IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE BENDAMUSTINE CONSOLIDATED CASES	Civil Action No. 13-2046-GMS **CONSOLIDATED**

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiff Cephalon, Inc. alleges that pharmaceutical products proposed by defendants Accord Healthcare Inc., Intas Pharmaceuticals Ltd., Hetero Labs Ltd., Hetero USA, Inc., Hospira Inc., InnoPharma, Inc., and Sagent Pharmaceuticals, Inc. (collectively, "the Defendants") infringe the asserted claims of the patents-in-suit. The court held a six-day bench trial in this matter on December 1 through December 8, 2015. (D.I. 449–454.) 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. (D.I. 455; D.I. 459.)

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 obvious under 35 U.S.C. § 103; (2) claims 1, 3, and 5 of the '270 patent are not invalid as anticipated under 35 U.S.C. § 102(b); (3) claims 1 and 19 of the '270 patent are not invalid due to the on-sale bar under 35 U.S.C. § 102(b); (4) claims 19–21 of the '270 patent are invalid as derived under 35 U.S.C. § 102(f); and (5) each of the parties' 52(c) motions are granted in part and denied in part. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Cephalon, Inc. ("Cephalon") is a corporation operating and existing under the laws of Delaware, with its principal place of business at 41 Moores Road, Frazer, Pennsylvania 19355.

2. Defendant Accord Healthcare, Inc. is a corporation organized and existing under the laws of the State of North Carolina, with its principal place of business at 1009 Slater Road, Suite 210-B, Durham, North Carolina, 27703.

3. Defendant Intas Pharmaceuticals Ltd. is a corporation organized and existing under the laws of India, with its principal place of business at Chinubhai Center Off. Nehru Bridge, Ashram Road, Ahmedabad 380009, Gujarat, India.

4. Accord Healthcare, Inc. is a wholly owned subsidiary of Intas Pharmaceuticals Ltd. (collectively, "Accord").

5. Defendant Hetero USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 1035 Centennial Avenue, Piscataway, New Jersey 08854.

6. Defendant Hetero Labs Ltd. ("Hetero Labs") is a corporation organized and existing under the laws of India, with its principal place of business at 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad – 500 018 A.P. India.

7. Hetero Labs Ltd. is a parent company of Hetero USA, Inc. (collectively, "Hetero").

8. Defendant Hospira Inc. ("Hospira") is a corporation organized and existing under the laws of Delaware, with its principal place of business at 275 North Field Dr., Lake Forest, Illinois 60045.

9. Defendant InnoPharma, Inc. ("InnoPharma") is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 10 Knightsbridge Road, Piscataway, New Jersey 08854.

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 433, Schedule A.) 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."

10. Defendant Sagent Pharmaceuticals, Inc. ("Sagent") is a corporation organized and existing under the laws of Delaware, with its corporate offices and a principal place of business at 1901 N. Roselle Road, Ste. 700, Schaumburg, IL 60195-3194.

11. The court has subject matter jurisdiction and personal jurisdiction over all parties.

B. Background

12. These consolidated actions arise out of Defendants' submission of several Abbreviated New Drug Applications ("ANDAs") under § 505(j) of the Federal Food, Drug and Cosmetic Act to the United States Food and Drug Administration ("FDA"), seeking approval to market and sell bendamustine hydrochloride for injection, 25 mg/vial and 100 mg/vial.

13. Bendamustine hydrochloride is an alkylating agent that has been used to treat cancer. As early as 1963, bendamustine hydrochloride was synthesized and was later shown to have therapeutic utility in the treatment of diseases such as chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer.

14. From 1971 to 1992, bendamustine was available to treat cancer in East Germany under the trade name Cytostasan®. After 1992, bendamustine hydrochloride has been marketed in Germany under the trade name Ribomustin®.

15. Cephalon, Inc. is the holder of approved NDA Nos. 22249 and 22303 for multiple TREANDA® products, indicated for the treatment of patients with chronic lymphocytic leukemia ("CLL") and indolent B-cell non-Hodgkin's lymphoma ("NHL") that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. The FDA approved the Treanda® 100 mg/vial product for the CLL indication on March 20, 2008 and on October 31, 2008, for the second-line indolent B-cell NHL indication. The FDA approved the Treanda® 25 mg/vial product on May 1, 2009 for those same indications.

