of trospium by making it "very difficult for water to get into the matrix." Tr. at 651:10-12 (Davis). Dr. Derendorf likewise stated on cross-examination that veegum "certainly has an effect on release." In light of this testimony, the court rejects Mr. Bhalani's assertion that the matrix is not "hydrophobic" and was termed "hydrophobic" due to a "poor choice of words." *Id.* at 1181:9-21 (Bhalani).

This finding is further supported by Sidmark's draft quality overall summary and product development report. The report states that stearic acid and talc are hydrophobic matrix formers, a

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Q: But you believe, it's your opinion that the mini-tabs are actually containers of particulates; true? That's your opinion?
A: They contain granules. Yes, they contain—they are made out of granules which can be characterized as particulates.
Q: It can be or is it your opinion that they are, sir?
A: They are not—not in the final product, they're not any more. In the process, they were. However, they don't contain any controlling membrane, so there is no—they're small, small particulates that are used in the preparation of the mini-tablets.
Q: You testified in your deposition that these were containers of particulates; true? The mini-tablets?
A: Yes, I accept that.
Q: And that the particulates that were contained in the mini-tablet were the granules; right? That's what you testified in your deposition?
A: Granules are particulates. Again, they are used to make mini-tablets. The final product is not a particulate.

Tr. at 980:20-981:15 (Derendorf).

point which Mr. Bhalani conceded. *See* PTX-880 at 18827; PTX-888 at 20007; PTX-131; Tr. at 1185:18-22 (Bhalani). Thus, the court rejects Dr. Derendorf's opinion that talc is hydrophilic ("water-loving") and that talc and stearic acid do not form a hydrophobic matrix, as inconsistent with this report and Paddock's ANDA. *See* PTX-131; Tr. at 918:19-24 (Derendorf). Similarly unpersuasive is Dr. Derendorf's explanation that the terming of these components as hydrophobic was "maybe a mistake." Tr. at 918:25-919:1 (Derendorf).

Moreover, the court also finds that povidone, which is contained in Paddock's granules, acts as a "binder" that "glues" the matrix together and slows trospium's release. *See id.* at 669:16-670:21; PTX-604; PTX-595. In particular, while it has been established that disintegrants can override povidone's release controlling property and cause rapid dispersion, there are no disintegrants present in Paddock's proposed product. Tr. at 670:16-18 (Davis). As such, the court concludes that povidone, as used in the Paddock proposed product, is a "controlled release" agent. *Id.*

The development of Paddock's formulation reinforces the court's "controlled release" finding. Specifically, Mr. Bhalani testified that Paddock's first formulation attempt utilized an extended release hydrophilic matrix system. *Id.* at 1139:8 (Bhalani). This formulation, however, resulted in trospium being released too quickly, with high AUC and C_{max} values, because hydrophilic molecules are very soluble in water. *See* PTX-130, 131 at 143-44; PTX-88 at 20029; Tr. at 1140:7-10, 1177:15-24 (Bhalani). In order to slow this release and lower the C_{max} and blood plasma exposure, Paddock's second formulation attempt used a hydrophobic matrix system "of a non[-]swelling type" which "release[d] by dissolution." *See* PTX-130, 131 at 143-44, 148; PTX-888 at 20029; PTX-132 at 679; Tr. at 1140:9-13, 1177:25-1178:3 (Bhalani); *id.* at 650:25-652:23 (Davis). This formulation change resulted in a slower trospium release that was closer to

being bioequivalent to SANCTURA XR®. *See* PTX-130, 131 at 143-44; PTX-888 at 20029; Tr. at 1140:9-13, 1141:11-14 (Bhalani). For its third and final formulation attempt, Paddock used a hydrophobic matrix system and added salt, which resulted in a C_{max} and AUC that are, according to Paddock, bioequivalent with SANCTURA XR®. *See* PTX-130, 131 at 148-49; PTX-888 at 20029; Tr. at 1140:9-1142:1 (Bhalani).

Finally, the court concludes that Dr. Derendorf's testimony that trospium release occurs rapidly via ion exchange is unsupported by the record generally and by Paddock's ANDA in particular. Tr. at 905:2-906:11, 896:3-14, 975:7-12 (Derendorf). On this point, the court finds Dr. Davis' testimony credible and instructive. Specifically, Dr. Davis explained that while ion exchange might occur in Paddock's formulation, its effect is limited by the rate at which water can penetrate the hydrophobic matrix. *Id.* at 761:14-21 (Davis). Because Paddock's matrix resists water penetration, the rate of trospium release is not controlled by ion exchange, but, instead, by a slow diffusion. *Id.* at 650:25-652:23; *see also* PTX-130, 131 at 148.

In light of these findings, the court concludes that Paddock's proposed product meets the limitations of claims 1 and 20 of the '978 Patent and, therefore, infringes these asserted claims.

5. The "Minimizing the Occurrence of Side Effects" Element of the Asserted Claims

As noted, claim 1 of the '449 Patent requires that the patented invention "results in minimizing the occurrence of side effects as compared to twice daily administration of 20 mg of immediate release trospium tablets." '449 Patent at col. 21:1-13. The defendants assert that the plaintiffs have failed to prove that their proposed products infringe this claim either directly or by inducement because the plaintiffs did not establish that SANCTURA XR® or the defendants' products "reduce" side effects. (D.I. 202 at 26.) In support of this argument, the defendants cite to the testimony of Dr. Oefelein, who stated that "[i]f the intent to minimize means to make as

small as possible, there is no data or evidence for me to answer that question." Tr. at 125:4-23 (Oefelein). The defendants also contend that the plaintiffs cannot prove infringement by inducement because they presented "no evidence to show that each element of the method claims are part of the proposed labels of [d]efendants' products" or that "the [d]efendants possessed the requisite levels of knowledge and intent." (D.I. 202 at 27 (citing *Global-Tech Appl., Inc.*, 2011 WL 2119109, at *4).)

