IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: ARMODAFINIL PATENT LITIGATION INC. ('722 PATENT LITIGATION)	MDL No. 10-md-2200 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. WATSON LABORATORIES, INC., Defendant.	Civil Action No. 10-cv-007 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. SANDOZ, INC., Defendant.	Civil Action No. 10-cv-055 (GMS) Civil Action No. 11-cv-782 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. LUPIN LIMITED, Defendant.	Civil Action No. 10-cv-210 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. APOTEX, INC., Defendant.	Civil Action No. 10-cv-695 (GMS) Civil Action No. 10-cv-1078 (GMS)

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiffs Cephalon, Inc. and Cephalon France (collectively, "the plaintiffs" or "Cephalon") allege that pharmaceutical products proposed by defendants Apotex, Inc., Lupin Limited, Sandoz, Inc., and Watson Laboratories, Inc. (collectively, "the defendants"), infringe the asserted claims of the patents-in-suit. (D.I. 1.) The court held a four-day bench trial in this matter on July 17 through July 20, 2012. (D.I. 304-307.) 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.[1] (D.I. 314; D.I. 319.)

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) the asserted claims of the patents-in-suit are not invalid as anticipated under 35 U.S.C. § 102(b); and (2) the asserted claims of the patents-in-suit are not invalid as obvious under 35 U.S.C. § 103. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT

A. The Parties[2]

[1] The defendants stipulated to infringement of the asserted claims of the patents-in-suit. (D.I. 258 at ¶ 3; Pretrial Order at ¶¶ 40-43.) The court also notes that the defendants had alleged that certain claims of the '570 Patent lacked written description. However, the defendants did not include this defense as an issue for trial in the Pretrial order, which excluded it from the case. *See* Pretrial Conference (June 25, 2012) Tr. at 42:13-15. In addition, the plaintiffs note that, after trial, in an email correspondence dated July 27, 2012, counsel for Watson confirmed on behalf of all defendants that "[d]efendants are no longer asserting lack of inventorship as a defense to the '570 patent-in-suit." Accordingly, the court does not address these issues in this Memorandum.

[2] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 258.) 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."

1. Plaintiff Cephalon, Inc. ("Cephalon") is a Delaware corporation having its corporate offices and principal place of business at 41 Moores Road, Frazer, Pennsylvania 19355.

2. Plaintiff Cephalon France ("Cephalon France") is a societe par action simplifiee ("SAS") under the laws of France, is a wholly-owned subsidiary of Cephalon, Inc., and is located at 20 Rue Charles Martigny, 94701 Maisons-Alfort Cedex, France.

3. Defendant Watson Laboratories, Inc. ("Watson") is a corporation organized and existing under the laws of Nevada, with a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054.

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

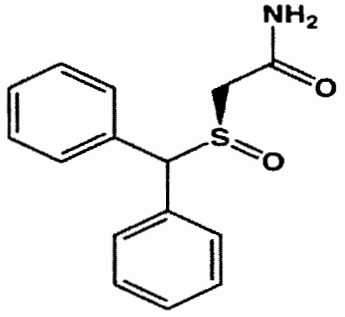
5. Defendant Lupin Limited ("Lupin") is a corporation organized and existing under the laws of India, with a principal place of business at B/4 Laxmi Towers Bandra Kurla Complex, Bandra (E), Mumbai 400 051, India.

6. Defendant Apotex, Inc. ("Apotex") is a corporation organized and existing under the laws of Canada, with a principal place of business at 150 Signet Drive, Toronto, Ontario M9L 1T9, Canada.

7. Apotex, Lupin, Sandoz, and Watson will be collectively referred to as "defendants."

B. Background

8. Armodafinil is a chemical compound known as (-)-2-[R-(-diphenylbenzhydrylsulphinyl)]acetamide and has the following chemical structure:



9. Armodafinil is also known by other names, including 2-[(R)-(diphenylmethyl)sufinyl]acetamide, CRL 40982, (-)-benzhydrylsulfinylacetamide, (-)-modafinil, and the levorotatory or laevorotatory enantiomer of modafinil.

10. Armodafinil is also known as the R-enantioer of modafinil. Modafinil is a racemic mixture containing equal amounts of both the R-enantiomer and S-enantiomer of modafinil.

11. Enantiomers have different three-dimensional spatial arrangements that make them non-superimposable mirror images of each other, much like a person's right and left hand.

12. Enantiomers may have identical physical properties (such as melting point, weight, and density) and, therefore, cannot necessarily be distinguished from each other based on measurements of these properties. However, they may be differentiated by their biological properties, and can be differentiated by their optical activity.

13. Substances that can rotate polarized light are said to be optically active because they interact with light and can rotate polarized light.

14. Enantiomers that rotate plane-polarized light clockwise are said to be dextrorotatory (from the Latin *dexter*, "right") or (+). Those that rotate plane-polarized light counterclockwise are called levorotatory or laevorotatory (from the Latin *laevus*, "left") or (-).

15. The R-enantiomer of modafinil (i.e., armodafinil) is also called (-)-modafinil because it rotates plane-polarized light counterclockwise.

C. The Patent-in-Suit

16. United States Patent No. 7,132,570 ("the '570 Patent"), entitled "Methods for the Production of Crystalline Forms and Crystalline Forms of Optical Enantiomers of Modafinil," naming Olivier Neckebrock and Pierre Leproust as inventors, was issued on November 7, 2006.

17. Cephalon holds approved New Drug Application ("NDA") No. 21-875 for armodafinil tablets in 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg dosage strengths.

18. Cephalon sells 50 mg, 100 mg, 150 mg, and 250 mg dosage strengths in the United States under the tradename Nuvigil®.

19. Nuvigil® is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea, narcolepsy, and shift work sleep disorder.

20. Polymorphic Form I armodafinil was chosen for Nuvigil® for its favorable aggregate of properties, including solubility and stability.[3]

21. Pursuant to 21 U.S.C. § 355 and attendant FDA regulations, the '570 Patent is listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") for Nuvigil®.

1. The Asserted Claims

[3] *See In re Armodafinil Litigation* Transcript ("Tr.") at 639:12-18, 641:1-23, 676:10-18 (Mallamo). The court finds Dr. John Mallamo's testimony as to the reason Form I was selected to be credible.

22. Cephalon originally asserted claims 1-9 of the '570 Patent against each of the defendants.[4]

i. *'570 Patent, Claim 1*

23. Claim 1 states: A laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 4.02, 3.98 (Å).

ii. *'570 Patent, Claim 2*

24. Claim 2 states: The laevorotatory enantiomer of modafinil according to Claim 1, wherein the polymorphic form produces a powder X-ray diffraction spectrum further comprising intensity peaks at the interplanar spacings: 13.40, 6.34, 5.01, 4.68, 4.62, 4.44, 4.20, 4.15, 3.90, 3.80, 3.43 (Å).

iii. *'570 Patent, Claim 3*

25. Claim 3 states: A laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising reflections at 15.4, 31.1, 33.1 and 33.4 degrees 2Θ.

iv. *'570 Patent, Claim 4*

26. Claim 4 states: The laevorotatory enantiomer of modafinil according to Claim 3, wherein the polymorphic form produces a powder X-ray diffraction spectrum comprising reflections at 9.8, 20.8, 26.4, 28.3, 28.7, 29.9, 31.6, 32, 34.1, 35.1 and 39 degrees 2Θ.

v. *'570 Patent, Claim 5*

27. Claim 5 states: A pharmaceutical composition comprising a laevorotatory enantiomer of modafinil according to any one of Claims 1 to 4.

vi. *'570 Patent, Claim 6*

28. Claim 6 states: A pharmaceutical composition consisting essentially of a laevorotatory enantiomer of modafinil according to any one of Claims 1 to 4.

vii. *'570 Patent, Claim 7*

29. Claim 7 states: A Form 1 polymorph of (-)-modafinil.

viii. *'570 Patent, Claim 8*

30. Claim 8 states: A pharmaceutical composition comprising a Form 1 polymorph of (-)-modafinil according to Claim 7.

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[4] *See infra* ¶¶ 63-64.

ix. *'570 Patent, Claim 9*

31. Claim 9 states: A pharmaceutical composition consisting essentially of a Form 1 polymorph of (-)-modafinil according to Claim 7.

32. The court held a *Markman* hearing on July 14, 2011 and, on July 25, 2011, issued an Order construing the disputed terms. (D.I. 172.)

33. The court construed disputed term "A laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising . . ." in Claims 1 and 3 to mean "A crystal form of Armodafinil having the claimed powder X-ray diffraction features." (*Id.* at 1.)

34. The court construed disputed term ". . . intensity peaks at the interplanar spacings . . ." in Claims 1 and 2 to mean: "Peaks in the powder x-ray diffraction pattern corresponding to the claimed crystal interplanar spacings with variances associated with X-ray diffraction spectroscopy." (*Id.* at 2.)

35. The court construed disputed term ". . . reflections at . . ." in Claims 3 and 4 to mean: "Peaks in the powder x-ray diffraction pattern, using chromium radiation, corresponding to the claimed value with variances associated with X-ray diffraction spectroscopy, or corresponding values based on another radiation source." (*Id.*)

36. The parties agreed prior to the *Markman* hearing that disputed term "A form I polymorph of (-)-modafinil" in Claims 5 and 8 means: "A composition comprising the specified pharmaceutically active component and optionally one or more pharmaceutically acceptable ingredients." (*Id.* at 3.)

37. The parties decided prior to the *Markman* hearing that the disputed term "A pharmaceutical composition consisting essentially of . . ." in Claims 6 and 9 means: "A composition consisting of the specified pharmaceutically active component and optionally unlisted pharmaceutically acceptable ingredients that do not materially affect the basic and novel properties of the specified pharmaceutically active component." (*Id.*)

2. The Accused Products

i. *ANDA No. 200-156 Submitted by Watson*

38. Under 21 U.S.C. § 355(j), Watson submitted to the FDA ANDA No. 200-156 to obtain approval for the commercial manufacture, use, marketing, and sale of generic armodafinil products in the United States in 150 mg and 250 mg dosage strengths.

39. Watson amended its ANDA No. 200-156 to obtain approval for the commercial manufacture, use, marketing, and sale of generic armodafinil products in the United States in 50

mg, 100 mg, and 200 mg dosage strengths (collectively, with respect to all five dosage strengths, "the Watson proposed generic armodafinil products").

40. Watson filed ANDA No. 200-156 to obtain approval to manufacture, use, market, and sell the Watson proposed generic armodafinil products in the United States before the expiration of the '570 Patent.

41. Watson's ANDA No. 200-156 contains a certification, pursuant to 21 U.S.C. § 355(j)(2)(a)(vii)(IV), alleging that the '570 Patent is invalid, unenforceable, and/or not infringed.

42. By letter dated November 24, 2009 ("Watson's Notice Letter"), Watson notified Cephalon that it had filed ANDA No. 200-156 seeking approval to market the Watson proposed generic armodafinil products, and that it was providing information to Cephalon pursuant to 21 U.S.C. § 355(j)(2)(B)(ii).

ii. *ANDA No. 200-511 Submitted by Sandoz*

43. Under 21 U.S.C. § 355(j), Sandoz submitted to the FDA ANDA No. 200-511 to obtain approval for the commercial manufacture, use, marketing, and sale of generic armodafinil products in the United States in 50 mg, 150 mg, and 250 mg dosage strengths.

44. Sandoz amended its ANDA No. 200-511 to obtain approval for the commercial manufacture, use, marketing, and sale of generic armodafinil products in the United States in 100 mg and 200 mg dosage strengths (collectively, with respect to all five dosage strengths, "the Sandoz proposed generic armodafinil products").

45. Sandoz filed ANDA No. 200-511 to obtain approval to manufacture, use, market, and sell the Sandoz proposed generic armodafinil products in the United States before the expiration of the '570 Patent.

46. Sandoz's ANDA No. 200-511 contains a certification, pursuant to 21 U.S.C. § 355(j)(2)(a)(vii)(IV), alleging that the '570 Patent is invalid, unenforceable, and/or not infringed.

47. By letters dated December 15, 2009 and July 27, 2011 (collectively, "Sandoz's Notice Letter"), Sandoz notified Cephalon that it had filed and amended ANDA No. 200-511 seeking approval to market the Sandoz proposed generic armodafinil products, and that it was providing information to Cephalon pursuant to 21 U.S.C. § 355(j)(2)(B)(ii).

iii. *ANDA No. 200-751 Submitted by Lupin*

48. Under 21 U.S.C. § 355(j), Lupin submitted to the FDA ANDA No. 200-751 to obtain approval for the commercial manufacture, use, marketing, and sale of generic armodafinil products in the United States in 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg dosage strengths (collectively, "the Lupin proposed generic armodafinil products").

49. Lupin filed ANDA No. 200-751 to obtain approval to manufacture, use, market, and sell the Lupin proposed generic armodafinil products in the United States before the expiration of the '570 Patent.

50. Lupin's ANDA No. 200-751 contains a certification, pursuant to 21 U.S.C. § 355(j)(2)(a)(vii)(IV), alleging that the '570 Patent is invalid, unenforceable, and/or not infringed.

51. By letter dated February 5, 2010 ("Lupin's Notice Letter"), Lupin notified Cephalon that it had filed ANDA No. 200-751 seeking approval to market the Lupin proposed generic armodafinil products, and that it was providing information to Cephalon pursuant to 21 U.S.C. § 355(j)(2)(B)(ii).

iv. *ANDA No. 20-1514 Submitted by Apotex*

52. Under 21 U.S.C. § 355(j), Apotex submitted to the FDA ANDA No. 20-1514 to obtain approval for the commercial manufacture, use, marketing, and sale of generic armodafinil products in the United States in 50 mg, 150 mg and 250 mg dosage strengths (collectively, "the Apotex proposed generic armodafinil products").

53. Apotex filed ANDA No. 20-1514 to obtain approval to manufacture, use, market, and sell the Apotex proposed generic armodafinil products in the United States before the expiration of the '570 Patent.

54. Apotex's ANDA No. 20-1514 contains a certification, pursuant to 21 U.S.C. § 355(j)(2)(a)(vii)(IV), alleging that the '570 Patent is invalid, unenforceable, and/or not infringed.

55. By letter dated July 6, 2010 ("Apotex Notice Letter"), Apotex notified Cephalon that it had filed ANDA No. 20-1514 seeking approval to market the Apotex proposed generic armodafinil products, and that it was providing information to Cephalon pursuant to 21 U.S.C. § 355(j)(2)(B)(ii).

D. Procedural History

56. Cephalon filed its Complaint for patent infringement against Watson on January 5, 2010, in what was labeled Civil Action No. 10-cv-0007 (GMS), alleging that Watson infringes the '570 Patent. (10-cv-0007 (GMS), D.I. 1.)

57. Cephalon filed its Complaint for patent infringement against Sandoz on January 22, 2010, in what was labeled Civil Action No. 10-cv-055 (GMS), alleging infringement of the '570 Patent and other Cephalon patents. (10-cv-055 (GMS), D.I. 1.)

58. Cephalon filed its Complaint for patent infringement against Sandoz on September 6, 2011, also alleging infringement of the '570 Patent in what was labeled Civil Action No. 11-cv-782 (GMS). (11-cv-782 (GMS), D.I. 1.)

59. Cephalon filed is Complaint for patent infringement against Lupin on March 16, 2012, alleging infringement of the '516 and '570 Patents, in what was labeled Civil Action No. 10-cv-210 (GMS). (10-cv210 (GMS), D.I. 1.)

60. Cephalon filed its Complaint for patent infringement against Apotex on August 18, 2010, alleging infringement of the '516 and '570 Patents, in what was labeled Civil Action No. 10-cv-695 (GMS), as well as on August 19, 2010, in what was labeled Civil Action No. 10-cv-1078 (GMS). (10-cv-695 (GMS) (D.I. 1); 10-cv-1078 (GMS) (D.I. 1).)

61. On December 18, 2010, these actions were centralized in the District of Delaware via the United States Judicial Panel on Multidistrict Litigation's Transfer Order. (10-md-2200 (GMS) (D.I. 1).)

62. On November 23, 2011, the court granted the parties' joint motion to consolidate case 11-cv-782 into the multidistrict litigation. (10-md-2200 (GMS) (D.I. 219).)

63. On March 31, 2012, the above-captioned defendants stipulated to infringement of the asserted claims of the patent-in-suit in the parties' Pretrial Order. (D.I. 259 at ¶¶ 40-43; *see also* D.I. 258.)

64. On July 11, 2012, Cephalon informed the court that, in an effort to streamline presentation of the evidence, it agreed that the defendants' right to enter the market with respect to the '570 Patent with their proposed armodafinil ANDA products, "will stand or fall based upon the outcome of this litigation with respect to claim 6 (as it depends upon claim 2) and claim 9 of the '570 Patent." (D.I. 295.) Thus, Cephalon limited its presentation of the evidence at trial to those claims. (*Id.*)

65. The court held a four-day bench trial in this matter on July 17, 2012 through July 20, 2012. (D.I. 304-307.)

66. On December 28, 2012, the plaintiffs filed a Motion to Amend the Caption (D.I. 322) to include Teva Sante SAS as a party-plaintiff, following Teva Pharmaceutical Industries Ltd.'s acquisition of Cephalon, Inc. (*Id.* at 2.) The court granted this motion on February 5, 2013. (D.I. 325.)

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. The parties have consented to personal jurisdiction and venue in this court for the purpose of adjudicating the present dispute. (D.I. 259 at 11.) 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) the asserted claims of the patents-

in-suit are not invalid as anticipated under 35 U.S.C. § 102(b); (2) the asserted claims of the patents-in-suit are not invalid as obvious under 35 U.S.C. § 103; and (3) the plaintiffs' Rule 52(c) motion is granted and the defendants' Rule 52(c) motion is denied. The court's reasoning follows.

A. Anticipation

The defendants contend that the asserted claims of the '570 Patent are invalid as inherently anticipated by Preparation I of the '855 Patent. Specifically, the defendants assert that a person of ordinary skill in the art "will necessarily and inevitably obtain Form I armodafinil from following the prior art Preparation I process." (D.I. 319 at 7.)

1. The Legal Standard

"[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). In sum, inherent anticipation "requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (quoting *In*

re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999)). "A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Labs, Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939)). To be inherent, an undisclosed feature must "necessarily and inevitably" flow from practice of what is disclosed. *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1371, 1378 (Fed. Cir. 2003).

Therefore, if the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (finding no inherent anticipation where testing evidence demonstrated that the prior art example could yield crystals of either the claimed polymorph or a different polymorph). Whether a prior art reference anticipates a patent claim is a question of fact and must be proven by clear and convincing evidence.[5] *See Advanced Display Sys.*, 212 F.3d at 1281.