16. The patents-in-suit are listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as "the Orange Book" with respect to Cephalon's NDA No. 22249 directed to TREANDA® (bendamustine hydrochloride) for Injection, 25 mg/vial and 100 mg/vial products.

C. The Patents-in-Suit

(1) The '190 Patent

17. U.S. Patent No. 8,436,190 ("the '190 patent"), entitled "Bendamustine Pharmaceutical Compositions," issued on May 7, 2013 to Jason Edward Brittain and Joe Craig Franklin.

18. The '190 patent issued from U.S. Patent Application No. 11/330,868, which was filed on January 12, 2006. U.S. Patent Application No. 11/330,868 claims priority to U.S. Provisional Application No. 60/644,354, filed on January 14, 2005.

19. The term of the '190 patent will expire on October 26, 2030. Pediatric exclusivity is set to expire on April 26, 2031.

(2) The '863 Patent

20. U.S. Patent No. 8,609,863 ("the '863 patent"), entitled "Bendamustine Pharmaceutical Compositions," issued on December 17, 2013 to Jason Edward Brittain and Joe Craig Franklin.

21. The '863 patent issued from U.S. Patent Application No. 13/719,379, which was filed on December 19, 2012. U.S. Patent Application No. 13/719,379 is a continuation of U.S. Patent Application No. 13/654,898, filed on October 18, 2012, which is a continuation of U.S. Patent Application No. 11/330,868, filed on January 12, 2006. U.S. Patent Application No. 11/330,868 claims priority to U.S. Provisional Application No. 60/644,354, filed on January 14, 2005.

22. The term of the '863 patent will expire on January 12, 2026. Pediatric exclusivity is set to expire on July 12, 2026.

(3) The '270 Patent

23. U.S. Patent No. 8,791,270 ("the '270 patent"), entitled "Bendamustine Pharmaceutical Compositions," issued on July 29, 2014 to Jason Edward Brittain and Joe Craig Franklin.

24. The '270 patent issued from U.S. Patent Application No. 13/969,724, which was filed on August 19, 2013. U.S. Patent Application No. 13/969,724 is a continuation of U.S. Patent Application No. 13/719,409, filed on December 19, 2012, which is a continuation of U.S. Patent Application No. 13/654,898, filed on October 18, 2012, which is a continuation of U.S. Patent Application No. 11/330,868, filed on January 12, 2006. U.S. Patent Application No. 11/330,868 claims priority to U.S. Provisional Application No. 60/644,354, filed on January 14, 2005.

25. The term of the '270 patent will expire on January 12, 2026. Pediatric exclusivity is set to expire on July 12, 2026.

(4) The '756 Patent

26. U.S. Patent No. 8,895,756 ("the '756 patent"), entitled "Bendamustine Pharmaceutical Compositions," issued on November 25, 2014 to Jason Edward Brittain and Joe Craig Franklin.

27. The '756 patent issued from U.S. Patent Application No. 13/719,409, which was filed on December 19, 2012. U.S. Patent Application No. 13/719,409 is a continuation of U.S. Patent Application No. 13/654,898, filed on October 18, 2012, which is a continuation of U.S. Patent Application No. 11/330,868, filed on January 12, 2006. U.S. Patent Application No. 11/330,868 claims priority to U.S .Provisional Application No. 60/644,354, filed on January 14, 2005.

28. The '756 patent will expire on January 12, 2026. Pediatric exclusivity is set to expire on July 12, 2026.

D. The Asserted Claims

29. Cephalon asserts claims 5 and 8 of the '190 patent against Accord and Hospira.

30. Claims 5 and 8 of the '190 patent read:

> 5. The lyophilized pharmaceutical composition according to claim 4,[2] wherein said bendamustine or bendamustine hydrochloride is present in said pharmaceutical composition at a concentration of about 12 to 17 mg/ml, said mannitol is present in said pharmaceutical composition at a concentration of about 20-30 mg/ml, and said tertiary-butyl alcohol is present in said pharmaceutical composition at a concentration of about 10-50% (v/v).
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> 8. The lyophilized pharmaceutical composition according to claim 5 containing not more than about 0.5% bendamustine ethylester.