The court disagrees with the defendants' assertions with respect to this claim. First, and as the plaintiffs correctly note, the defendants' labels indicate that their products are designed for once-a-day administration for the treatment of OAB[69] and state that use of the proposed products results in a dry mouth rate of 10.7 percent. (D.I. 203 at 23 (citing Tr. at 680:4-682:2 (Davis); PTX-157; PTX-141; PTX-129).) As noted in connection with the defendants' infringement of claim 1 of the '359 Patent, the defendants' label data reporting a reduction in dry mouth over the twice-a-day trospium formulation was copied from the SANCTURA XR® label. *Id.* As stated in its analysis above, the court concludes that the defendants adopted and, thus, can be held to their published label information because they choose not to report their own data studies or remove this representation.[70]

Second, the court finds the cited portion of Dr. Oefelein's testimony irrelevant for the proposition the defendants pose. Specifically, Dr. Oefelein stated that he had no evidence to prove the "minimizing the occurrence of side effects" element in response to a question posed on cross-examination where "minimizing" was hypothetically defined as "make as small as possible." Tr. at 124:4-125:23 (Oefelein). The court, however, has not construed "minimizing

[69] Per Dr. Davis' testimony, drug manufacturers intend for patients to follow product labels, such as the label instruction here indicating that the trospium formulation is intended for once-a-day dosing. Tr. at 680:4-682:2 (Davis).

[70] *See supra* Section III.3.E.

the occurrence of side effects" to mean "make as small as possible." Rather, and as noted above in connection with the court's indefiniteness examination, "minimizing" as used in the patents-in-suit did not require construction[71] and has been viewed by experts on both sides to be synonymous with "reduce." Dr. Oefelein testified that he did find the "minimizing" element met where the term means "one formulation improving over the other," such that the occurrence of side effects in one formulation is less than a prior formula. *Id.* at 123:18-124:3. Consequently, the court finds the defendants' argument in connection with Dr. Oefelein's testimony unavailing.

Third, and with respect to the defendants' argument related to the intent element of inducement, the court finds, based on the evidence before it, that the defendants had knowledge of the '449 Patent and intended for their products to be used in a manner consistent with the labeled conditions of use copied from the SANCTURA XR® label. *See Global-Tech Appl., Inc.*, 2011 WL 2119109 at *10 (concluding that the copying of a patented invention, even in the absence of knowledge of the patent, can meet the intent element). This conclusion is further supported by the defendants' own statements to the FDA that their proposed products were developed to "mimic" or "match" the claimed invention. *See, e.g.*, Tr. at 634:6-14, 644:25-645:14, 617:17-618:11 (Davis); *see also* PTX-162; PTX-147; PTX-145.

In view of the foregoing, the court concludes that the defendants' proposed products meet the "minimizing" limitation and induce infringement of claim 1 of the '449 Patent. *See Adams Resp. Therapeutics*, 616 F.3d at 1288-89. The court further concludes, based on this finding, that the defendants infringe claim 18 of the '449 Patent requiring side effects to be selected "from a

[71] The parties initially submitted "minimizing the occurrence of adverse side effects following oral administration of an immediate release formulation containing 40 mg of trospium chloride" as a term requiring construction, but ultimately agreed the limitation should be defined to mean "the claimed dosage form minimizes the occurrence of adverse side effects following oral administration of an immediate release formulation containing 40 mg of trospium chloride." (D.I. 144 at 2.)

group consisting of dry mouth, constipation, dyspepsia, abdominal pain, and a combination thereof." Tr. at 686:3-10 (Davis).

IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) all asserted claims of the patents-in-suit are invalid due to obviousness; (2) the asserted claims of the patents-in-suit are not invalid due to anticipation; (3) claim 1 of the '978 Patent and claim 1 of the '449 Patent are not invalid due to indefiniteness; (4) claim 1 of the '359 Patent is not invalid due to written description; (5) the defendants' proposed products infringe the asserted claims of the patents-in-suit; and (6) each of the parties' Rule 52(c) motions are granted in part and denied in part.[72] An appropriate order will follow.

Dated: March 31, 2012

CHIEF, UNITED STATES DISTRICT JUDGE

[72] As noted, all parties submitted Proposed Findings of Fact and Conclusions of Law, requesting that the court find in its favor on issues of obviousness, anticipation, indefiniteness, written description, and infringement. For the reasons stated above and based on the court's findings, the parties Rule 52(c) motions are granted in part and denied in part.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC., ALLERGAN USA, INC., ALLERGAN SALES, L.L.C., ENDO PHARMACEUTICALS SOLUTIONS INC., and SUPERNUS PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 09-cv-511 (GMS)
WATSON LABORATORIES, INC.— FLORIDA, SANDOZ INC., and PADDOCK LABORATORIES, INC.,	)	
Defendants.	)	

ORDER

At Wilmington this 31st day of March, 2012, IT IS HEREBY ORDERED THAT:

1. The asserted claims of the patents-in-suit are invalid due to obviousness;

2. The asserted claims of the patents-in-suit are not invalid due to anticipation;

3. Asserted claim 1 of the '978 Patent and asserted claim 1 of the '449 Patent are not invalid due to indefiniteness;

4. Asserted claim 1 of the '359 Patent is not invalid due to written description;

5. The defendants' proposed products infringe the asserted claims of the patents-in-suit; and

6. The parties' Rule 52(c) motions (D.I. 201-203) are GRANTED IN PART AND DENIED IN PART.

7. The Clerk of Court is directed to enter final judgment in favor of the defendants and against the plaintiffs.

CHIEF, UNITED STATES DISTRICT JUDGE