3. The Parties' Contentions and Discussion

The defendants maintain that the asserted claims of the '570 Patent are inherently anticipated because, as compared to claim 6 of the '855 Patent, the asserted claims recite only the interplanar spacings and 2-theta values intrinsic to Form I armodafinil. (D.I. 319 at 6.) Thus, the defendants contend that the only question at trial was "which polymorphic form of armodafinil inherently results from performing Preparation I of the '855 Patent." (*Id.*) The defendants argue

[5] "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)).

that their experts, Drs. Mark Hollingsworth and Albert Lee, performed Preparation I of the '855 Patent as persons of ordinary skill in the art in the late 1990s and early 2000s[6] and obtained Form I armodafinil, thus proving anticipation by clear and convincing evidence.

Specifically, the defendants detail that Dr. Hollingsworth completed two reproductions of Preparation I and many additional recrystallizations from ethanol, as set out in Preparation I in the '855 Patent, and then confirmed that his experiments produced Form I armodafinil each time using the "gold standard"[7] XRPD analysis.[8] (*Id.* at 7.) The defendants assert that Dr. Hollingsworth performed each step of the four step process outlined in Preparation I[9] and, therefore, produced more credible results than the plaintiffs' experts, who, the defendants allege, performed only three steps of the Preparation on Cephalon's instructions.[10] (*Id.* at 7-8.) The defendants highlight that

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[6] (D.I. 319 at 7-8 (citing Tr. at 95:4-6, 96:23-25, 98.24-25, 100:17-101:2, 103:6-7, 123:17-21 (Hollingsworth)).) The defendants also note that, while the parties' experts offered different views as to the definition of a person of ordinary skill in the art, their experts agreed that their opinions are not dependent on the definition the court adopts. (*Id.* at 7 n.1.) Thus, the defendants' experts' testimony with respect to the issue of validity remain unchanged even if the court adopts, as it does, the plaintiffs' experts' definition of a person of ordinary skill in the art. (*Id.*) *See infra* Section III.B.2.

[7] (*Id.* at 7 (citing Tr. at 82:5-9, 106:6-7 (Hollingsworth)).) Dr. Hollingsworth testified that he determined that the crystalline armodafinil he obtained at the end of Preparation I was Form I by comparing the XRPD data he generated for each sample to the characteristic peaks of Form I disclosed and claimed in the '570 Patent. (*Id.* at 9 (citing Tr. at 106:6-7, 109:9-12, 109:17-21, 110:8-14, 111:5-6 (Hollingsworth); Tr. at 773:22 (Myerson); DTX-163:6-7, .13; DTX-225A.5, .389-.390, .448, .459, .596; JTX-40.41, .47; JTX-41.53).)

[8] Armodafinil polymorphs may be characterized and differentiated by a variety of analytical techniques. The technique used by the experts in this case and called for in the '570 Patent is X-ray power diffraction, otherwise known as XRPD. The XRPD technique detects the intensity of x-rays reflected off of a sample that is rotated through various angles and produces a pattern, or fingerprint, that is unique to a particular crystal form. (D.I. 314 at 4 (citing PTX-585-51, -60; Tr. at 607:23-608:1 (Bernstein)).) XRPD directly represents the physical dimensions—for instance, the interplanar spacings within the crystal structure. (*Id.* (citing Tr. at 505:20-507:7 (Bernstein)).) Melting point is another way to distinguish between one polymorph and another. (*Id.* (citing JTX-26-30 to 31; Tr. at 658:13-62:24 (Mallamo)).)

[9] Specifically, the defendants outline Preparation I as including: (1) step (a), which, in the overall synthesis, separates the two enantiomers of modafilic acid by reacting the enantiomers with a complexing agent and is conducted four times (D.I. 319 at 8 (citing Tr. at 971:1-21 (Hollingsworth); JTX-39.13 *et seq.*, .27 *et seq.*, .43 *et seq.*, .93 *et seq.*)); (2) step (b), which, through performing the step four times, liberates the R-modafilic acid from the complex created in step (a) (*id.* (citing Tr. at 98:13-17, 98:24-25, 99:6-7 (Hollingsworth); JTX-39.33 *et seq.*, .59 *et seq.*, .85 *et seq.*; JTX-40.35 *et seq.*)); (3) step (c), which provides for the conversion of the product of step (b) into its methyl ester (*id.* (citing Tr. at 100:3-9, 100:17-101:14-16 (Hollingsworth); JTX-39.77 *et seq.*; JTX-40.77 *et seq.*)); and (4) step (d), which is to be performed twice, and converts the methyl ester into armodafinil and purifies the resulting armodafinil by "recrystallization from ethanol" (*id.* at 8-9 (citing Tr. at 101:21-102:1, 102:12-14, 103:7, 106:1-2 (Hollingsworth); JTX-103.3 col. 3, l. 50, col. 3, ll. 5-9; JTX-39.107 *et seq.*; JTX-40.91 *et seq.*)).)

[10] The defendants assert that the plaintiffs' experts, Drs. Smith and Selbo, did not accurately perform Preparation I as a person of ordinary skill in the art because they were instructed by Cephalon to perform a truncated

Dr. Hollingsworth did not end his analysis after he completed two replications of Preparation I, but instead performed two additional recrystallizations from ethanol and obtained Form I armodafinil both times. (*Id.* at 9 (citing Tr. at 111:20-21, 112:10-12, 112:22-113:3, 113:10-15 (Hollingsworth); DTX-163.9-.10; DTX-255A.487, .501; JTX-40.57).) He also performed an additional ethanol recrystallization after completing the second synthesis and, once more, obtained Form I armodafinil according to his XRPD examination. (*Id.* (citing Tr. at 113:19-114:4 (Hollingsworth); DTX-163.16; DTX-255A.6, .380-.382, .625; JTX-41.67).) Thus, Dr. Hollingsworth performed, over the course of his two replications of Preparation I, five recrystallizations from ethanol and, per his analysis, obtained Form I armodafinil each of those five times. (*Id.*)

The defendants further assert that Dr. Hollingsworth's work demonstrates that Form I armodafinil results even before a person of ordinary skill in the art fully completes Preparation I. Specifically, the defendants detail that Dr. Hollingsworth's testing and XRPD analysis demonstrates that he obtained Form I after the methanol evaporation part of step (d) in both reproductions of Preparation I, as well as after the ether wash part of step (d) in both preparations. (*Id.* at 10 (citing Tr. at 115:15-22, 116:7-14, 116:10-117:17 (Hollingsworth); DTX-163.3, .18; DTX-255A.1, .3, .4, .387-.388, .423-.425, .562-.563, .578-.580; JTX-40.23).) In sum, the defendants contend, with respect to Dr. Hollingsworth's testing, that they have proven by clear and convincing evidence that Form I armodafinil necessarily flows from the replication of Preparation I.[11]

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method. (*Id.* at 11 (citing Tr. at 127:1-13 (Hollingsworth); Tr. at 277:3-8, 18-21 (Lee); Tr. at 720:11-17 (Selbo)).) Specifically, and as described in greater detail below, the defendants contend that Cephalon told its experts not to perform the "critical ethanol recrystallization part of step (d)" because they knew "that Dr. Hollingsworth's experiments showed that Form I inevitably results from a faithful and complete replication of Preparation I." (*Id.* (citing Tr. at 710:22-711:7, 720:10-17 (Selbo)).)

[11] Specifically, Dr. Hollingsworth performed XRPD analysis on nine samples at various stages of step (d) and obtained Form I armodafinil each time over the course of his two Preparation I replications. (*Id.* at 10 (citing Tr.

Moreover, the defendants note that Dr. Lee also replicated Preparation I twice following the laboratory work Cephalon's experts, Drs. Smith and Selbo, prepared. The defendants assert, however, that Dr. Lee completed Preparation I beyond the plaintiffs' truncated method, and obtained Form I armodafinil both times. (*Id.* at 10-12.) Specifically, the defendants contend that step (d) of Preparation I involves three parts: (1) dissolving the substance in methanol and treating with ammonia gas; (2) evaporating the methanol and washing with ether; and (3) recrystallizing from ethanol to obtain crystals. (*Id.* at 11 (citing JTX-103.3 col. 3, ll. 43-57).) The defendants maintain that Drs. Smith and Selbo performed the first two parts of step (d), but failed to complete the ethanol recrystallization step on Cephalon's instruction. (*Id.* (citing Tr. at 721:19-23 (Selbo)).) Dr. Lee, however, synthesized crystalline armodafinil twice using Drs. Smith and Selbo's methods, including heating to 70-90 degrees Celsius in step (b) and then finished the Prepation by performing ethanol recrystallization as a person of ordinary skill in the art. (*Id.* (citing Tr. at 277:3-8, 283:6-284:14, 286:1-287.3, 298:3-8 (Lee); DTX-212).) Dr. Lee confirmed that his samples were armodafinil by sending them to Dr. Robie, an expert in X-RPD analysis, who searched two databases of known crystal materials for matches to the patterns of the samples and identified both as Form I. (*Id.* at 11-12.) This finding, the defendants argue, confirms Dr. Hollingsworth's conclusion that Form I armodafinil naturally and inevitably results from Preparation I.

Finally, the defendants contend that their inherent anticipation position is supported by: (1) the Kofler hot bar analyses disclosed in the '855 Patent; (2) non-instantaneous melting point data listed at the end of Preparation I; and (3) three declarations submitted to the PTO during prosecution of the '570 Patent. (*Id.* at 12-16.) With regard to the first, the defendants maintain that Form I inevitably results from Preparation I when the melting point analysis disclosed in the

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at 118:4 (Hollingsworth); DTX-163.3-.4, .6-.7, .9-.10, .11, .13, .16; DTX-255A.1, .3-.6, .380-.382, .387-.390, .423-.425, .430-.435, .448, .459, .487, .501., .562-.564, .578-.580, .596, .625; JTX-40.23, .41, .47, .57; JTX041.53, .67).)

'855 Patent, which would have been determined by using a Kofler hot bar,[12] is performed. (*Id.* at 12-13 (citing Tr. at 142:16-20, 143:2-144:30 (Hollingsworth)).) The '855 Patent provided a 153-154 degrees Celsius instantaneous melting point range for the armodafinil produced by Preparation I. (*Id.* at 13 (citing JTX-103.3 col. 3, 1. 55).) According to Dr. Hollingsworth, if any form(s) of armodafinil resulted from Preparation I, it would necessarily convert to Form I during the instantaneous melting point measurement, such that the polymorph would become Form I. (*Id.* (citing Tr. at 145:20-22 (Hollingsworth)).) The data Cephalon provided in the '570 Patent's file history confirms this assertion, the defendants argue, because that information demonstrated that Forms II and IV converted to Form I at temperatures well within the Kofler hot bar's operating range. (*Id.* (citing Tr. at 143:18-144:12 (Hollingsworth)).)

Second, the defendants contend that the non-instantaneous melting point data confirms that Preparation I results in Form I armodafinil. Specifically, the defendants note that, during the prosecution of the '570 Patent, Cephalon provided the PTO with a comparison of the instantaneous melting point data at the end of Preparation I (153-154 degrees Celsius), to the instantaneous melting points observed with its own Form I armodafinil (156-164 degrees Celsius), to show that the product of Preparation I was not Form I armodafinil. (*Id.* at 14 (JTX-103.3 col. 3, l. 55; JTX-38.28-.29, n.7).) However, the defendants argue that Cephalon did not "disclose to the PTO that the Kofler hot bar used to measure the instantaneous melting point is an archaic 'museum piece.'" (*Id.* (citing Tr. at 185:16-18 (Hollingsworth); Tr. at 337:18-21 (Lee)).) Dr. Hollingsworth observed the non-instantaneous melting points after the ethanol recrystallization steps from his first reproduction of Preparation I ranged from 150.4-153.8 degrees Celsius, which is in the same

[12] As Dr. Hollingsworth explained, the Kofler hot bar is a metallic strip along which temperature increases from one end to the other. (*Id.* at 13 (citing Tr. at 143:2-11 (Hollingsworth)).) The operator spreads the material to be analyzed on the bar, observes where along the bar the material melts, and notes the temperature at that point on the bar. (*Id.*)

range as the non-instantaneous melting points of Cephalon's data for Form I armodafinil. (*Id.* (citing Tr. at 139:15-24 (Hollingsworth); Tr. at 782:5-7, 782:14-783:12 (Myerson); JTX-40.63, .65; JTX-38.29 at n.7; JTX-40.19, .63, .65, .67; JTX-41.69).) Dr. Lee found similar results. (*Id.* (citing Tr. at 304:17-21 (Lee)).) Moreover, the defendants detail that the plaintiffs' experts did not use the Kofler hot bar to analyze armodafinil's melting point, and instead used more accurate equipment to test their samples. (*Id.* (citing Tr. at 185:16-18, 192:12-18 (Hollingsworth); Tr. at 303:16-18 (Lee); JTX-48.20; Tr. at 777:18-23 (Myerson)).) Therefore, the defendants assert that, according to the most reliable melting point data available, the crystals that result from following Preparation I are Form I armodafinil and the PTO did not have this information available when considering the '570 Patent's claims. (*Id.* at 14-15.)

. Finally, the defendants allege that the three declarations submitted to the PTO during the '570 Patent prosecution by Drs. Blomsma, Peterson, and Mallamo support the conclusion that Form I armodafinil naturally and inevitably results from Preparation I. In particular, the defendants note that of the thirty-four experiments described in these declarations that resulted in crystals, thirty, or nearly ninety-percent, unambiguously resulted in Form I armodafinil. (*Id.* at 15 (citing Tr. at 130:19-22 (Hollingsworth)).) While, as the defendants acknowledge, the experiments contained in these declarations were not faithful reproductions of Preparation I and, therefore, are not directly probative of the anticipation question, they do demonstrate that "even under conditions that in some instances differed markedly from Preparation I, Form I armodafinil resulted almost all of the time." (*Id.* (citing Tr. at 131:2-7 (Hollingsworth); JTX-38.1-.45).) Moreover, the four experiments that did not result in Form I were sufficiently dissimilar from Preparation I and, therefore, "provide no useful evidence regarding what crystal form is made by following

Preparation I."[13] (*Id.*) The defendants detail that Drs. Peterson and Mallamo's declarations referenced experiments similarly demonstrating the ease with which Form I armodafinil is made and that those experiments that did not result in Form I were outside the scope of Preparation I, such that these declarations reinforce Dr. Hollingsworth's conclusion.[14]

Conversely, the plaintiffs argue that, in view of the relevant law and consistent with the evidence presented in Cephalon's PTO declarations, testing did not show that Preparation I in the '855 Patent necessarily and inevitably produces a pharmaceutical composition consisting of "the specified pharmaceutically active component"—Form I armodafinil—and other pharmaceutically acceptable ingredients, as required by the asserted claims. (D.I. 314 at 8.) Rather, the plaintiffs maintain that the defendants' testing "showed that mixtures of polymorphic forms and various uncharacterized impurities result" from reproducing Preparation I and, further, that the defendants' experiments were flawed and insufficient because they departed from the express method taught in the '855 Patent and are not representative of its full scope. Therefore, the plaintiffs argue, the defendants have not proven inherent anticipation by clear and convincing evidence.

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[13] Specifically, the defendants note that Dr. Blomsma admitted that the work done by third party Crystallics and represented in his declaration, were not reproductions of Preparation I and, instead, were results obtained from a "high-throughput polymorph screen." (*Id.* at 15 (citing Tr. at 820:8-18, 822:25-823:6, 824:15-19 (Blomsma); Tr. at 137:12-13 (Hollingsworth); JTX-38.2).) Additionally, the two experiments Dr. Blomsma described in his declaration that did not result in Form I, did not replicate Preparation I. In particular, the first experiment was conducted at a scale 4,000 times smaller than that of Preparation I and the second experiment used an exotic cooling rate of 300 degrees celcius per minute. (*Id.* (citing Tr. at 137:12-138:17 (Hollingsworth); Tr. at 692:7-15, 695:24-696:6 (Mallamo); JTX-38.8 (Ex. No. 3).)

[14] The defendants note that Dr. Peterson's declaration references five experiments, four of which resulted in Form I armodafinil being produced. (*Id.* at 16 (citing Tr. at 136:9-11 (Hollingsworth); JTX-38.13-.15).) The one experiment that resulted in a different polymorphic form was "outside the scope of Preparation I because the starting material was spiked with racemic modafinil, a clear departure from Preparation I." (*Id.* (citing Tr. at 136:11-13, 18-21 (Hollingsworth); JTX-38.14 at ¶ 7).) Therefore, the defendants assert, the experiments described in Dr. Peterson's declaration are not probative of whether Form I necessarily results from Preparation I. (*Id.* (citing Tr. at 137:1-7 (Hollingsworth)).) In addition, the defendants state that Dr. Mallamo's declaration discloses similar results, as it detailed obtaining Form I armodafinil in seven of eight recrystallizations. (*Id.* (citing Tr. at 131:17-18 (Hollingsworth); Tr. at 695:1-3 (Mallamo); JTX-38.41-.42).) Again, the one experiment that did not result in Form I, the defendants maintain, was outside the scope of Preparation I because it employed a rapid cooling rate and a mixture of ethanol with toluene, a solvent that a person of ordinary skill in the art would not have understood the term "ethanol" to embrace. (*Id.* (citing Tr. at 131:18-132:14 (Hollingsworth); JTX-38.42).)

In consideration of the record and the relevant law, the court concludes that the defendants have not met their burden of demonstrating that Preparation I of the '855 Patent necessarily and inevitably results in Form I armodafinil or a composition consisting essentially thereof and, therefore, have not proved invalidity by inherent anticipation. The court reaches this conclusion for three reasons. First, the court finds that the defendants have not demonstrated clearly and convincingly through their experts' experiments and testing that the performance of Preparation I necessarily and inevitably results in Form I armodafinil.[15] Second, the court concludes that the defendants have failed to show by clear and convincing evidence that the result of performing Preparation I meets the requirements of the asserted claims of the patent-in-suit.[16] Third, the court concludes that the defendants have not demonstrated clearly and convincingly that their reproductions of the '855 Patent's Preparation I were consistent with how a person of ordinary skill in the art would have performed the Preparation and, therefore, have not proven that their experts' experiments accurately demonstrate that Form I armodafinil inevitably results from Preparation I.[17]

a. Whether Preparation I of the '855 Patent Inherently Produces Form I Armodafinil or a Composition Consisting Essentially Thereof

The evidence presented at trial demonstrates that the Preparation of Form I and a "recrystallization from ethanol" can yield different forms, mixtures of forms, and unknown impurities, depending on the variables selected in conducting the Preparation.[18] In fact, and as the

[15] *See infra* Section III.A.3.a.