31. Cephalon asserts claim 1 of the '863 patent against Accord and Hospira.

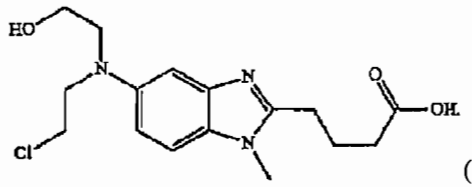
32. Claim 1 of the '863 patent reads:

> 1. A stable lyophilized preparation comprising bendamustine hydrochloride, mannitol, and a trace amount of tertiary-butyl alcohol (TBA), wherein the ratio by weight of bendamustine hydrochloride to mannitol is 15:25.5.

33. Cephalon asserts claims 1 and 19–21 of the '270 patent against all of the Defendants, and claims 3 and 5 of the '270 patent against Accord, Hetero, Hospira, and Sagent.

34. Claims 1, 3, 5 and 19–21 of the '270 patent read:

> 1. A pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride, said composition containing not more than about 0.9% (area percent of bendamustine) of HP1:

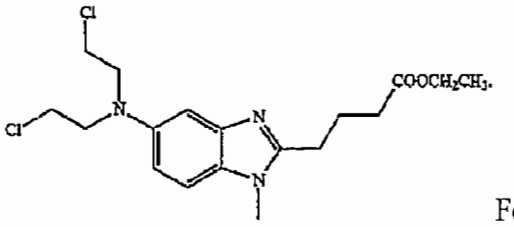


(HPI)

> 3. The pharmaceutical composition of claim 1, wherein the amount of HP1 is not more than 0.5% (area percent of bendamustine).
>
> 5. The pharmaceutical composition of claim 1, wherein the amount of HP1 is not more than 0.4% (area percent of bendamustine).

[2] Claim 4 of the '190 patent reads: A lyophilized pharmaceutical composition made from the pharmaceutical composition according to claim 1. Claim 1 of the '190 patent reads: A pharmaceutical composition comprising bendamustine or bendamustine hydrochloride, mannitol, tertiary-butyl alcohol and water.

19. The pharmaceutical composition of claim 7,[3] containing not more than about 0.5% (area percent of bendamustine) of a compound of Formula IV:



Formula IV

20. A method of treating cancer in a patient comprising administering to the patient a pharmaceutical composition of bendamustine hydrochloride according to claim 7.

21. The method according to claim 20, wherein the cancer is chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or breast cancer.

35. Cephalon is asserting claims 1 and 4 of the '756 patent against Accord, Hetero, Hospira, and Sagent.

36. Claims 1 and 4 of the '756 patent read:

1. A vial containing a reconstituted solution of bendamustine hydrochloride and mannitol in sterile water for injection, wherein the ratio by weight of bendamustine hydrochloride to mannitol in the vial is 15:25.5, and wherein the bendamustine hydrochloride is present in the vial at a concentration of 100 mg per 20 mL.

4. A 20 mL vial containing 100 mg of bendamustine hydrochloride and 170 mg of mannitol reconstituted in sterile water for injection.

E. The Accused Products

(1) The Hetero ANDA

37. Hetero Labs filed ANDA No. 204081 ("the Hetero ANDA") with the FDA, under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of a bendamustine hydrochloride powder for IV (infusion), 25mg/vial and 100 mg/vial ("Hetero's ANDA Product").

38. The Hetero ANDA lists Hetero USA, Inc. as the U.S. agent for the Hetero ANDA.

[3] Claim 7 of the '270 patent reads: A pharmaceutical composition of bendamustine hydrochloride, containing less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants.

39. The Hetero ANDA contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certifications") alleging that the claims of the '190, '863, '270, and '756 patents are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Hetero's ANDA Product.