[16] *See infra* Section III.A.3.b.

[17] *See infra* Section III.A.3.c.

[18] The court notes that, as was established at trial, many organic compounds, including active pharmaceutical ingredients ("APIs") used in drug products, exist as solids, and some exist in more than one solid state form. For instance, some compounds can be formed into multiple, different crystal structures—a phenomenon known as "polymorphism." *See* JTX-32-2; JTX-26-3, -4; JTX-23-2; *see also* Tr. at 499:2-18 (Bernstein). Some solid compounds also may be crystalline solvates, meaning that their crystal structure is uniquely based on the inclusion of both the compound and a solvent. *See* Tr. at 526:4-15 (Bernstein). The term "crystallization" or "recrystallization"

court details below, the defendants' experimental evidence yielded mixtures of forms that contained impurities. Based on the evidence before it, the court concludes that the defendants' evidence fails to clearly and convincingly demonstrate that Form I armodafinil claimed in the '570 Patent necessarily results from Preparation I.

As detailed above, Dr. Hollingsworth carried out two experiments, Run 1/2 and Run 3/4, to perform Preparation I and conducted XRPD testing on the armodafinil he produced. (*Id.* (citing Tr. at 91:2-4, 106:3-7 (Hollingsworth)).) Dr. Hollingsworth testified that Run 1/2 generated pure Form I armodafinil. (*Id.* (citing Tr. at 106:8-19 (Hollingsworth); Tr. at 748:25-749:19 (Myerson); PDX-5-14).) Dr. Hollingsworth's second experiment, Run 3/4, was conducted after the first recrystallization from ethanol and produced Form I accompanied by some other unknown crystalline impurities and, after a second recrystallization from ethanol, produced a mixture of Form I and Form II. (*Id.* at 9-10 (citing Tr. at 195:16-200:7 (CDX-1 to 4), 249:23-251:13 (CDX-5, CDX-6) (Hollingsworth); Tr. at 748:25-749:19 (PDX-5-14).) In addition, Dr. Hollingsworth testified that he performed XRPD testing on samples that were produced at two intermediate points along step (d)—after the methanol evaporation and after the ether wash—and concluded that both samples contained Form I.[19] (*Id.* at 10 (citing Tr. at 114:23-117:17 (Hollingsworth)).)

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refers to a process whereby a molecule in solution undergoes a change in phase that results in the formation of a solid. The court finds credible Drs. Bernstein and Blomsma's testimony with respect to the definition and nature of crystallization or recrystallization. *See, e.g.,* Tr. at 583:19-585:19 (Bernstein); *see also* Tr. at 823:7-824:2 (Blomsma). Thus, the court finds that, for a compound that exhibits polymorphism or forms solvates, different conditions of crystallization can yield different polymorphs and, due to this unpredictability in the process, even crystallizations under seemingly identical conditions might yield different crystal forms.

[19] The court notes here that it finds that the intermediate, incomplete results fail to establish that practice of Preparation I necessarily and inevitably produces Form I. Specifically, Dr. Hollingsworth testified that he did not heat the solution to 30-40 degrees Celsius for dissolution as called for in step (b) and discussed in this section. As Drs. Smith and Selbo explained in connection with their own reasonable experiments and in testimony the court finds credible, these intermediate products were not the result of an accurate reproduction of Preparation. Moreover, for the Run 3/4 material after methanol evaportation, Dr. Hollingsworth acknowledged that he did not have the particular peaks for Form I claimed in the '570 Patent. *See* Tr. at 247:10-248:16 (Hollingsworth). Moreover, this product was subjected to extensive vacuum drying, which was neither taught in Preparation I nor done in Run 1/2. These inconsistent in the performance of Preparation I do not demonstrate the inherency of Form I armodafinil by clear and convincing evidence.

However, in his second Run 3/4 recrystallization, Dr. Hollingsworth used a slightly higher solute concentration of about 13.8% and obtained a mixture that was mostly[20] Form II armodafinil, instead of Form I, which he obtained in other experiments using a 9.6% solution. (*Id.* (citing Tr. at 195:16-200:4, 208:4-7, 210:5-12 (Hollingsworth); Tr. at 748:25-749:19 (Myerson)).) Drs. Myerson and Bernstein credibly testified that Dr. Hollingsworth's formation of Form II and unknown crystals confirms that small variations in procedure can yield very different polymorphic results. (*Id.* (citing Tr. at 730:17-731:4 (Myerson); Tr. at 535:17-537:2 (Bernstein)).) Dr. Hollingsworth also acknowledged that his mixture of Forms I and II is not a composition containing only one pharmaceutically active form of armodafinil, as is required by the asserted claims of the '570 Patent.[21] (*Id.* (Tr. at 253:15-254:12 (Hollingsworth)).)

Cephalon's experts, Drs. Smith and Selbo, performed a synthesis of armodafinil up to the same points as Dr. Hollingsworth in step (d), using different, but reasonable experimental conditions that the court finds credible,[22] and found their products to be amorphous, non-crystalline forms. (*Id.*) Therefore, while Dr. Hollingsworth found that the methanol evaporation and ether wash steps produced Form I, Drs. Smith and Selbo concluded that these steps do not necessarily and inevitably produce Form I. (*Id.* (citing Tr. at 716:14-19 (Selbo)).) Moreover, while the defendants' expert, Dr. Lee, attempted to reproduce Drs. Smith and Selbo's work and completed Preparation I through the final recrystallization step—at which point he found Form I with unknown impurities—Dr. Robie did not analyze Dr. Lee's intermediate products after the methanol evaporation and ether wash. (*Id.* (citing Tr. at 277:3-8, 309:18-25, 317:8-25; 361:10-13, 361:23-362:12 (Lee)).) Dr. Lee also stated on cross-examination that he did not follow Drs. Smith

[20] Dr. Myerson testified that Dr. Hollingsworth's second Run produced approximately ninety-percent Form II armodafinil and only ten-percent Form I. *See* Tr. at 730:17-22 (Myerson).

[21] *See infra* Section III.A.3.b.

[22] *See* Tr. at 710:6-717:7, 713:20-716:19 (Selbo); *see also* PTX-174; PTX-175.

and Selbo' s procedures exactly, but instead made some "variations in heating rate, colling time[,] and the use of filter paper. (*Id.* (citing Tr. at 292:6-11 (Lee)).)

In view of the foregoing, the court concludes that the defendants have not demonstrated that the Form I armodafinil claimed in the '570 Patent inevitably results from performing Preparation I because it is clear from the evidence presented that variations in the Preparation I process—variations not detailed in that Preparation—lend to different outputs, some of which are inconsistent with the asserted claims.[23] *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d at 1047-48 (finding no inherent anticipation where the testing evidence demonstrated that the prior art in question could yield crystals of the claimed polymorph or a different polymorph).

The court finds that this conclusion is further reinforced by the declarations Drs. Mallamo, Peterson, and Blomsma submitted to the PTO in connection with the '570 Patent. Specifically, Dr. Mallamo's declaration detailed various experiments demonstrating that, depending on the conditions used, a "recrystallization in ethanol" does not necessarily produce Form I armodafinil. (*Id.* at 10 (citing Tr. at 633:9-14, 644:16-645:10, 655:4-9, 657:11-16, 660:21-661:22 (Mallamo); JTX-120-5 at ¶ 18).) In addition, other testing described in the declarations reported that the instantaneous melting point of the product in the '855 Patent was inconsistent with Form I armodafinil, which would indicate that they result in different products. (*Id.* at 10-11 (citing JTX-120-6 at ¶ 20; *see also* Tr. at 738:18-739:16 (Myerson)).) In view of the foregoing, the court disagrees with the defendants' assertion that, as Dr. Hollingsworth opined, the declarations are invalid and support a finding of anticipation. Rather, the court finds that Dr. Hollingsworth's testimony regarding the Mallamo declaration are predicated on an overly narrow interpretation of "ethanol."[24] In addition, the court finds Dr. Hollingsworth's argument that Drs. Peterson and

[23] *See infra* Section III.A.3.b.
[24] *See infra* Section III.A.3.c.i.

Blomsma's declarations are invalid to be unpersuasive. Specifically, these declarations detail that a wide variety of conditions for recrystallization from ethanol can result in multiple polymorphic forms, which, the court concludes, supports the plaintiffs' assertion that there is lack of predictability for Form I over the '855 Patent. (*Id.* at n.10 (citing JTX-120-5 at ¶¶ 16-18).)

b. Whether the Product of Preparation I of the '855 Patent Meets the Requirements of the Asserted Claims of the '570 Patent

Claims 6 and 9 must be considered with the limitations of the claims from which they depend—Claims 1-4 and 7. The defendants claim that, rewritten to include these limitations, the asserted claims are:

> 6. A pharmaceutical composition consisting essentially of a laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 3.98, 13.40, 6.34, 5.01, 4.68, 4.62, 4.44, 4.20, 4.15, 3.90, 3.80, 3.43 (Å).
> 9. A pharmaceutical composition consisting essentially of a Form I polymorph of (-)-modafinil.

(D.I. 319 at 29.) Dr. Hollingsworth explained that, while the language of the claims appear to be different, they cover "essentially the same thing." (*Id.*) Specifically, the XRPD data incorporated in Claim 6 is that of Form I armodafinil, which is expressly recited in Claim 9. (*Id.* (citing Tr. at 78:23-79:8, 79:19-24 (Hollingsworth); Tr. at 388:14-25 (Cima)).) According to the defendants, the elements of Claims 6 and 9 combine to require: (1) a pharmaceutical composition; (2) consisting essentially of; and (3) Form I armodafinil. The defendants also assert that Claims 6 and 9 allow for the presence of more than one pharmaceutically active component. (*Id.* at 29.) Specifically, the defendants maintain that the language "unlisted pharmaceutically acceptable ingredients" encompasses other ingredients, including other active components of armodafinil, so

long as they "do not materially affect the basic and novel properties" of Form I. (*Id.* (citing Tr. at 155:7-12 (Hollingsworth).)

The defendants further support this claim by noting that the '570 Patent states that the invention "relates to the use of" armodafinil Forms II-IV "for the manufacture of a medication" and that "pharmaceutical compositions according to this invention may also contain another crystalline form of (-)-modafinil . . . in particular [F]orm I and/or another active ingredient . . . as a mixture with one or more other polymorphic forms of modafinil" such as Forms II through V. (*Id.* (citing JTX-1.24-.25 col. 12, ll. 64-col. 13, ll. 2, col. 13, ll. 9-32).) Thus, the defendants argue, the '570 patent teaches that "unlisted pharmaceutically acceptable ingredients" encompasses a mixture of Form I with armodafinil's other polymorphic forms. (*Id.* at 31-32 (citing Tr. at 151:3-9, 154:3-11, 155:7-12 (Hollingsworth)).)

Conversely, the plaintiffs maintain that asserted Claims 6 and 9, taken together, specify pharmaceutical compositions with an active component "consisting essentially of" Form I armodafinil, meaning that Form I must be the only pharmaceutically active crystal form of armodafinil present in the compositions, and that any additional ingredients be pharmaceutically acceptable. (D.I. 314 at 7 (citing Tr. at 256:5-14 (Hollingsworth); Tr. at 756:6-16 (Myerson)).) The plaintiffs also state that unasserted Claims 5 and 8 of the '570 Patent recite a composition "comprising" Form I armodafinil, which would allow for other active ingredients and forms of armodafinil. (*Id.* (citing JTX-1-38 at 40:33-35 & 40:38-39; *see* D.I. 172).) Finally, the plaintiffs assert that, as it is "specified" in Claims 4 and 7, Claims 6 and 9 require that Form I armodafinil be "'the,' as in only, pharmaceutically active component present in the claimed compositions." (*Id.* at 11 (citing Tr. at 255:11-19, 256:12-14 (Hollingsworth)).) Thus, because Form II is

pharmaceutically active, its presence is excluded from Claims 6 and 9. (*Id.* (citing JTX-1-24; JTX-12-10).)

With respect to both parties' arguments, the court first notes that, contrary to each sides' references to the "court's construction" of the terms in question, it did not construe the terms "pharmaceutical composition comprising" or "pharmaceutical composition consisting essentially of." Rather, the parties informed the court via letter on July 13, 2011 that the parties had conferred and agreed on the meaning of these two disputed terms. (D.I. 143.) Therefore, the parties' arguments—and particularly those of the defendants, who repeatedly reference how the court construed "pharmaceutical composition consisting essentially of" to allow for more than one pharmaceutically active form of armodafinil—strike the court as misleading. Because the parties reached agreement on the meaning of these terms before the *Markman* hearing, the court did not construe these terms and made note of this point in its July 25, 2011 Order construing the disputed terms of the '570 Patent. (D.I. 172 at 3.) The court also did not have the benefit of reviewing the record or the parties' arguments in connection with these terms and the parties do not meaningfully present such support for their opposing positions in their Proposed Findings of Fact and Conclusions of Law.

In consideration of the record before it, the court agrees with the plaintiffs that the term "pharmaceutical composition consisting essentially of," requires, as specified in Claims 4 and 7, that Form I armodafinil be the only pharmaceutically active component present in the claimed composition. In reaching this conclusion, the court considers, as the plaintiffs suggest, that the definition of this term states "composition consisting of the specified pharmaceutically active component." The court finds that the use of "the" in the parties' construction indicates "only." As noted above, unasserted Claims 5 and 8 of the '570 Patent recite a composition "comprising" Form

I armodafinil, which, as compared to Claims 6 and 9, would allow for other active ingredients and forms of armodafinil. (D.I. 314 at 7 (citing JTX-1-38 at 40:33-35 & 40:38-39).) Notably, even the defendants' expert, Dr. Hollingsworth, agreed that the term "pharmaceutical composition consisting essentially of" refers to the "specified pharmaceutically active component," which is Form I.[25] The court concludes that the defendants' experiments have failed to show that a composition "consisting essentially of" Form I armodafinil is the necessary and inevitable result of Preparation I. Specifically, Dr. Hollingsworth's Run 3/4 experiment showed either mixtures of Form I with other unknown crystalline material or, when using a higher concentration of solute, mostly Form II armodafinil. Thus, the defendants' testing demonstrates that a reasonable "recrystallization from ethanol" does not inevitably and necessarily produce a product within the scope of the asserted claims.[26]

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[25] In particular, Dr. Hollingsworth testified:

Q: And you saw and you reviewed that there were, in fact, two different claims in the '570 Patent. There was Claim 5 that called for a pharmaceutical composition comprising Form I, and there was Claim 6, a pharmaceutical composition consisting essentially of Form I. Correct?
A: That's correct.
Q: And the Court's definition of pharmaceutical composition comprising was construed to mean a composition comprising the specified pharmaceutically active component. Do you see that?
A: Yes.
Q: And in the rest of the claim, the specified pharmaceutically active component is Form I, armodafinil; is that correct?
A: Yes, that's correct.
Q: Okay. And so that claim would have included Form I armodafinil even if there was some other crystal form of Form I armodafinil; right?
A: Yes, I agree.
Q: Okay. But the definition of, in Paragraph 6, a pharmaceutical composition consisting essentially of is construed differently to mean, a composition consisting of the specified pharmaceutically active component. Do you see that?
A: Right, I see that.
Q: Okay. You understand the difference between comprising and consisting of?
. . . .
A: Yes. I see how the Court has construed.
Q: And the pharmaceutically active component in Claim 6 and 9 is Form I armodafinil; is that correct?
A: Yes.

Tr. at 255:4-256:15 (Hollingsworth).

[26] As noted, Dr. Hollingsworth's Run 3/4 resulted in a product consisting of 90% Form II armodafinil and only 10% of Form I. *See supra* note 20.

In addition to the foregoing arguments, the plaintiffs note that Claims 6 and 9 recite a "pharmaceutical composition." (*Id.* at 12.) In light of this requirement, the plaintiffs assert that the defendants have failed to prove invalidity because they have not demonstrated that the product of Preparation I is suitable for pharmaceutical use. (*Id.* (citing Tr. at 541:5-542:8 (Bernstein); Tr. at 756:11-16 (Myerson); PTX-36-2 at ¶ 6).) The plaintiffs note that even the defendants' expert, Dr. Cima, acknowledged that one would need to prove that the amount and type of any impurities in an armodafinil product intended for human use are safe.[27] (*Id.* (citing Tr. at 457:15-18, 459:1-11 (Cima)).) Because the defendants "made no effort to determine the type or quantity of impurities in the samples from their experiments, or determine if they were pharmaceutically acceptable, the plaintiffs assert that the defendants have not proven by clear and convincing evidence that the result of Preparation I meets the "pharmaceutical composition" requirement of Claim 6. (*Id.*)

In response, the defendants maintain that the plaintiffs' argument is unfounded and "misses the point." (D.I. 319 at 32.) Specifically, the defendants state that their experts made armodafinil according to the Preparation I and determined that it was Form I. (*Id.*) Therefore, according to the defendants, whether the particular crystals Drs. Hollingsworth and Lee made via Preparation I could be directly formulated into a pharmaceutical composition is irrelevant to the anticipation analysis because the '855 Patent expressly discloses that armodafinil produced by Preparation I was used in the tablets or capsules in human clinical trials and that it has therapeutic efficacy. (*Id.* at 5-6; at 33 (citing Tr. at 298:20-23 (Lee)).) Therefore, the defendants maintain that because Form I armodafinil can be obtained with the purity level necessary for human consumption by

[27] Specifically, Dr. Cima noted that, "you have to prove, before administering to humans, that the amount of impurities and the type of impurities are safe. All pharmaceutical products have impurities in them. But what happens before you administer it to a human is that you establish in some way—it could be toxicology experiments in animals, two species, that sort of thing—you establish that these are going to be safe." Tr. at 459:1-11 (Cima).

performing Preparation I, the impurities contained in Drs. Hollingsworth and Lee's experiment results do not need to be identified, as performance of Preparation I will result in a product that is a pharmaceutical composition. (*Id.* at 33 (citing *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (recognizing that a single reference may anticipate where the "common knowledge of technologists is not recorded in the reference")).)

Moreover, the defendants note that the "therapeutic" and "pharmaceutical" compositions claimed in the '855 Patent are presumed enabled. (*Id.* (citing 35 U.S.C. § 282).) The '855 Patent, according to the defendants, "does not describe any purification of armodafinil beyond step (d) of Preparation I" and, therefore, "Form I armodafinil made according to Preparation I is either pharmaceutically acceptable as-is, or techniques to further purify the product of Preparation I were so well-known and routine that they need not be expressly described." (*Id.* at 27 (citing Tr. at 383:16-21, 430:16-432:16, 458:7-20 (Cima)).) Specifically, and in support of the latter, the defendants note that the '855 Patent does not contain explicit instructions regarding purification or formulation techniques—yet still enables claims to pharmaceutical compositions "consisting essentially of" armodafinil—demonstrates the routine nature of the purification process. (*Id.* (citing Tr. at 150:22-151:21 (Hollingsworth); JTX-103.5 col. 7, ll.18-col. 8, ll. 29, claims 1-6).) Thus, the defendants argue that the plaintiffs are incorrect in asserting that the '855 Patent does not anticipate the '570 Patent because the defendants did not prove that Preparation I is suitable for use in a pharmaceutical composition. (*Id.* at 33.)

The court disagrees, and concludes that the defendants have not proven anticipation by clear and convincing evidence. As noted, the defendants contend that the claimed pharmaceutical compositions can contain additional components, such as impurities, that do not affect the basic and novel properties of Form I and that different solid state forms of armodafinil and chemical

impurities would not affect those properties. (D.I. 314 at 12 (citing Tr. at 154:3-155:12 (Hollingsworth)).) However, Drs. Bernstein and Myerson's testified credibly that different solid state forms and/or impurities can, in fact, affect the properties of Form I and the ultimate result of Preparation I.[28] *See* Tr. at 539:22-540:19 (Bernstein). The defendants' expert, Dr. Cima, agreed with Dr. Bernstein that the product of Preparation I will contain impurities, such as unreacted starting materials, reaction byproducts, or unreacted chemicals. (D.I. 314 at 12 (citing Tr. at 457:19-458:2 (Cima); Tr. at 540:20-541:1 (Bernstein)).)

Here, as the plaintiffs note, Dr. Hollingsworth's XRPD analysis from Run 3/4 after the first ethanol recrystallization—the number of ethanol recrystallization required by the '855 Patent[29]—

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[28] Dr. Bernstein agreed with Professor Guillory's chapter, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids, Polymorphism" in *Pharmaceutical Sciences*. *See* JTX-027. Specifically, Dr. Bernstein testified:

> Q: If we go to Page 21 of the exhibit, which is Page 201 of the article, and highlight 1, to the end of the paragraph, can you read what is written here and explain, Professor?
> A: "The presence of impurities can have a profound effect on the growth of crystals. Some impurities can inhibit growth completely and some may enhance growth." Again, you get both sides of the coin. "Still others may exert a highly selective effect, acting only on certain crystallographic faces and thus modifying the crystal habit." Crystal habit is the shape of a crystal. "Some impurities can exert an influence at very low concentrations, less than one part per million, whereas others need to be present in fairly large amounts to have any effect."
> Q: Do you agree with Professor Guillory that impurities can have a profound effect on growth of crystals?
> A: They certainly do.
> Q: Referring to the '855 Patent, Preparation I, would there have been impurities in the material crystalized in that product?
> A: At the end of the synthesis, certainly.
> Q: Does the '855 Patent characterize the type and amount of impurities in its product?
> A: No, not at all.
> Q: Is that silence with respect to impurities reflected in the literature?
> A: Yes.
> . . . . .
> A: This is a U.S. patent application 2010/0234468.
> Q: And does this application address, reflect on information or lack of information of the '855 Patent with respect to impurities?
> A: . . . . Yes, it does. . . . The first line in Section 6 refers to the '85 Patent. . . . The Patent does not disclose or provide any information on purifying the resultant compounds or even allude to the likelihood of the presence of impurities in the final compounds or in the chiral intermediates or the effect of the impure intermediates on the purity of the final compounds.

Tr. at 539:22-542:1 (Bernstein).

[29] *See* JTX-1-3 at 3:50. The plaintiffs note that, unlike Preparation I's reference to only one "recrystallize[ation] from ethanol," Cephalon's work routinely involved two recrystallizations in order to get a more pure product. *See* Tr. at 740:9-742:7 (Myerson); JTX-10303 at 3:50

showed the presence of three peaks that could not be attributed to the Form I fingerprint. (*Id.* (citing Tr. at 249:23-251:13 (Hollingsworth); PTX-411).) Dr. Hollingsworth testified that he believed those peaks to represent a chemical impurity, but that he did not know the amount or identity of the impurity. (*Id.* at 12-13 (citing Tr. at 251:9-24 (Hollingsworth); Tr. at 746:7-12 (Myerson)).) In addition, Dr. Lee did not test his experimental products, Samples 10 and 12S, for impurities and, instead, sent them to Dr. Robie for XRPD testing. This testing indicated that, for Samples 10 and 12S, there were five and nine XRPD peaks, respectively, and that the impurities did not match to Form I armodafinil's fingerprint. (*Id.* at 13 (citing Tr. at 364:19-365:23 (Robie)).) Drs. Lee and Robie did not seek to identify these impurities, however, and did not test to determine the quantity of the impurities in the Preparation I product. (*Id.* (citing Tr. at 365:24-366:10, 366:15-18 (Robie)).) Dr. Robie did not know whether or how these impurities would impact the mixture, as he is not an expert in polymorph identification, and did not opine on whether the product was a pharmaceutical composition. (*Id.* (citing Tr. at 366:19-22, 366:23-367:5, 367:9-11 (Robie)).)

In consideration of Dr. Bernstein and Dr. Myerson's convincing and credible testimony—particularly their testimony related to the impact of impurities—the court finds, with respect to Drs. Hollingsworth and Lee's experiments, that the defendants have not demonstrated clearly and convincingly that the product of Form I will inevitably and necessarily produce a "pharmaceutical composition" as required by the asserted claims.

c. Whether the Defendants Demonstrated That Their Experiments Were Accurate and Obtained the Same Product Described in Preparation I of the '855 Patent

As discussed above, the court finds that the evidence presented establishes that Preparation I and a recrystallization from ethanol can yield different forms, mixtures of forms, and unknown

impurities, depending on how one performing the Preparation selects numerous variables not specified in the '855 Patent. The plaintiffs' and defendants' witnesses agreed that the '855 Patent does not mention or describe polymorphism, or any polymorphic form of armodafinil. (*Id.* at 8-9 (citing Tr. at 157:5-7, 234:9-17 (Hollingsworth); Tr. at 307:8-11 (Lee); Tr. at 537:3-6, 630:8-12 (Bernstein); Tr. at 648:6-8, 653:18-654:4 (Mallamo)).) Moreover, Preparation I does not disclose the crystallization conditions needed to make any particular polymorph, such as the solvent, the cooling rate, and the concentration—all factors which, according to Drs. Bernstein and Myerson's credible testimony—can affect the result.[30] (*Id.* at 9 (citing Tr. at 564:19-566:19 (Bernstein); Tr. at 745:3-7, 750:10-12, 764:2-7 (Myerson); Tr. at 157:14-158:11 (Hollingsworth); JTX-7-3 Tbl. 1).) Dr. Myerson also agreed with Dr. Bernstein that Preparation I of the '855 Patent did not specify such details as "reaction time, filtration temperature, the washing conditions, [or the] dry conditions," all of which will impact the "impurity profile" of the resulting product.[31] *See* Tr. at 731:5-734:25 (Myerson). Likewise, the defendants' expert, Dr. Hollingsworth, agreed on cross-

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[30] *See supra* note 18.

[31] Specifically, Dr. Myerson explained, in testimony the court finds credible, as follows:

> Q: What would the principal consequence be of variation in [the Preparation I] steps, in your opinion?
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> A: I think what we would see is a difference in the impurity profile. So in each step, you are getting a particular product, you are going to get unreacted species that are left over that you haven't used, as well as side products that are impurities. So the impurities will be unreacted species and these side products. By changing the conditions in a step, that impurity profile will change. Now, this has a cascading effect, because the product of one step is used as the starting material in the next step. So you are starting with something with a different impurity profile, and that will cascade through the process, and the whole process will change.
>
> Q: Does that matter for the impurities in the final recrystallization step?
>
> A: . . . . Impurities can have profound effects on recrystallization. They can inhibit the formation of crystals completely, they can cause amorphous material to come out, or they can change the polymorphic form of the crystallization.
>
> . . . . .
>
> Q: [I]f impurities had blocked the formation of Form I in the '855 Preparation I procedure, what would have happened, if you know?
>
> A: You would have gotten a different polymorph form or an amorphous form.
>
> Q: And how, if at all, would the properties or characteristics of that form vary from Form I?
>
> A: They would have completely different properties and characteristics.

Tr. at 732:7-734:25 (Myerson).

examination that "impurities in [a] system" "can matter." (*Id.* at 12 (citing Tr. at 163:22-25 (Hollingsworth)).) In view of the foregoing, and for the reasons detailed below, the court concludes that the defendants have failed to prove anticipation by clear and convincing evidence because they have not established that their Preparation I experiments were accurate and produced the material intended by the '855 Patent's Preparation. Therefore, the defendants have not shown that the Form I armodafinil claimed in the asserted claims of the '570 Patent is, in fact, the necessary and inevitable result of performing Preparation I.

i. The Defendants' Experts' Performance of Preparation I

The plaintiffs contend that the defendants' inherent anticipation defense fails because their experts failed to follow Preparation I as written or consider the range of variables that would have been reasonably available to skilled artisans. In particular, the plaintiffs assert that defects in following Preparation I and/or selecting the method for performing Preparation I, render the results insufficient in establishing the necessary and inevitable result of that Preparation.

First, the plaintiffs note that the defendants did not correctly follow step (b) of the '855 Patent which states that "the (-)-bezhydrylsulfinylacetate of (-)-α-methylbenzylamine (17 g) obtained in this way is dissolved in 800 ml of warm water (30-40 degrees Celsius)." *See* JTX-103-3 at 3:22-24. The '855 Patent also states elsewhere that this step should be performed at 30-45 degrees Celsius. *See id.* at 2:31-32. However, Drs. Hollingsworth and Lee testified that they did not perform Preparation I as written and, instead, used higher temperatures of 70 and 90 degrees Celsius. *See* Tr. at 234:18-235:10 (Hollingsworth); Tr. at 312:24-313:6 (Lee). Dr. Hollingsworth testified that, in his opinion, dissolution at the stated 30 to 40 degrees Celsius may be impossible, but that he had not fully tested his theory and the experiment forming the foundation

for Preparation I could have used 30 to 40 degrees Celsius. *See id.* at 238:8-22, 236:1-9 (Hollingsworth).

The plaintiffs contend that the defendants' experts' decision to use a different temperature is significant because, even using a melting point test method different from what is specified in the '855 Patent, Dr. Hollingsworth and the other experts obtained a product that had a "very wide range" of melting points inconsistent with the narrow melting point reported in the '855 Patent. (D.I. 314 at 18 (citing Tr. at 237:18-238:7 (Hollingsworth); Tr. at 780:7-19 (Myerson)).) Therefore, because they did not follow the stated procedure in step (b) and did not obtain the reported melting point, the defendants' experiments, the plaintiffs argue, cannot be considered probative of whether Preparation I would inherently or naturally result in Form I armodafinil by the required clear and convincing standard. In view of the foregoing credible arguments, the court agrees. *See Valeant Int'l (Barbados) SRL v. Watson Pharm., Inc.*, No. 10-20526-CIV, 2011 WL 6792653, at *5 (S.D. Fla. Nov. 8, 2011) ("Thus, because Dr. Adlington did not follow the explicit disclosure of Example I of the Mehta patent, his experiment is simply not probative of the issue of inherent anticipation").

Second, the plaintiffs assert that the defendants did not test a representative range of conditions in conducting their Preparation I experiments. Specifically, Preparation I has four major synthetic steps, but allows skilled artisans the selection of conditions used to carry out the many steps listed. *See* JTX-103-3 at 3:5-56. However, instead of testing a variety of conditions, the defendants' experts chose to use a "narrow set of experimental conditions," which, the plaintiffs allege, is legally insufficient to demonstrate inherency. (D.I. 314 at 19.) The court agrees and concludes that the defendants have not demonstrated that all reasonable ways to practice

Preparation I would necessarily result in Form I armodafinil consistent with the limitations of the asserted claims.

For instance, in step (a), the reaction time, reaction temperature, and recrystallization conditions are not specified; in step (b), the reaction time, filtration temperature, washing conditions, and drying conditions are not specified; and in step (c), the filtration conditions, washing conditions, and drying conditions are not specified. *See* Tr. at 307:25-308:4 (Lee); Tr. at 731:5-732:6 (Myerson). Further, step (d) leaves entirely open the specific experimental conditions for "recrystallize[ation] from ethanol," and does not specify the form of the crude product to be recrystallized, the identity, and quantity of the impurities in the crude product, the grade of ethanol, the amount of solvent, the starting temperature, the cooling rate, the final temperature, or the drying conditions. *See* Tr. at 566:20-567:9 (Bernstein); Tr. at 654:5-11 (Mallamo); Tr. at 308:5-19 (Lee); Tr. at 839:15-840:21 (Coquerel); JTX-120-3 at ¶ 9.

Thus, one reproducing Preparation I would need to make several decisions, unsupported by the '855 Patent, and, as the testimony at trial demonstrated, there are a variety of reasonable conditions that can be used for crystallization and the specific conditions of crystallization selected can affect the solid state ultimately formed. *See* Tr. at 542:17-543:2, 564:19-21 (Bernstein); PTX-585-49; JTX-120-5 at ¶¶ 17, 18. Indeed, the plaintiffs' and defendants' experts agreed that, depending on the choices made, the resulting product will contain different kinds and/or amounts of impurities, which can affect whether and which final solid state form—crystals, solvates, or amorphous compound—will result. *See* Tr. at 157:14-158:11, 163:22-25 (Hollingsworth); Tr. at 732:7-23 (Myerson); 533:22-535:16 (Bernstein). Specifically, the plaintiffs contend that solvent composition, concentration, and cooling rate can impact the final solid state form. For the reasons detailed in the discussion below, the court agrees.

With regard to the defendants' experts' selection of the concentration of armodafinil used in the recrystallization step, the plaintiffs persuasively argue that their selection was inconsistent with the prior art and affected the product they obtained. The defendants used only one concentration in all but one of their recrystallizations—a recrystallization that yielded a different result—such that their testing does not necessarily contemplate the full scope of Preparation I. As the testimony presented made clear, standard textbooks indicate that the "MINIMUM AMOUNT(!)" of solvent, i.e., a larger percentage or concentration of solute, should be used in recrystallizations. Tr. at 746:13-748:5 (Myerson); JTX-97-6. In fact, Cephalon's scientists routinely use a 20% concentration. *See* JTX-38-41, -42 (Examples Nos. 5/2502, 1/0054(a), 1/0920, and ON II/149E Step a); Tr. at 164:1-165:11 (Hollingsworth). Even Dr. Hollingsworth testified that skilled artisans might select a range of concentrations to use and that the 20% concentrations shown in the PTO declarations were reasonable. (D.I. 314 at 21 (citing Tr. at 167:15-21, 168:15-20, 167:9-14 (Hollingsworth); JTX-38-41, -42).)

Despite the availability of this range, the defendants' experts did not use a 20% concentration. Rather, Dr. Hollingsworth used a 9.6% concentration, which was not the minimum amount of solvent taught by the prior art, despite the fact that the '570 Patent and the PTO declarations noted that Form I is preferentially obtained using a lower concentration solution. (*Id.* (citing Tr. 159:1-3, 160:23-161:2, 165:21-166:6, 178:14-22 (Hollingsworth); 748:13-20 (Myerson)).) Similarly, defendants' counsel instructed Dr. Lee to use the same 9.6% concentration that Dr. Hollingsworth used to obtain some amounts of Form I. (*Id.* (citing Tr. at 309:7-12, 319:16-320:5 (Lee)).) Notably, the one time that Dr. Hollingsworth used a 13.8% solution in his second recrystallization in Run 3/4, he obtained a mixture of crystalline forms that was predominately Form II armodafinil, demonstrating that reasonable variations in Preparation I can yield different

polymorphs of armodafinil. (*Id.* (citing Tr. at 195:16-197:25, 207:12-208:7 (Hollingsworth)).) Thus, because a person of ordinary skill in the art could have reasonably selected among various levels of solution concentration in performing Preparation I and the defendants' experts tested this Preparation using primarily one selection, the court finds that the defendants have not demonstrated clearly and convincingly that Preparation I inevitably results in Form I armodafinil consistent with the asserted claims.[32]

Similarly, the plaintiffs assert that the defendants' experts' selection of ethanol grade was too narrow and insufficient to establish Form I as the inevitable product of Preparation I. Specifically, the plaintiffs note that step (d) of Preparation I calls for "recrystalliz[ation] from ethanol" without specifying a particular grade. (D.I. 319 at 21 (citing JTX-103-3 at 3:50).) As the trial testimony established, ethanol is available in several grades, including azeotropic (i.e., containing water), denatured (i.e., containing an additive), and absolute (i.e, pure or 100%). Tr. at 761:1-15 (Myerson). Drs. Hollingsworth and Lee used only absolute ethanol, which, the defendants assert was reasonable because Cephalon's "own data confirms that recrystallizing armodafinil from ethanol would result in the most stable form (Form I) a substantial majority of the time. (D.I. 319 at 35 (citing JTX-38.8-.9; JTX-38.13-.14 at ¶¶ 4-5, .41-.42; Tr. at 798:7-799:17 (Peterson); JTX-123.19-125.19).)

However, as the plaintiffs correctly point out, "ethanol" can be interpreted more broadly than just absolute ethanol and, in fact, the '570 Patent describes more than one type of ethanol, including absolute ethanol, azeotropic ethanol, and denatured ethanol. *See* JTX-1-32 at 27:24-43;

[32] The defendants do not meaningfully contest the plaintiffs' argument, except to simply contend that their experts' selection of concentration was "reasonable" and that a person of ordinary skill in the art would have, as Dr. Hollingsworth, conducted a small-scale crystallization to determine a suitable concentration of armodafinil for the recrystallization part of step (d). (D.I. 319 at 35.) Thus, because their experts used suitable concentrations in performing Preparation I, the defendants argue that their selections were reasonable and do not undermine their anticipation argument. (*Id.*)

see also PTX-101-13 at 4:7-10; PTX-100-1 at Abstract; PTX-124-13; Tr. at 217:6218:5, 219:15-221:2 (Hollingsworth). This broader definition of ethanol is also reflected in organic chemistry laboratory texts. *See* PTX-589-8; JTX-56-6 at Tbl. 3-2. Also, notably, Louis Lafon, the inventor of the '855 Patent, distinguished the term ethanol from "absolute ethanol" in other patents. *See* PTX-139-3 at 4:45-47; PTX-139-5 at 7:1-3, 53-55; PTX- 139-6 at 9:46-48. Therefore, a narrow interpretation of ethanol as synonymous with absolute ethanol is not the "sole, universally accepted definition." (D.I. 319 at 22.) As Dr. Myerson explained in testimony the court found credible, the proper interpretation of ethanol depends upon the totality of the circumstances and includes consideration of, for instance, whether the case involves a polymorph patent specifically discussing solvent mixtures. *See* Tr. at 765:14-773:1. To this end, the court finds that the documents on which Dr. Hollingsworth relied to limit ethanol to absolute ethanol can reasonably be distinguished because, unlike the context of those references, ethanol is not used in the '855 Patent for a therapeutic purpose or as an excipient. (D.I. 319 at 22 n.22 (citing Tr. at 210:13-212:5; JTX-1165; JTX-28-3).)

Here, the '570 Patents and Cephalon's experiments show that the different polymorphic forms of armodafinil can result from recrystallization from different grades of ethanol, such that, for example, the use of denatured ethanol can, under some conditions, lead to Form II armodafinil. (*Id.* at 22 (citing JTX-1-32 at 27:23-47; JTX-1-33 at 29:30-51; JTX-1204 at ¶ 13; Tr. at 657:11-658:5 (Mallamo)).) Thus, the court finds that the defendants have failed to establish, based on their testing of only one type of ethanol, that Form I will necessarily and inevitably result from Preparation I.[33]

[33] The defendants note that Cephalon's own data confirms that recrystallizing armodafinil from ethanol would result in the most stable form, Form I, a "substantial majority of the time." (*Id.*) Specifically, the defendants note that, leaving aside the fact that they did not concern reproductions of Preparation I, the declarations submitted during the prosecution of the '570 Patent demonstrate that the Form I polymorph is obtained in almost every recrystallization

Moreover, regarding cooling rates, Preparation I does not specify the method or rate of cooling of the armodafinil/ethanol solution during the "recrystallize[ation] from ethanol" in step (d). Although the cooling method used affects the cooling rate and, therefore, the polymorphic form of the recrystallization product, the defendants' experts' used only one of the multiple reasonable cooling methods available. (*Id.* at 23 (citing Tr. 157:16-158:7, 226:20-227:10 (Hollingsworth); Tr. at 750:10-752:12 (Myerson); Tr. at 565:8-566:19 (Bernstein); JTX-27-13).) Specifically, Dr. Hollingsworth used a very slow cooling, which resulted in an overall temperature change of about 0.3 degrees Celsius per minute cooling and, on instruction of counsel, Dr. Lee used a slow cooling as well, resulting in an average cooling rate of 0.55 degrees Celsius. (*Id.* (citing Tr. at 750:10-752:14 (Myerson); Tr. at 179:1-181:3 (Hollingsworth); Tr. at 324:24-327:4, 327:9-11 (Lee); DTX-212-12 ll. 2-9).)

Notably, Drs. Hollingsworth and Lee were familiar with the '570 Patent before they conducted their experiments. The '570 Patent explains that a crystallization using ethanol and slow-cooling at a rate of 0.6 degrees Celsius per minute or less is preferred to crystallize Form I

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of armodafinil from ethanol. (*Id.*) The defendants note that the data in the declarations shows that other forms of armodafinil were produced only where extreme conditions inconsistent with the standard recrystallization disclosed in the '855 Patent were used. (*Id.*) Further, the defendants refer to the fact that, in a conventional polymorph screen performed by Cephalon/Lafron around 2000, Form I armodafinil was obtained from a wide variety of recrystallization conditions. (*Id.* at 36 (citing Tr. at 845:23-846:4, 852:14-853:18, 854:13-25, 856:6-857:1 (Serrure); Tr. at 872:23-873:5 (Neckebrock)).) In particular, the defendants detail that the screen demonstrated that recrystallization of armodafinil from ethanol, even under extreme conditions outside of the '855 Patent, almost inevitably results in Form I armodafinil. (*Id.* (citing DTX-51A.6, .9, .17, .20; DTX-51.4, .7; JTX-101.3, .6).) A high-throughput screen—which is not a conventional screen—performed by Crystallics BV in 2003 at Cephalon's request provides, the defendants argue, further evidence that Form I armodafinil results from a wide range of recrystallization conditions. (*Id.* (citing Tr. at 615:1-11 (Bernstein); Tr. at 820:13-18 (Blomsma); Tr. at 861:3-11 (Rose); JTX-38.2 at ¶ 3; JTX-62.1, .21).) The defendants highlight that Form I was made in 948 out of the 1,035 successful recrystallizations conducted and that 177 of the recrystallizations were unsuccessful because the resulting material could not be identified. Thus, the defendants argue, based on the result of the Crystallics screen, Cephalon reported to the FDA "more than 95% of the assigned crystals were [Form I]" and that "scale-up recrystallization studies only produced Form [I] along with additional solvate." (*Id.* at 37 (citing JTX-123.19; JTX-125.19; JTX-14.10).)

The court disagrees, however, with the defendants' contention that these results show that "nearly any set of conditions that could be described as 'recrystallization' of armodafinil (from ethanol or solvents) will produce the most stable polymorph—Form I" and that this data "refutes criticism that Drs. Hollingsworth and Lee tested only a narrow set of recrystallization conditions" (*id.*) for the reasons detailed above. *See supra* notes 13, 14 and accompanying text.

armodafinil. (*Id.* (citing Tr. at 159:1-19 (Hollingsworth); Tr. at 281:18-20 (Lee); JTX-1-21 at 5:50, -22 at 7:1-6).) However, the evidence at trial established that there were multiple, reasonable cooling methods available to skilled artisans at the time of the '855 Patent. For instance, standard references taught that a person of ordinary skill in the art could have "set aside" the recrystallized solution "to cool until crystals are formed," or more rapid cooling could be used. *See* JTX-56-8; JTX-15-8. In fact, the testing Cephalon submitted to the PTO indicated the use of bench top, room temperature cooling as well as more rapid cooling via an ice bath. *See* JTX-120-19 (Example No. 05/2505); JTX-120-20. Dr. Hollingsworth testified that different cooling methods are appropriate under certain circumstances and Dr. Lee testified that bench top cooling was reasonable. *See* Tr. at 176:2-177:2 (Hollingsworth); Tr. at 321:11-323:18 (Lee). Moreover, while Drs. Hollingsworth, Lee, and Cima testified that the defendants' experts' selections were reasonable and, indeed, the standard operating procedure considering the purpose of recrystallization, there was also literature available at the time that encouraged the use of rapid cooling to obtain fine crystals. *See* Tr. at 125:11-19, 172:23-173:14, 176:2-177:2 (Hollingsworth); Tr. at 298:18-23 (Lee); Tr. at 393:19-394:15 (Cima); *see also* JTX-15-8. Thus, because the defendants' use of only slow cooling is not representative of the full possible scope contemplated by the '855 Patent, the court finds their experiments insufficient to prove the inherency of Form I armodafinil.

ii. The Form I and Preparation I Melting Points

In addition to the foregoing, the court concludes that the defendants have not demonstrated that the products they obtained through their Preparation I experiments were Form I or an accurate result, because Drs. Hollingsworth and Lee did not measure the melting point of their final products in the manner specified in the '855 Patent. Specifically, and as referenced above in connection with the defendants' arguments, Preparation I reports an instantaneous melting point

of 153 to 154 degrees celcius for the final armodafinil product and provides a way to confirm whether a particular substance is the same as the Preparation product. *See* JTX-103-3 at 3:55. The instantaneous melting point reported in Preparation I was measured using a Kofler hot bar device, which the defendants' experts dismissed as a "museum piece." (D.I. 319 at 14 (citing Tr. at 185:16-18 (Hollingsworth); Tr. at 337:18-21 (Lee)).) However, as Drs. Bernstein and Mallamo convincingly explained, determination of the instantaneous melting point is particularly important for compounds like armodafinil that degrade upon slow heating. (D.I. 314 at 14.)

Moreover, the instantaneous melting point is of particular importance in the instant case because, as Dr. Mallamo explained, the instantaneous melting point reported in the '855 Patent suggests that the Preparation does not result in Form I armodafinil because, using the Kofler hot bar, Form I armodafinil has an instantaneous melting point of 159 degrees Celsius or higher, while pure Form II armodafinil has an instantaneous melting point of 156 degrees Celsius. (*Id.* (citing JTX-120-5 to 6 at ¶¶ 19, 20; JTX-120-22; JTX-120-22; Tr. at 658:16-659:17 (Mallamo)).) Instantaneous melting points of Form I/Form II mixtures ranged from 156 to 160 degrees Celsius. (*Id.* (citing JTX-120-22).) Thus, importantly, none of the pure polymorphic forms or mixtures of polymorphic forms had instantaneous melting points approaching the 153 to 154 degrees Celsius data points recorded for the product of Preparation I.[34] Based on this information, Dr. Mallamo concluded, and the court agrees, that "the data supports a conclusion that the [armodafinil] described in Preparation I of the [] '855 [P]atent is NOT the claimed Form I [armodafinil]" of the '570 Patent. (*Id.* at 15 (citing JTX-120-6 at ¶ 20 (emphasis in original); Tr. at 700:1-701:2 (Mallamo)).) Dr. Myerson also reviewed the information presented and derived the same conclusion. (*Id.* (citing Tr. at 738:18-739:16 (Myerson)).)

[34] In fact, the instantaneous melting point reported for the product of Preparation I was closer to the data point for Form II than Form I armodafinil. (D.I. 314 at 15.)

This conclusion is further supported by the fact that the defendants presented no evidence indicating that Form I has an instantaneous melting point of 153 to 154 degrees Celsius, the range reported by Preparation I. (*Id.*) Notably, even Dr. Hollingsworth agreed that the instantaneous melting point reported in the '855 Patent does not appear to correspond to the instantaneous melting point reported for Form I, a conclusion with which Dr. Myerson agreed. (*Id.* (citing Tr. 263:13-264:3 (Hollingsworth); Tr. at 773:23-774:10, 776:7-777:14 (Myerson)).) In addition, neither Dr. Hollingsworth nor Dr. Lee used a Kofler hot bar to measure the instantaneous melting point of their samples and, instead, used capillary methods to determine melting point. (*Id.* (citing Tr. at 185:12-21 (Hollingsworth); Tr. at 303:16-18, 336:23-337:24, 328:7-9 (Lee)).) These capillary methods, however, are different from the Kofler hot bar method in that they involve a non-instantaneous, gradual heating of the sample in a measuring procedure that could take as long as ten to fifteen minutes. (*Id.* (citing Tr. at 192:24-193:4 (Hollingsworth); Tr. at 564:10-14 (Bernstein)).) In addition, absolute values of melting points obtained using different instrumentation cannot be directly compared. (*Id.* (citing JTX-120-7 n.7).)

Moreover, the court finds credible the plaintiffs' contention that the use of instantaneous melting point is particularly important for armodafinil. Specifically, Drs. Mallamo and Myerson detail that the Kofler hot bar "procedure is clearly rapid and is very useful for substances which tend to decompose upon gradual heating." (*Id.* at 16 (citing PTX-147-10).) Research at Cephalon confirmed that non-instantaneous methods using slow heating rates—such as differential scanning calorimetry—were not appropriate for armodafinil because armodafinil can degrade during these slower melting tests.[35] (*Id.* (citing JTX-111-1; Tr. at 659:18-660:14, 706:4-16 (Mallamo); Tr. at

[35] While the defendants' expert, Dr. Lee, alleged that he did not observe any decomposition of the samples, the plaintiffs persuasively note that Dr. Lee did not actually observe any of the melting point determinations in his experiments, such that his lack of observation is not dispositive on this point. (*Id.* at 16 n.17 (citing Tr. at 327:17-328:9 (Lee)).)

737:12-738:13, 778:15-22 (Myerson)).) In fact, the court notes that this conclusion is consistent with the data presented to the PTO, which shows that Form I can exhibit widely variant "melting points"—melting points from 146.9 to 157 degrees Celsius—when measured by capillary melting point tests. (*Id.* (citing JTX-120-7 n.7, -23; Tr. at 659:2-17 (Mallamo)).) In reaching this finding, the court also notes that, because Dr. Lee only measured two different armodafinil samples using one method, his testing does not contradict the fact that Form I armodafinil can exhibit widely variant melting points using the capillary method. (*Id.* at 16 n.18 (citing Tr. at 336:21-337:4 (Lee); Tr. at 659:2-17 (Mallamo); JTX-210-7 n.7, -23).) Dr. Hollingsworth's melting point test also exhibits this wide variability. (*Id.* (citing Tr. at 139:10-140:22 (Hollingsworth)).) Thus, because neither Dr. Hollingsworth nor Dr. Lee attempted to correlate and calibrate their melting points to the instantaneous melting point reported in the '855 Patent, and as Dr. Myerson credibly testified, "absolute [melting point] values obtained using different instrumentation cannot be directly compared," the defendants have failed to demonstrate the accuracy of their experiments.

The court further notes that it reaches this conclusion despite Dr. Hollingsworth's assertion that various polymorphic forms of armodafinil produced from Preparation I would have converted to Form I during testing on a Kofler hot bar. *See* Tr. at 142:21-146:1 (Hollingsworth). Specifically, the court finds that this contention is refuted by the fact that the instantaneous melting points of Form II and of the mixtures involving Form II and IV could be discretely measured and recorded as data points. (D.I. 314 at 15 n.15 (citing JTX-120-22).) Moreover, Dr. Hollingsworth's conclusion is further undermined by his own testimony that he has never used or seen a Kofler hot bar, and that any product converted to Form I on the hot bar would not be a "pharmaceutical composition" and, thus, would not meet the limitations of asserted Claims 6 and 9. (*Id.* (citing Tr. at 191:14-192:7, 189:2-9 (Hollingsworth)).)

ii. The Preparation I and Form I Yields

The court further concludes that the defendants have failed to demonstrate that their experts produced Form I by performing Preparation I and, further, that their experiments were accurate because their yields differed from the yield listed in Preparation I. Specifically, the court finds that the '855 Patent indicates that the "overall yield" for Preparation I—after completing all steps of (a) to (d)—is 32%. *See* JTX-10303 at 3:51; *see also* Tr. at 649:21-650:3 (Mallamo); Tr. at 736:8-23 (Myerson). Specifically, the '855 Patent states yields of 42% from step (a), about 100% from step (b), 85% from step (b), and step (d) must have a yield of about 90%. (D.I. 314 at 16 (citing Tr. at 332:3-17 (Lee); Tr. at 650:4-14 (Mallamo)).) Dr. Mallamo testified that such a yield is consistent with his experience. *See* Tr. at 650:4-14 (Mallamo).

However, in Dr. Hollingsworth's experiments, he had an overall yield of 8.2% for Run 1/2 and an overall yield of 9% for Run 3/4. *See* Tr. at 735:3-9, 735:17-736:3 (Myerson). Clearly, Dr. Hollingsworth's yields are far lower than the 32% overall yield reported in Preparation I. In addition, Dr. Lee had an overall yield of 7.4% for Run I (Sample 10) and an overall yield of 3.2% for Run 2 (Sample 12S). (D.I. 314 at 17 (citing Tr. at 333:12-20 (Lee)).) Dr. Lee acknowledged on cross-examination that, if Preparation I requires a 32% yield, a point with which Dr. Lee disagreed, then the difference between his yield and the required yield was much greater than could be accounted for by reasonable experimental error. (*Id.* (citing Tr. at 329:3014, 333:21-25 (Lee)).)

In response to the plaintiffs' assertion that the defendants' experts generated yields lower than those required for Preparation I, the defendants note that the '570 Patent, which discusses Preparation I of the '855 Patent in detail, explains that the "overall yield" at the end of Preparation I is 5.7%, a figure much closer to defendants' experts' yields. (D.I. 319 at 38 (citing JTX-1.19 col. 2, ll. 5-13; JTX-40.37; Tr. at 301:7-12, 343:9-15 (Lee)).) The defendants also note that the '570

Patent discloses that the 25% overall yield of the synthesis process described therein is "markedly greater than that obtained in U.S. Patent No. 4,927,855." *See* JTX-1.25 col. 14, ll. 35-43; Tr. at 342:7-23 (Lee). The defendants further maintain that, because Cephalon has not filed a Certificate of Correction correcting the allegedly inaccurate yield numbers, the plaintiffs are simply making the argument to challenge anticipation and assert that their experts' performance of Preparation I confirms this. (D.I. 319 at 38-39.)

The plaintiffs contend, however, that the figures detailed in the '570 Patent are, in fact, inaccurate and that the overall yield of Preparation I was 32%, not the 5.7% reported in the '570 Patent specification. *See* Tr. at 686:16-20, 690:12 (Mallamo). Dr. Mallamo acknowledged this error in testimony at trial and noted that he was not aware of the mistake in the '570 Patent when he submitted his declaration to the PTO. *See id.* at 686:25-687:19, 689:12-14 689:23-690:12, 705:14-20. Dr. Mallamo further testified that a step (d) yield of only 32% would be inconsistent with Cephalon's actual experience of obtaining a very high yield using the step (d) chemistry. *See id.* at 650:4-14). In addition, the plaintiffs note that other patent literature discussing the '855 Patent also accepts 32% as the overall yield for all of Preparation I, rather than as the yield for only step (d). *See* PTX-124-3:1-11; PTX-123-3:1-14. The court found Dr. Mallamo's testimony to be credible. Nevertheless, mistakes in the '570 Patent regarding the yield of Preparation I are irrelevant here because they do not pertain to the Form I composition claims at issue. (D.I. 314 at 17 (citing Tr. at 785:18-787:10 (Myerson)).)

As the difference in yields relates to anticipation, Dr. Myerson credibly testified that such low yields are problematic because they suggest different impurity profiles. *See* Tr. at 735:17-736:7 (Myerson). This is important because, as Dr. Hollingsworth testified, the "presence of impurities can have a profound effect on the growth of crystals." (D.I. 314 at 17 (citing Tr. at

163:22-25, 227:11-23 (Hollingsworth)).) Dr. Myerson also confirmed this point in the context of Preparation I. (*Id.* (citing Tr. at 732:3-734:16 (Myerson)).) In light of Dr. Mallamo's testimony and the evidence before it, the court concludes that the yield percentage the defendants' experts obtained from their reproduction of Preparation I does not alone demonstrate anticipation by clear and convincing evidence and does not shift the court's overall anticipation conclusion.

4. **Conclusion**

In view of the foregoing, the court concludes that the defendants have failed to demonstrate inherent anticipation by clear and convincing evidence. As noted, the defendants' experts' experiments did not show that the result of Preparation I is a product in which Form I armodafinil is the only active pharmaceutical ingredient, as at least one experiment resulted in the formation of a Form I/Form II product. For the reasons stated above, the court concludes that the claim construction "consisting essentially of the specified pharmaceutically active ingredient"—a construction on which the parties agreed and the court did not construe during *Markman*—requires that Form I be the only pharmaceutically active ingredient.

Importantly, however, even assuming that the claim term allows for the presence of another pharmaceutically active ingredient, the court finds that the defendants have failed to demonstrate that their experts' experiments were conducted consistent with Preparation I or that their selection of such variables as cooling rate, ethanol grade, and concentration, realized the full scope of reasonable experimental possibilities in Preparation I. Specifically, because the '855 Patent does not disclose many details for its procedure, skilled artisans would have to use their judgment to complete the experiment. As detailed above, the evidence presented at trial demonstrated that several reasonable selections were available to one of skill in the art and that even slight differences in procedure may lead to differences in the form of armodafinil produced. The defendants' experts,

however, used a limited set of testing parameters, which, after reading the '570 Patent, they would have understood to favor the formation of Form I. *See Glaxo Group*, 376 F.3d at 1348-49. This limited testing and selection of variables, where reasonable alternatives were available, does not show clearly and convincingly that Form I armodafinil is the necessary and inevitable result of Preparation I.

Finally, the court notes that the '855 Patent was before the PTO during prosecution of the '570 Patent. The PTO originally rejected the pending Form I armodafinil claims as either anticipated by or obvious in part over the '855 Patent. *See* JTX-2-1412 to 1414. After Cephalon responded, however, the PTO withdrew the rejection (1) acknowledging that the '855 Patent "is silent regarding the conditions that were used to perform the recrystallization," (2) noting that "Applicants have established by way of declarative evidence that recrystallization of [armodafinil] from ethanol, as taught by the Lafon '855 Patent, leads to the production of various polymorphic forms of the compound, depending upon the particular conditions employed to perform the recrystallization, and (3) concluding that "it cannot be said that practicing the teachings of the Lafon patent would necessarily result in a polymorphic form of [armodafinil] as recited in the instant claims." PTX-122-2 to 3; *see also* Tr. at 757:22-759:11 (Myerson). While the PTO did not have the defendants' experts' testing to consider, that testing only involved a limited set of conditions that do not refute the testing Cephalon provided. Moreover, Cephalon presented evidence to the PTO showing that Form I armodafinil does not have an instantaneous melting point consistent with the melting point of Preparation I, and the defendants did not provide any rebuttal testing of this fact. Thus, the court finds that the evidence presented to the PTO and the PTO's decision to allow asserted Claims 6 and 9 further demonstrates that the defendants have not proven inherent anticipation by the required standard.

B. 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 failed to prove by clear and convincing evidence that the patent-in-suit is, 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 inquiries. *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.[36] *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" 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 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 reliance on ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected

[36] The court precluded Cephalon from relying on secondary considerations as sanction for its discovery violations. *See* D.I. 225 at 2; D.I. 293.

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 a 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) (citation omitted).

"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 unpredictablily 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. The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the patent-in-suit would have either: (1) a bachelor's degree in chemistry, chemical engineering, or related disciplines and either: (a) at least three years of experience related to organic synthesis, active pharmaceutical ingredient ("API") manufacturing and formulation, or detection and/or evaluation of solid state forms in the pharmaceutical industry, or (b) an advanced degree in chemistry, chemical engineering, or related

disciplines[37]; or (2) training as a chemist (or similar field) involved in the discovery, preparation, and/or characterization of crystal/polymorphic forms and having an advanced degree in organic chemistry, chemical engineering, or a related field, or equivalent work experiences such as at least a bachelor of science degree and about two to three years of experience preparing and characterizing crystal/polymorphic forms.[38] The court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.[39]

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

As a threshold matter, it is important to identify what the asserted claims cover. As detailed above, the asserted Claims 6 and 9 of the patent-in-suit cover a pharmaceutical composition with an active component consisting essentially of Form I armodafinil. Armodafinil is not a naturally occurring compound and was invented by Cephalon and claimed in the '855 Patent, which is directed to that molecule. *See* JTX-103-1 at Abstract. As discussed, Preparation I of the '855 Patent discloses how to synthesize armodafinil.[40] *See id.* In May 2000, Cephalon employee and named inventor of the '570 Patent, Oliver Neckebrock, performed a series of recrystallization experiments that determined that armodafinil exhibits polymorphism. *See* Tr. at 636:3-638:4, 644:16-645:10 (Mallamo); Tr. at 874:10-875:13, 879:5-21 (Neckebrock); PTX-135-4. These experiments revealed two crystal forms, designed Form I (Type I or α) and Form II (Type 2 or β).[41] *See* PTX-572-19. In June 2005, Cephalon filed U.S. Patent Application No. 10/539,918 ("the

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[37] The plaintiffs' identification of a person of ordinary skill in the art is derived from Dr. Bernstein's testimony. *See* Tr. at 545:11-547:15 (Bernstein).

[38] D.I. 259 at Ex. 3.

[39] The parties' experts testified that their obviousness conclusions would remain the same regardless of which definition of a person of ordinary skill in the art the court adopts. *See supra* note 6.

[40] Polymorphs of man-made compounds such as armodafinil must be synthesized by human effort because they do not exist in nature. *See* Tr. at 503:4-9 (Bernstein).

[41] In August 1989, Cephalon employee Pierre Leproust synthesized a solid state form of armodafinil that, as a result of Mr. Neckebrock's experiments, was eventually identified as Form I. Tr. at 645:11-25 (Mallamo); Tr. at 803:16-804:16 (Leproust); PTX-132-10 (Ref. 05/2502); PTX-392.

'918 Application") with the PTO, claiming priority to a French application filed in December 2002.[42] The application describes five different polymorphic forms of armodafinil (Forms I, II, III, IV, and V), as well as two solvates of armodafinil. *See* JTX-2-12 to -14. The application also includes XRPD fingerprint information for Form I, including interplanar spacings, reflection values, relative intensities, and the results of single crystal x-ray analysis. *See, e.g.*, JTX-1-19 to 20 at 2:48-3:10, -38 at 40:1-10. Cephalon later filed an Amendment that provided claims covering the armodafinil Form I polymorph. *See* JTX-71-2 to 3.

Both at trial and in their post-trial briefings, the defendants focused their obviousness arguments on the assertion that the '855 Patent, combined with other references the PTO did not consider,[43] invalidates the asserted claims of the patent-in-suit. Specifically, the defendants argue that a skilled artisan would have: (1) been motivated to identify the most stable polymorph of armodafinil—Form I—for use in a pharmaceutical composition; (2) expected to obtain the most stable polymorph of armodafinil using well known and merely routine techniques and predictable steps; (3) known that the D-spacings and 2-Theta values recited in the asserted claims are intrinsic to Form I and would have been measured using routine techniques;[44] and (4) been motivated to

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[42] Based on the work of Mr. Leproust and Mr. Neckebrock, and the priority date of the French application, the date of invention for the claims of the '570 Patent is prior to December 20, 2001. The defendants argued at trial that the plaintiffs used "erroneous patent evergreening techniques to extend its PROVIGIL/NUVIGIL monopoly." (D.I. 319 at 2-3.) The court rejects this argument, however, in light of its anticipation and obviousness findings.

[43] The defendants note that they presented numerous references at trial not considered by the PTO, including, for example JTX-24, JTX-32, JTX-57, and JTX-94. (*Id.* at 40 n.9.) These references were presented at trial to provide greater detail as to the state of the art in the early 2000s.

[44] The defendants assert, as a part of their obviousness argument, that the D-Spacings and 2-Theta values recited in the asserted claims are intrinsic to Form I armodafinil and, therefore, do not constitute an invention. (*Id.* at 25 (citing Tr. at 382:12-18, 389:1-3 (Cima)).) Specifically, the defendants note that, upon obtaining armodafinil's most stable form, a person of ordinary skill in the art would have known to conduct XRPD testing to properly characterize the polymorph and would have recorded these properties. (*Id.*) Therefore, the defendants contend that the plaintiffs cannot use these values to distinguish the asserted claims from the prior art.

Notably, both the plaintiffs' and defendants' experts agree that the actual crystal structure of a polymorph and the XRPD values associated with the crystal structure are inherent characteristics of the polymorph. (*Id.* (citing Tr. at 71:8-73:11 (Hollingsworth); Tr. at 382:12-18, 421:8-25 (Cima); Tr. at 607:23-608:5 (Bernstein)).) The plaintiffs, however, reference these values in connection with their argument that the crystal structure and recrystallization are unpredictable to the extent that a skilled artisan would not have a reasonable expectation of success in identifying and/or obtaining Form I. The plaintiffs do not assert that the measured values are, themselves,

make a pharmaceutical composition consisting essentially of Form I armodafinil. (D.I. 319 at 17-26.)

The plaintiffs, in response, presented testimony that a person of skill in the art did not have prior art disclosures of armodafinil to have predicted whether armodafinil would crystallize in polymorphic forms or what the structure of any of those forms would be, much less have a basis to have predicted Form I. In sum, the plaintiffs assert that the fundamental unpredictability of polymorphism and the uniqueness of armodafinil would not have allowed a skilled artisan to have a reasonable expectation of success that armodafinil is polymorphic. Because these arguments dominated the parties' invalidity arguments at trial, the court will focus its discussion on whether the development and use of Form I armodafinil in a pharmaceutical composition would have been obvious to a skilled artisan in 2002 based on the '855 Patent and the other references discussed at trial.

a. Whether Obtaining Form I Armodafinil Would Have Been Obvious to a Person of Skill in the Art in 2002

The defendants assert that a skilled artisan in 2002 would have been motivated to obtain armodafinil's most stable polymorph—Form I—because the therapeutic effectiveness of armodafinil would have been well known in the art. (D.I. 319 at 17.) The defendants present several arguments in support. First, the defendants note that the '855 Patent expressly discloses the synthesis of crystalline armodafinil and teaches its therapeutic use in pharmaceutical compositions for administration to humans. (*Id.* (citing JTX-103.1-.5 Abstract, col. 2, ll. 61-66, col. 3, ll. 5-57, col. 6, ll. 44-67, col. 8, ll. 26-29; Tr. at 381:11-12, 388:7-9, 429:23-430:7 (Cima)).) In addition, the '855 Patent specifically discloses that those compositions "consist essentially of"

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the invention. Therefore, the court addresses this aspect of the defendants' obviousness argument in connection with its discussion of the level of predictability in the crystallization and polymorphism fields. *See* Section III.B.3.a.

armodafinil. (*Id.* (citing JTX-103.5, claims 2-6; Tr. at 383:6-9, 425:13-403:7 (Cima); Tr. at 623:18-20 (Bernstein)).) Second, the defendants argue that, because armodafinil was known to be crystalline, a skilled artisan would have known that, like all crystalline compounds, armodafinil has a most stable polymorph. (*Id.* (citing Tr. at 390:21-23, 436:18-21, 437:5-6, 467:16-18 (Cima)).) The defendants' obviousness expert, Dr. Michael Cima, testified that the stable form of a polymorph has the lowest thermodynamic energy and that less stable forms naturally tend to transform into the most stable form over time. *See* Tr. at 390:6-20, 453:20-23 (Cima).

Third, the defendants contend that, by the early 2000s, it was well known in the art that the most stable polymorph "is by far and away the preferred in a marketed [drug] formulation." (D.I. 319 at 18 (citing Tr. at 396:5-8 (Cima); Tr. at 827:11-16 (Besselievre); Tr. at 840:22-841:11 (Coquerel); Tr. at 864:20-865:10 (Rose)).) In addition to Dr. Cima's testimony in support of this contention, the defendants also identified several references stating, collectively, that the most stable polymorphic form is the preferred form for drug formulation.[45] (*Id.*) Identification of the most stable polymorph is crucial, the defendants charge, because of "the significant adverse consequences associated with a change in the polymorphic form during [development,] manufacture[,] or storage." (*Id.* (citing Tr. at 617:2-8 (Bernstein); Tr. at 396:5-8, 298:10-13, 399:2-5, 453:20-23 (Cima); JTX-104.1; JTX-21.4; JTX-5.1-.5).)

[45] Specifically, the defendants referenced: Bryn, S. et al, *Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*, Pharm. Res. 12(7):945-954 (1995) (JTX-021); Chemburkar et al., *Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development*, 4 Organic Process & Research Development, 413-417 (2000) (JTX-0005); Gu, Chong-Hui et al., *Polymorph Screening: Influence of Solvents on the Rate of Solvent-Medicated Polymorphic Trnasformation* 90 (11) Journal of Pharmaceutical Sciences 1878-1890 (2001) (JTX-104) ("Usually, the most stable polymorphic form is preferred in a market formulation . . ."; ""Overlooking the most stable polymorph may cause a failure of a marketed product due to phase transformation during storage . . ."); Guillory, J. Keith, *Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*, Polymorphism in Pharmaceutical Sciences 183-226 (Harry G. Brittain, ed., 1999) (JTX-27) ("It is essential to ascertain whether the crystalline material . . . is thermodynamically stable before conducting pivotal trials, since a more stable form may be obtained subsequently, and it may be impossible to produce the metastable form in future synthesis."); Morissette et al., *High-Throughput Crystallizations: Polymorphs, Salts, Co-Crystals and Solvates of Pharmaceutical Solids* 56:275-300 (2004) (JTX-0007).

Moreover, the defendants note that skilled artisans would have known to obtain and use the most stable form for drug development and manufacture because of Abbott Laboratories' ("Abbott") experience with its drug ritonavir, wherein Abbott failed to confirm that it had the most stable polymorphic form of the API and proceeded to market a less stable form. (*Id.* (citing JTX-5.1; PTX-585.130 at pp. 248-49).) Because the less stable form converted to the most stable form during manufacturing, Abbott was forced to reformulate its product after spending hundreds of millions of dollars to develop and market the product, allowing time for competitors to take over the market. (*Id.* at 18-19 (citing JTX-104.1; Tr. at 395:21-397:18 (Cima)).) Thus, the defendants assert that a person of skill in the art would have had a commercial motivation to identify and use the most stable polymorphic form of armodafinil in a pharmaceutical composition and, because Form I is the most stable polymorph of armodafinil, a skilled artisan would have been led directly to Form I. (*Id.* at 19.)

However, in consideration of the evidence presented at trial and for the reasons that follow, the court disagrees and concludes that the defendants have not proven by clear and convincing evidence that obtaining Form I armodafinil would not have been obvious to a person of skill in the art in 2002. As the plaintiffs' expert, Dr. Bernstein, explained in testimony the court finds credible, polymorphism is inherently unpredictable and, based on the unique nature of armodafinil, a skilled artisan would not have had a reasonable expectation of success that armodafinil is polymorphic in 2002. (D.I. 314 at 31 (citing Tr. at 496:3-503:2, 511:17-25, 547:16-18, 548:1-551:14, 562:16-563:17, 586:9-588:22 (Bernstein)).) Notably, the unpredictable nature of polymorphism was discussed in publications at the time and, in fact, in some of Dr. Cima's publications. For instance, publications at the time discussing polymorphic crystallization experiments noted that: "[t]here are

no failsafe methods to predict the extent of polymorphism of a given compound"[46]; "[u]nlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of . . . polymorphs have defied prediction"[47]; and "[t]he large number of crystallization trials performed in these experiments reflects the reality that nucleation rate has an extremely non-linear dependence on the experimental conditions, and as such, the probability of a chance occurrence of a particular form is increased by a [high throughput] approach."[48]

The unpredictability of crystallization and polymorphism was also detailed in other publications and known by people actually working in the field at the time. (*Id.* at 32 (citing Tr. at 551:12-14 (Bernstein); Tr. at 823:23-824:12 (Blomsma); Tr. at 836:23-837:4, 843:9-18 (Coquerel)).) For example, a 2001 paper by Dr. Zaworotko, one of the defendants' experts who submitted an expert report on their behalf, characterized efforts to predict crystal structures as "continu[ing] to represent a challenge of the highest level of scientific and technological importance," given that "it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition." *See* JTX-86-2.

The evidence at trial further demonstrated that the crystal structure itself is fundamentally unpredictable. *See* Tr. at 496:3-500:18 (Bernstein). Even Dr. Cima agreed that the specific structure of Form I—i.e., the physical dimensions within the crystal and corresponding interplanar XRPD limitations of Claim 6 and its properties—could not have been reasonably predicted, though he disagreed that this information would be relevant for a skilled artisan seeking to obtain and use

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[46] *See* JTX-35-1: Peterson, M.L et al., *Iterative High-Throughput Polymorphism Studies on Acetaminophen and an Experimentally Derived Structure for Form III*, 1241 Am. Chem. Soc., 10958-10959 (2002).

[47] *See* JTX-7-22: Morissette et al., *High-Throughput Crystallization: Polymorphs, Salts, Co-Crystals and Solvates of Pharmaceutical Solids* 56:275-300 (2004).

[48] *See id.* at -4.

Form I armodafinil. *See id.* at 420:12-421:17, 435:15-436:25 (Cima). Even if there were a way of predicting that a compound would be polymorphic and what the crystal structures might be, the evidence presented shows that person of skill would not know how to make a specific polymorph or predict its properties. *See id.* at 500:11-18, 505:8-10, 505:20-507:7, 548:1-549:5 (Bernstein). Thus, because the existence, structure, and methods of making polymorphs were not predictable, crystal forms could only be prepared and identified by trial and error experimentation. *See* Tr. at 555:9-556:3, 571:24-572:12 (Bernstein); Tr. at 447:8-12 (Cima); Tr. at 233:3-234:3 (Hollingsworth). Notably, even Dr. Cima's expressed the same understanding in his peer-reviewed publications.[49]

With respect to armodafinil in particular, the court finds, based on the foregoing, that researchers in the field could not have predicted whether it would exhibit polymorphism or what recrystallization conditions would generate a particular crystalline form or solvate. (D.I. 314 at 33 (citing Tr. at 828:18-21, 829:2-9, 829:13-830:10, 841:25-843:2 (Coquerel); Tr. at 732:24-733:12, 734:17-25, 757:22-759:11 (Myerson); Tr. at 547:4-15 (Bernstein)).) The prior art disclosure of the enantiomeric molecule armodafinil consisted entirely of the '855 Patent and the defendants did not present secondary references to be combined with or to modify that Patent. (D.I. 314 at 30-31 (citing Tr. at 28:14-18; Tr. at 381:2-383:24, 425:1-16 (Cima)).) As Dr. Bernstein explained, in testimony the court finds credible, the '855 Patent did not provide any basis for a skilled artisan to have known whether armodafinil would crystallize in polymorphic forms or what the structure of

[49] *See* PTX-26-4 ("[T]he only manner in which one can be assured of having a complete knowledge of the polymorphic landscape on which to base a development choice (usually the most thermodynamically form) is to subject the API to a variety of crystallizing conditions that can expose the diversity of forms."); JTX-7-22 ("[D]iscrete crystal forms are considered non-obvious and patentable" and, due to the unpredictability, "in order to obtain patent protection on these forms . . . it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials."); *see also* Tr. at 468:4-8 (Cima). Dr. Cima also acknowledged that the statements of unpredictability and patentability in his 2004 article are not limited to metastable forms. *See* Tr. at 467:6-468:3 (Cima).

those forms would be, due to the unique nature of armodafinil and the unpredictability of polymorphism. (*Id.* (citing Tr. at 496:3-503:2, 511:17-25, 547:16-18, 548:1-551:14, 562:16-563:17, 586:9-588:22 (Bernstein)).) In fact, prior to the '570 Patent, there was no disclosure of Form I armodafinil or anything to indicate that Form I armodafinil was the most stable form. (*Id.* at 34 (citing Tr. at 571:7-12 (Bernstein)).)

Moreover, beyond the absence of any express disclosure, there was no implicit disclosure of Form I armodafinil in the '855 Patent.[50] First, while the result of Preparation I is described as being "in the form of white crystals" that was "recrystallized from ethanol," the '855 Patent is silent was to whether it may or may not have been a solvate, hydrate, a mixture of materials, or a different form of armodafinil. (*Id.* (citing Tr. at 553:7-21 (Bernstein); Tr. at 838:3-839:7 (Coquerel)).) Further, other than stating "recrystallization from ethanol," the '855 Patent does not specifically address any of the multitude of crystallization conditions available and that were set out in Table 1 of Dr. Cima's paper, *High-Throughput Crystallization: Polymorphs, Salts, Co-Crystals and Solvates of Pharmaceutical Solids*.[51] *See* JTX-7; *see also* Tr. at 567:6-9 (Bernstein). The '855 Patent also does not provide any indication as to what thermal conditions might lead to Form I. (D.I. 314 at 34 (citing Tr. at 566:25-567:5 (Bernstein)).)

Second, the reported melting point for the Preparation I material does not indicate whether armodafinil could be polymorphic and is consistent with the material being a solvate. (*Id.* at 34-35 (citing JTX-103-3 at 3:55; Tr. at 554:3-10 (Bernstein)).) The evidence presented demonstrates that the existence of solvates is not hypothetical, as it was later discovered that an ethanol solvate

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[50] In addition, there was no implicit disclosure of the polymorphism of armodafinil generally or Form I in particular and these would not have been reasonably predictable from the potential pharmaceutical use disclosed in the '855 Patent. *See* Tr. at 569:16-20 (Bernstein). To the contrary, as Dr. Bernstein explained and as was expressed in the peer-reviewed literature, pharmaceutical compounds are no more polymorphic than other compounds. *See id.* at 493:21-494:1, 569:21-571:1; PTX-28-2.

[51] Table I in Dr. Cima's article lists over thirty of the most notable composition and processing variables available that can affect polymorphic form. *See* JTX-7-3.

of armodafinil may be formed. (*Id.* at 35 (citing Tr. at 252:17-253:14 (Hollingsworth)); PTX-129-3).) Thus, the '855 Patent disclosure of "white crystals" prepared from ethanol would not have suggested to a skilled artisan that armodafinil is polymorphic. (*Id.* (citing Tr. at 562:16-563:7 (Bernstein); Tr. at 838:23-839:7 (Coquerel)).) Rather, "white crystals" does not disclose any information beyond describing the substance. (*Id.*)

Third, while the molecular structure of the armodafinil molecule was known based on the '855 Patent, the court finds that that Patent provides no basis to predict polymorphism of armodafinil Form I. *See* Tr. at 556:4-14. Specifically, the inability to predict polymorphism from molecule structure was known in the literature and was not contradicted at trial by any material on which Dr. Cima relied. For instance, an article by Professor Gautam Desiraju, one of the leading researchers in organic solid-state chemistry, explained that there were "major obstacles in routinely predicting crystal structures from molecular structure," including that "the crystal structures of many 'simple' organic compounds need not be simple at all" and "chemists seem unable to accurately foresee" how functional groups of molecules will interact to form crystals. *See* JTX-23-2; *see also* Tr. at 556:15-558:9 (Bernstein); JTX-86-2). This inability to predict polymorphism from molecular function was also discussed in Dr. Bernstein's 2011 article, which explained that there is no evidence of a correlation between the number of hydrogen-bonding functionalities and the tendency to form multiple crystal forms.[52] Dr. Bernstein also provided persuasive, concrete examples as evidence of this point. For instance, neither sucrose nor ibuprofen were known to be polymorphic despite having been prepared in large quantities for long periods of time. *See* Tr. at 558:14-559:19 (Bernstein); PDX-1-14. Thus, Dr. Bernstein explained that there was no way to

[52] The court concludes, based on Dr. Bernstein's credible testimony, that Dr. Cima's assertions to the contrary are unsupported. *See* Tr. at 439:7-25 (Cima); Tr. at 559:25-562:15 (Bernstein).

predict whether armodafinil would be consistent or inconsistent with the absence of known polymorphism for sucrose and ibuprofen. *See* Tr. at 559:20-560:23 (Bernstein).

Fourth, contrary to Dr. Cima's assertions, the court finds that neither the polymorphism of armodafinil nor Form I was reasonably predictable based on the polymorphism of racemic modafinil because, importantly, there was no evidence that modafinil is polymorphic.[53] The defendants also did not present evidence in the prior art that a polymorphic racemate would suggest a polymorphic enantiomer or single enantiomer. (D.I 314 at 36 (citing Tr. at 547:22-25, 548:1-20, 567:19-23 (Bernstein)).) Dr. Bernstein, however, presented examples of cases where the racemic compound exhibits polymorphism but the enantiomer does not. (*Id.* (citing Tr. at 567:24-569:9 (Bernstein); PDX-1-15; JTX-8-10 (racemic crystals preferred over enantiomeric crystals).)

Fifth, the court disagrees with the defendants' assertion that Claims 6 and 9 would have been obvious to a person of ordinary skill in the art because that skilled artisan would have been motivated to find the most stable polymorphic form of armodafinil, Form I, and would have a reasonable expectation of success in finding Form I because it would have been easy to obtain. Rather, the court finds that the "motivation" to identify armodafinil's most stable form for pharmaceutical composition, is not equivalent to a skilled artisan having a reasonable expectation of success in obtaining Form I armodafinil for several reasons. Importantly, and as Dr. Bernstein credibly explained, the "most stable" form of a crystal does not refer to a specific material, but, instead, is a relative term that refers to the lowest energy crystalline form known at a given time. (*Id.* at 37 (citing Tr. at 510:2-511:16 (Bernstein); PDX-1-16; PDX-1-17).) Indeed, as the Abbott ritonavir example shows, more stable forms of a crystal can be identified after significant testing. (*Id.* (citing Tr. at 507:14-23, 512:10-513:16, 531:9-533-4 (Bernstein); Tr. at 733:16-734:15

[53] As the plaintiffs note, the defendants withdrew the one piece of evidence in support of this argument, JTX-11, because they could not establish it to be prior art. *See id.* at 413:19-415:24.

(Myerson); Tr. at 396:12-397:21 (Cima); JTX-104-1).) To this end, in the court's view, Dr. Cima's description of the skilled artisan's alleged motivation to develop new and improved crystalline forms does not render obvious the specific solution of Form I.[54] (*Id.* at 38 (citing Tr. at 511:14-25, 512:25-513:3 (Bernstein)).)

Moreover, it is clear from the evidence that for persons of skill, other considerations, beyond thermodynamic stability are involved in the calculus that leads to the selection of a polymorph or solid form for use in a pharmaceutical product. Specifically, some drug products employ metastable or amorphous forms of the API because the "most stable" form has undesirable characteristics. (*Id.* (citing Tr. at 512:17-20, 530:8-11, 617:11-23 (Bernstein); Tr. at 441:22-442:16 (Cima); Tr. at 224:9-226:19 (Hollingsworth)).) For instance, a solid material must be sufficiently soluble for its intended pharmaceutical use, yet, solubility and stability are inversely related—the more stable the polymorph, the less soluble it will be. (*Id.* at 39 (citing Tr. at 832:22-833:4 (Coquerel); Tr. at 522:5-525:7, 529:3-530:7 (Bernstein); Tr. at 676:10-18 (Mallamo)).) Ritonavir is an example where the later discovered "most stable" form proved undesirable due to its low solubility. (*Id.* (citing Tr. at 531:9-532:7 (Bernstein)).) Similarly, the more stable polymorph of chloramphenicol palmitate has almost no bioavailability compared to the less stable form. (*Id.* (citing Tr. at 522:5-525:7 (Bernstein)).) Here, there was no disclosure in the prior art as to Form I armodafinil or that Form I was the most stable polymorph and, moreover, its relative stability could not be anticipated because relative energies are not predictable. (*Id.* at 38 (citing Tr. at 513:17-20, 617:11-23 (Bernstein)).)

[54] Dr. Bernstein explained that the motivation of a skilled artisan to find the "most stable form" of armodafinil would be no different than the motivation to find an effective drug with the lowest toxicology profile, which likewise does not render obvious a specific drug that has the lowest toxicology profile. *Id.* at 572:24-573:12 (Bernstein).

In view of the foregoing, the court concludes that a person of ordinary skill in the art would not have had a reasonable expectation of success in obtaining the specific Form I armodafinil claimed in the '570 Patent.

b. Whether a Person of Ordinary Skill in the Art Could Have Obtained Form I Armodafinil Through Routine Experimentation and Techniques

The defendants next assert that a person of ordinary skill in the art in 2002 would have expected to obtain the most stable polymorph of armodafinil using well known and merely routine techniques, such as ageing and polymorph screening, because the most stable polymorph is "by far the easiest [] to obtain." (D.I. 319 at 19-20.) Specifically, the defendants allege that a skilled artisan in the early 2000s would have known of a technique called ageing, also known as solvent-mediated polymorphic transformation, and would have known it to be an efficient method to obtain the most stable polymorph of a crystalline compound. (*Id.* at 20 (citing Tr. at 401:16-402:8, 402:13-15, 402:22-403:2 (Cima); JTX-104.1-.2 ("An efficient method to discover the most stable polymorph is the technique of solvent-mediated polymorphic transformation.").) The defendants note that Dr. Bernstein even acknowledged that slurrying, a type of ageing involving mechanical mixing, is "often used" in industrial crystallizations and "leads to a conversion generally of a mixture of polymorphs to the most stable form." (*Id.* (citing Tr. at 576:24-578:15 (Bernstein)).)

During the ageing process, crystals are allowed to remain in contact with the solvent and the metastable polymorphs dissolve and recrystallize into a more stable form, continuing until only the most thermodynamically stable polymorph remains. (*Id.* (citing JTX-27.8; JTX-104.2); Tr. at 403:23-404:6 (Cima)).) Thus, the defendants assert that a skilled artisan motivated to obtain armodafinil's most stable polymorph would have a reasonable expectation of success in doing so using the ageing experiment. (*Id.* at 20-21 (citing Tr. at 404:21-406:13 (Cima)).) Moreover, the

defendants note that that expectation of success would be reinforced by the disclosure in the '855 Patent of crystalline armodafinil and ethanol as the appropriate solvent for use in ageing armodafinil. (*Id.* at 21 (citing Tr. at 404:14-20 (Cima)).) Likewise, Cephalon's own documents illustrate that a skilled artisan would have reasonably expected to obtain Form I armodafinil through an ageing experiment because Cephalon used this experiment to verify the most stable form of armodafinil and expected it to produce the most stable form. (*Id.* (citing JTX-123.19; PTX-289.2 ("If the polymorphic mixture had converted into only one crystal form, it could be concluded that the 'surviving' form was the more stable (less soluble) form at room temperature. The theory behind this conclusion is that crystals of the more soluble form will dissolve, then recrystallize as the less soluble form . . . . The process will continue until all of the solid phase has converted to the less soluble crystal form.").) Thus, the defendants contend, the '855 Patent's disclosures coupled with Cephalon's own experimentation demonstrates that a person of ordinary skill in the art would have a reasonable expectation of success in obtaining Form I through routine experimentation. (*Id.* at 21-22.)

In addition to the availability of ageing experiments, the defendants assert that a skilled artisan in 2002 would have reasonably expected to obtain armodafinil's most stable polymorph through a conventional polymorph screen technique. (*Id.* at 22 (citing Tr. at 406:14-407:13 (Cima)).) Specifically, the defendants note that by the early 2000s, it was widely recognized that most drug compounds exist in multiple polymorphic forms and that there is an importance in examining polymorphism even for those artisans seeking the most stable polymorph form as a drug product. (*Id.* at 22-23 (citing JTX-22.4, .6; JTX-27.5 ("Those who study polymorphism are rapidly reaching the conclusion that all compounds . . . can crystallize in different crystal forms or

polymorphs"); JTX-94.7; PTX-28.3; JTX-58.19 ("[I]t is clear that probably every organic medicinal can exist in different polymorphs"); Tr. at 594:11-595:15 (Bernstein)).)[55]

Beyond this general knowledge, the defendants cite the FDA's 1987 guidelines, which instructed drug developers to examine polymorphism and stressed the importance of controlling a compound's polymorphic form. (*Id.* at 23 (citing JTX-24.35; JTX-21.2; Tr. at 409:5-410:11 (Cima)).) Thus, the defendants contend that by the early 2000s it was routine practice in the pharmaceutical industry to conduct a polymorphic screen on drug candidates to confirm the most stable polymorph and identify additional metastable polymorphs. (*Id.* (citing Tr. at 406:14-407:10, 410:12-23; 416:12 (Cima); JTX-20.5-.6; JTX-21.1-.10; JTX-22.5).) The defendants further argue that a skilled artisan would have been motivated to screen armodafinil because, "like almost every other crystalline drug compound," it could exist in multiple polymorphic forms and it has characteristics associated with polymorphism, such as low solubility in water and a molecular weight below 350. (*Id.* (citing Tr. at 411:11-16, 412:4-12 (Cima); JTX-22.6; JTX-27.5; JTX-103.3 col. 3, ll. 51-53; PTX-585.127 at p. 242; Tr. at 530:12-22, 592:4-593:8 (Bernstein)).) Dr. Bernstein agreed that if the product obtained from Preparation I were a candidate to be an active ingredient in a pharmaceutical composition, there would have been a motivation to perform polymorphic screening. (*Id.* at 24 (citing Tr. at 618:4-10 (Bernstein)).)

In sum, the defendants argue that, for commercial success and regulatory reasons, a skilled artisan would have been motivated to conduct a polymorph screen of armodafinil and that it would have been "a simple and routine matter for [that artisan] to identify the most stable polymorph" using this technique. (*Id.* (citing Tr. at 406:14-407:10, 416:13-21 (Cima)).) Dr. Cima testified

[55] The defendants note that Dr. Walter McCrone, who Dr. Bernstein acknowledged to be a historically prominent scholar, concluded that every compound has different polymorphic forms. (D.I. 319 at 22 (citing Tr. at 594:11-595:15 (Bernstein)).)

that a person of ordinary skill in the art would have expected to obtain the most stable polymorph of armodafinil at least ninety-percent of the time from a conventional polymorphic screen. Tr. at 381:18-24, 416:22-417:3 (Cima). Moreover, Dr. Cima opined that a skilled artisan would have known how to adjust the parameters of a polymorph screen to ensure the formation of armodafinil's most stable polymorph. *See id.* at 417:4-14. Thus, the defendants contend, the "evidence conclusively establishes that a [person of ordinary skill in the art] would have had more than a reasonable expectation of success of obtaining armodafinil's most stable polymorph—Form I—through a conventional polymorphic screen." (D.I. 319 at 24 (citing Tr. at 411:18-23, 416:22-417:3, 418:3-15, 447:13-21 (Cima)).)

However, for the reasons that follow, the court concludes that the defendants have failed to demonstrate clearly and convincingly that a person of ordinary skill in the art in 2002 would have a reasonable expectation of success of obtaining Form I armodafiinil using routine techniques and methods. First, and as Dr. Bernstein explained in testimony the court finds credible, even assuming that there would have been a motivation to obtain the "most stable" form of armodafinil, a skilled artisan would have expected to resort to trial and error experimentation, using a large number of conditions, to try to make this form. (D.I. 314 at 39 (citing Tr. at 500:11-18 (Bernstein)).) Specifically, trial and error crystallization experimentation is necessary because polymorphs are unpredictable. (*Id.* (citing Tr. at 571:24-572:23 (Bernstein); Tr. at 823:7-14 (Blomsma)).) Crystallizing new polymorphs often requires hundreds to thousands of experiments that analyze the effects of various parameters such as temperature, solvent and solvent mixtures, mixing time, cooling rates, stirring rates, and concentrations, as well as methods and processes for precipitation, cooling, evaporation, slurry, and thermo-cycling. (*Id.* at 40 (citing JTX-18-43 at ¶ 6; Tr. at 575:18-576:21 (Bernstein)).)

For example, the plaintiffs cite to a May 2002 article co-authored by Dr. Cima, which shows that, at that time, 7,776 crystallization experiments, representing 2,592 unique conditions, were used in experiments for polymorphs of acetaminophen. (*Id.* (citing JTX-35-2; PTX-38-3; Tr. at 580:23-581:9, 582:3-19, 583:8-13 (Bernstein)).) In addition, for each solvent system, several other parameters would be varied, including the heating parameters, cooling, stirring, etc. (*Id.* (citing Tr. at 583:14-18 (Bernstein)).) The large number of conditions used reflects the fact that the authors, including Dr. Cima, could not predict which conditions to use or the results of their experiments. Tr. at 582:20-25 (Bernstein). The unpredictability of polymorph crystallization further required the use of multiple replicates and these experiments were run in triplicate because crystallization results are not necessarily reproducible even under seemingly identical conditions. (D.I. 314 at 40 (citing JTX-35-2; Tr. at 583:19-585:19 (Bernstein); Tr. at 823:15-22 (Blomsma)).)

The difficulty presented by the large number of crystallization conditions is also reflected in Dr. Cima's 2002 patent application, which states that "[a]t present, industry does not have the time or resources to test hundreds of thousands of combinations to achieve an optimized solid form[]. At the current state of the art, it is more cost effective to use non-optimized or semi-optimized solid-forms in pharmaceutical and other formulations." *See* PTX-27-12 at ¶ 30; *see also* Tr. at 579:17-580:16 (Bernstein). In view of the foregoing, the court finds Dr. Bernstein's testimony on this issue more credible than Dr. Cima's litigation testimony that only metastable forms, which he contends are not used in pharmaceuticals, are unpredictable. *See* Tr. at 442:20-21, 465:7-468:3 (Cima). The court also concludes that the number of crystallization conditions was so large that, even if a "most stable" crystal form could have been predicted, a person of ordinary skill in the art would not have a defined, finite set of reasonably predictable experiments or variables and would have had to rely on trial and error experimentation.

Second, this conclusion is reinforced by the fact that there were no specific teachings or suggestions in the prior art to study armodafinil, notwithstanding the twelve years between publication of the '855 Patent on the enantiomer and the filing of the '570 Patent. (D.I. 314 at 41 (citing Tr. 573:21-574:4 (Bernstein)).) Moreover, and contrary to Dr. Cima's conclusion that a skilled artisan would know what conditions to use in a polymorph screen, Dr. Bernstein testified persuasively that the prior art did not teach or suggest a limited number of conditions (i.e., solvents, concentrations, cooling, heating, and stirring rates) that would be tested in screening experiments for armodafinil.[56] Tr. at 573:13-20, 575:11-14, 586:9-20 (Bernstein); *see also* Tr. at 831:21-832:11 (Coquerel). To this end, there was on way to reasonably predict the outcome of any vast number of possible conditions that could have been chosen, as the selection of certain sets of conditions, but not others, could have resulted exclusively in forms other than Form I or mixtures of forms. (D.I. 314 at 41 (citing Tr. at 573:13-20, 575:11-14, 586:9-20 (Bernstein); JTX-38-42 (describing the conditions for Example No. ON II/149 H, which yielded Form II); Tr. at 198:1-10, 210:5-12 (Hollingsworth); Tr. at 366:19-25 (Robie)).) Thus, the court finds that the absence of known test conditions in the prior would not have allowed a person of ordinary skill in the art to anticipate a reasonable expectation of success.

Third, and with respect to the defendants' assertion that the ageing technique was known and would have allowed a skilled artisan to obtain Form I, the court disagrees that they have proven this by clear and convincing evidence. Specifically, the defendants derive their various ageing, slurry, or solvent-mediated transformation methods from the Gu article. *See* JTX-104-1-2. Importantly, however, this article does not disclose any general applicable method to obtain the

[56] The court notes that, while the '855 Patent states that the product of Preparation I was "recrystallization from ethanol," it omits key information necessary to conduct a specific recrystallization experiment, as discussed above in connection with the defendants' anticipation argument. Further, the results of being "recrystallized from ethanol" were still unpredictable. *See* Tr. at 566:13-567:9 (Bernstein); Tr. at 102:25-105:21 (Hollingsworth).

most stable form. *See* Tr. at 630:18-24 (Bernstein). Rather, as Dr. Bernstein described, these experiments can, at best, convert a mixture of forms to the most stable form already present in the mixture, but not necessarily to the most stable form overall. *See id.* at 576:22-577:24. Indeed, the Gu experiments were all based on pre-seeding the samples with ten-percent of the more stable Form II to induce transformation of the less stable Form I. *See* JTX-104-3 ("To determine the crystal growth rate of Form II, 90% of Form I and 10% of Form II were geometrically mixed . . ."); *see also* JTX-104-5, Table 1 ("Time (h) for 10% Form II to Convert to 75% Form II"). The defendants did not present evidence that Form I armodafinil would have been available in advance for use in such an ageing experiment.

In addition, and notwithstanding the pre-seeding with the most stable form, Gu shows and Dr. Cima acknowledged, that in nearly half of Gu's experiments there was no conversion of a less stable Form I to a more stable Form II. (D.I. 314 at 42 (citing JTX-104-5, Table 1; Tr. at 456:19-457:9 (Cima)).) Thus, even with pre-seeding, conversion did not occur in nearly half of the solvent systems, further evidencing that Gu's method is not a generally applicable method to obtain the most stable form of a material. (*See id.* (citing Tr. at 630:18-24 (Bernstein); DTX-201-2 ("It is still unpredictable whether one polymorph will nucleate or grow faster than another from the same liquid, even with the knowledge of their structures and thermodynamic relations."); Tr. at 223:5-224:8 (Hollingsworth)).) Therefore, even if ten-percent of armodafinil Form I was available for use in an experiment according to Gu, there would have been no reasonable expectation of success to convert a mixture of crystalline forms to a pharmaceutical composition consisting essentially of Form I as the active ingredient, as required by asserted Claims 6 and 9.

c. Whether a Person of Ordinary Skill in the Art Would Have Been Motivated to Make a Pharmaceutical Composition Consisting Essentially of Form I Armodafinil

The defendants assert that, in addition to being motivated to use Form I armodafinil in a pharmaceutical composition,[57] a skilled artisan in 2002 would have known that crystalline armodafinil could be successfully formulated into an effective pharmaceutical composition for use in humans based on the '855 Patent. (D.I. 319 at 26.) In light of these teachings, the defendants contend that a person of ordinary skill in the art would have reasonably expected to successfully formulate Form I into a pharmaceutical composition. (*Id.* (citing Tr. at 425:8-16, 432:8-16, 433:24-434:7, 460:18-461:3 (Cima)).) In support of this position, the defendants argue that there "are extremely rare circumstances where the most stable form of a compound is not sufficiently soluble and instead a metastable or pseudopolymorphic form has been developed as a drug product." (*Id.* (citing Tr. at 461:19-462:17 (Cima)).) However, the defendants contend that the '855 Patent teaches that armodafinil's most stable form would be sufficiently soluble and bioavailable to be effective in a pharmaceutical composition and that a skilled artisan would not have to resort to less stable forms. (*Id.* (citing Tr. at 401:8-15, 425:1-426:15 (Cima)).)

The defendants state that, while the '855 Patent details that armodafinil is insoluble in water, a person of ordinary skill in the art would have understood that language to indicate that armodafinil has low solubility in water at neutral pH and not complete insolubility. (*Id.* (citing Tr. at 427:2-21, 429:1-16 (Cima)).) Specifically, the defendants assert that this understanding would be evident based on the fact that the '855 Patent describes the efficacious use of armodafinil pharmaceutical compositions in human clinical trials, demonstrating that armodafinil has sufficient solubility and bioavailability when formulated into tablets or capsules. (*Id.* (citing JTX-103.4 col. 6, ll. 44-66; Tr. at 428:16-20 (Cima); Tr. at 676:10-18 (Mallamo)).) In addition, a skilled artisan would have expected armodafinil's most stable polymorph to be sufficiently soluble and

[57] *See supra* Section III.B.3.a.

bioavailable for use in a pharmaceutical composition because racemic modafinil, with lower solubility, was known to be effective in PROVIGIL, Cephalon's earlier commercial drug product and, indeed, the '855 Patent confirms that armodafinil had "better bioavailability" than racemic modafinil. (*Id.* at 26-27 (Tr. at 457:13-426:15, 427:12-21, 428:2-11 (Cima); JTX-103.4 col. 6, ll. 33-37).)

Again, however, the court disagrees and concludes that the defendants have not demonstrated by clear and convincing evidence that a person of ordinary skill in the art would have a reasonable expectation of success in developing a pharmaceutical composition consisting essentially of Form I based on the '855 Patent or routine purification techniques for the following reasons. Specifically, and as Dr. Cima acknowledged in his testimony, the '855 Patent does not disclose the solid-state form of armodafinil used in its tablets and gel capsules or indicate that it consisted essentially of Form I. (D.I. 319 at 42 (citing Tr. at 460:5-9 (Cima)).) Dr. Cima's contention that routine techniques could be used to purify the product of Preparation I is unsupported and, in any event, would not be sufficient to show that the purification would have yielded a pharmaceutical composition consisting essentially of Form I.

Rather, many steps are required between making the product of Preparation I and making a tablet of armodafinil. (*Id.* (citing Tr. at 460:2-461:3 (Cima)).) Despite this fact, Dr. Cima provided no testimony and cited no evidence as to how these steps could affect the material's crystal form, which is a critical omission considering that, as was demonstrated at trial, even small changes in processing conditions can affect a material's crystal form. (*Id.* (citing Tr. at 535:17-537:2, 564:19-565:7, 566:13-19 (Bernstein); JTX-7-3 (table summarizing many, but not all, of the variables that can play a role in the crystallization process and affect the resulting polymorphism); Tr. at 696:23-697:20 (Mallamo)).) Indeed, this was proven by Dr. Hollingsworth, who converted

a mixture containing mostly Form I armodafinil to mostly Form II armodafinil by using a second recrystallization step, the key technique Dr. Cima proposed to "purify" the product of Preparation I for pharmaceutical use. (*Id.* (citing Tr. at 195:16-200:22, 208:4-7, 210:5-12 (Hollingsworth); Tr. at 430:16-24 (Cima); Tr. at 749:11-19 (Myerson)).) For these reasons, the court concludes that Dr. Cima's contention that the Preparation I product could be purified to yield a pharmaceutical composition consisting essentially of Form I falls short of proving obviousness by clear and convincing evidence. *See* Tr. at 541:5-542:8, 553:7-21 (Cima); Tr. at 838:3-22 (Coquerel).

4. Conclusion

In view of the foregoing, the court concludes that the defendants have failed to demonstrate obviousness of the asserted claims by clear and convincing evidence. Here, for the reasons detailed above, Form I would not have been obvious because there was no more than a general motivation to find new crystal forms of armodafinil with nothing directed to the unknown Form I itself. However, for a patent challenger to establish obviousness, it is insufficient to allege a general motivation to discover an undefined solution that could take many possible forms. *See Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373-74 (Fed. Cir. 2008) ("[K]knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method.").

Moreover, in this case, the prior art did not suggest the particular structure of Form I and there was no suggestion of the structure or method of making Form I armodafinil in the alleged prior art. As Dr. Bernstein explained, a skilled artisan could not have predicted the particular structure of Form I and, likewise, nothing taught or suggested the means of obtaining Form I, which was also unpredictable. Notably, in *Pfizer, Inc. v. Apotex, Inc.*, the Federal Circuit concluded that the non-obviousness of crystal forms is distinct from the obviousness of a

pharmaceutically acceptable salt. 480 F.3d 1348 (Fed. Cir. 2007). Unlike the general notion to find a new or improved crystal form, in *Pfizer* "it [was] not the case where the prior art teaches merely to pursue a general approach that seemed to be a promising field of experimentation or gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* at 1366 (quotations omitted). Instead, a limited number of pharmaceutically acceptable salt anions would have been known to the skilled artisan, who was "capable of further narrowing that list of 53 anions to a much smaller group . . . with a reasonable expectation of success." *Id.* at 1367. There, the Federal Circuit concluded that the "type of experiments used by Pfizer to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success." *Id.*

Here, the defendants have not produced sufficient evidence to demonstrate that skilled artisans would have had reason to select the route that produced the claimed invention or that the prior art provided indication of which parameters were critical or likely to prove successful amongst the numerous testing conditions and variables available. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012); *see also Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011). Instead, the evidence presented makes clear that the prior art did not direct persons of skill in the field to the specific conditions to use for seeking new polymorphs of armodafinil and none necessarily produced material suitable for a pharmaceutical composition consisting essentially of Form I, as required by Claims 6 and 9. Consequently, because the prior art did not suggest how to make Form I armodafinil consistent with the asserted claims, the defendants have failed to demonstrate,

for the reasons expressed more fully above, obviousness by clear and convincing evidence.[58] *See Unigene Labs.*, 655 F.3d at 1361 (citation and quotations omitted) (noting that "[t]o render a claim obvious, prior art cannot be 'vague' and must, collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution").

Further, the defendants' contention based on allegedly "obvious to try" experiments to prepare the most stable form of armodafinil falls short of proving that Form I would have been obvious. "Obvious to try" is not equivalent to obviousness in every case, particularly where, as here, the prior art provided at most general motivation to conduct trial and error experimentation in a decidedly unpredictable field. *See In re Kubin*, 561 F.3d at 1359-60 (cautioning that "obvious to try" does not necessarily mean obviousness under Section 103); *In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011), *cert. denied*, 132 S. Ct. 1796 (2012) (rejecting "obvious to try" argument because the claimed invention would not have been an expected result). Rather, the "Court in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008). "To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [] 'identified, predictable solutions' may present a difficult hurdle [for patent challengers] because potential solutions are less likely to be genuinely predictable." *Eisai Co., Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1075, 1088 (Fed. Cir. 2008). That an invention would have been obvious as a "result of routine

[58] The court also notes that the novel crystal forms here are distinguishable from the nucleic acid sequence at issue in *In re Kubin*, which the Federal Circuit found was directly related to, and determinable from, a naturally occurring polypeptide. 561 F.3d 1351, 1360-61 (Fed. Cir. 2009) (noting that "prior art "teach[es] a protein identical to NAIL, a commercially available monoclonal antibody specific for NAIL, and explicit instructions for obtaining the [claimed] DNA sequence for NAIL"). Here, however, and unlike the prior art in *Kubin*, which taught a five-step "protocol for cloning [the claimed] nucleic acid molecules encoding" the known NAIL protein, the prior art had "no narrow set of conditions" (561 F.3d at 1360), and "no recipe for planning or designing a polymorph screen," the results of which are entirely unpredictable (Tr. at 574:20-575:17 (Bernstein).) Importantly, the skilled artisan here lacked any defined set of rules to determine how molecules can form into crystals.

pharmaceutical development, not invention"—as the defendants generally assert here—has been rejected where the experiments were unpredictable.[59]

Specifically, the Federal Circuit has clarified that "obvious to try" is also not obvious when a skilled artisan would have to: (1) "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful"; or (2) "explore a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *See In re O'Farrell*, 83 F.2d 894, 903 (Fed. Cir. 1988); *see also In re Kubin*, 561 F.3d at 1359-60 (reaffirming holdings in *O'Farrell* in view of *KSR*).

As detailed above, the defendants argue that the '855 Patent discloses ethanol as the recrystallization solvent for the preparation and isolation of armodafinil, such that the skilled artisan would not have to choose between a wide range of solvents to obtain Form I. Tr. at 268:1-4 (Hollingsworth); Tr. at 318:1-319:24 (Lee). However, the court finds that this argument is based on an impermissible hindsight analysis, because a person of ordinary skill in the art in 2002 would not have known of the existence of Form I, and could not have known the method to produce Form I with any solvent. A skilled artisan would have known this method only after the '570 Patent, which identified Form I armodafinil and detailed the method to recrystallize Form I from ethanol

[59] *See Merck & Co., Inc. v. Sandoz, Inc.*, No. 10-1625, 2012 WL 266412, at *2 (D.N.J. Jan. 30, 2012) (citations and quotations omitted). In *Merck*, the defendant argued that the invention was the result of "routine pharmaceutical development," but entailed a freeze-drying process that was "very hard to predict." *Id.* at *8-9 ("[T]he skilled artisan must experiment with freeze-drying and cannot predict the outcome of the experiments."). As a result, the court concluded that the defendants could not "prove that [the claimed invention] was a predictable solution, and thus [could not] prove obviousness through this approach." *Id.* at *9.

under slow cooling conditions. *See* JTX-1-32 at 27:37; *see also Glaxo Group*, 376 F.3d at 1348-49. The defendants also cannot establish obviousness through non-prior art experiments (Tr. at 419:14-420:8), but must instead demonstrate that the claimed invention "would have been obvious at the time the invention was made." 35 U.S.C. § 103(a); *KSR Int'l v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). Here, the evidence presented at trial demonstrated that the results of crystallization and polymorphism testing were unpredictable, which required crystallization experiments using a large number of variable conditions. Thus, even if the general idea of using crystallization experiments were obvious to try, such unpredictable trial and error experimentation fails to render Form I obvious because the testing required was more than simply routine. *See In re Cyclobenzaprine*, 676 F.3d at 1073 (finding non-obviousness where "skilled artisans would not have encountered finite, small, or easily traversed options in developing a therapeutically effective, extended-release formulation"); *see also Sanofi-Synthelabo v. Apotex*, 550 F.3d 1075, 1088 (Fed. Cir. 2008).

C. Injunctive Relief

The plaintiffs assert that, pursuant to 35 U.S.C. §§ 271(e)(4)(A), (B), the court "shall order the effective date of any [FDA] approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed" and may grant "injunctive relief . . . against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation in the United States of an approved drug." *See* 35 U.S.C. §§ 271(e)(4)(A), (B). The plaintiffs also request that, because the defendants have stipulated that their proposed generic armodafinil ANDA products will infringe Claims 6 and 9 of the '570 Patent, and because both of those claims are not invalid, the FDA be enjoined from approving defendants' ANDAs. The defendants further request that the defendants be enjoined

from commercially manufacturing, using, offering for sale, or selling their proposed armodafinil ANDA products prior to the expiration of the '570 Patent, including any associated extensions and exclusivities.[60]

In light of the court's holdings in this action, the court agrees that the plaintiffs are entitled to the requested injunctive relief detailed in this section.

IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) the asserted claims of the patent-in-suit are not invalid due to anticipation; (2) the asserted claims of the patent-in-suit are not invalid due to obviousness; and (3) the plaintiffs' Rule 52(c) motion is granted and the defendants' Rule 52(c) motion is denied. An appropriate order will follow.

March 30, 2013

CHIEF, UNITED STATES DISTRICT JUDGE

[60] The plaintiffs note that they reserve arguments under 35 U.S.C. § 285 for costs and for fees. (D.I. 314 at 50.)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: ARMODAFINIL PATENT LITIGATION INC. ('722 PATENT LITIGATION)	MDL No. 10-md-2200 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. WATSON LABORATORIES, INC., Defendant.	Civil Action No. 10-cv-007 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. SANDOZ, INC., Defendant.	Civil Action No. 10-cv-055 (GMS) Civil Action No. 11-cv-782 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. LUPIN LIMITED, Defendant.	Civil Action No. 10-cv-210 (GMS)
CEPHALON, INC., CEPHALON FRANCE, and TEVA SANTE SAS, Plaintiffs, v. APOTEX, INC., Defendant.	Civil Action No. 10-cv-695 (GMS) Civil Action No. 10-cv-1078 (GMS)

ORDER

At Wilmington, this 30th day of March, 2013, IT IS HEREBY ORDERED THAT:

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

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

3. The defendants are enjoined from commercially manufacturing, using, offering for sale, or selling their proposed armodafinil ANDA products prior to the expiration of the '570 Patent, including any associated extensions and exclusivities and the FDA is enjoined from approving the defendants' armodafinil ANDAs prior to expiration of the '570 Patent;

4. The plaintiffs' Rule 52(c) motion (D.I. 314) is GRANTED and the defendants' Rule 52(c) motion (D.I. 319) is DENIED;

5. The plaintiffs' Motion for Judgment as a Matter of Law (D.I. 300) is terminated as MOOT in light of this Order (D.I. 329);

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

CHIEF, UNITED STATES DISTRICT JUDGE