40. By letters dated November 6, 2013; May 19, 2014; October 6, 2014; November 20, 2014; and January 6, 2015, Hetero Labs sent notice to Cephalon that it was seeking approval to market Hetero's ANDA Product prior to the expiration of the'190 patent, the '863 patent, the '270 patent, and the '756 patent.

(2) The InnoPharma ANDA

41. InnoPharma filed ANDA No. 205476 ("the InnoPharma ANDA") with the FDA, under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of a bendamustine hydrochloride powder for IV (infusion), 25mg/vial and 100 mg/vial ("InnoPharma's ANDA Product").

42. InnoPharma's ANDA contains Paragraph IV certifications alleging that the claims of the '190, '863, '270, and '756 patents are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of InnoPharma's ANDA Product.

43. By letters dated November 8, 2013; March 26, 2014; and April 2, 2015, InnoPharma sent notice to Cephalon that it was seeking approval to market InnoPharma's ANDA Product prior to the expiration of the '190 patent, '863 patent, the '270 patent, and the '756 patent.

(3) The Hospira ANDA

44. Hospira filed ANDA No. 204086 ("the Hospira ANDA") with the FDA, under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of bendamustine hydrochloride for injection, for intravenous infusion, 25mg/vial and 100 mg/vial ("Hospira's ANDA Product").

45. Hospira's ANDA contains a Paragraph IV certification alleging that the claims of the '190 are invalid, unenforceable and/or will not be infringed by the manufacture, use, or sale of Hospira's ANDA Products.

46. By letter dated November 19, 2013, Hospira sent notice to Cephalon that it was seeking approval to market Hospira's ANDA Product prior to the expiration of the '190 patent.

(4) The Accord ANDA

47. Accord filed with FDA, under 21 U.S.C. § 355(j), ANDA No. 205574 ("the Accord ANDA") seeking approval to engage in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of a bendamustine hydrochloride powder for IV (infusion), 25mg/vial and 100 mg/vial ("Accord's ANDA Product").

48. The Accord ANDA and amendments thereto contain Paragraph IV certifications alleging that the claims of the '190, '863, '270, and '756 patents are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Accord's ANDA Product.

49. By letters dated November 18, 2013; February 28, 2014; September 8, 2014; and February 12, 2015, Accord sent notice to Cephalon that it was seeking approval to market Accord's ANDA Product prior to the expiration of the '190 patent, the '863 patent, the '270 patent, and the '756 patent.

(5) The Sagent ANDA

50. Sagent filed ANDA No. 206186 ("the Sagent ANDA") with FDA, under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of a bendamustine hydrochloride powder for IV (infusion), 25mg/vial and 100 mg/vial ("Sagent's ANDA Product").

51. Sagent's ANDA contains Paragraph IV certifications alleging that the claims of the '190 patent, the '863 patent, the '270 patent, and the '756 patent are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Sagent's ANDA Product.

52. By letters dated July 25, 2014; November 5, 2014; and March 17, 2015, Sagent sent notice to Cephalon that Sagent had filed the Sagent ANDA seeking approval to market Sagent's ANDA Product prior to the expiration of the '190 patent, the '863 patent, the '270 patent, and the '756 patent.

F. Procedural History

53. In Complaints dated November 6, 2014 and February 23, 2015, Cephalon filed suit against Hetero asserting infringement of the '270 patent and the '756 patent. (Civil Action No. 1:13-cv-2046-GMS (D.I. 34); Civil Action No. 1:15-cv-179-GMS (D.I. 1).)

54. In Complaints dated December 20, 2013; May 9, 2014; September 25, 2014; and February 23, 2015, Cephalon filed suit against InnoPharma asserting infringement of the '190 patent, the '863 patent, the '270 patent, and the '756 patent. (Civil Action No. 1:13-cv-2081-GMS (D.I. 1); Civil Action No. 1:14-cv-590-GMS (D.I. 1); Civil Action No. 1:14-cv-1238-GMS (D.I. 1); Civil Action No. 1:15-cv-178-GMS (D.I. 1).)

55. In Complaints dated December 26, 2013, September 26, 2014, February 23, 2015, and April 10, 2015, Cephalon filed suits against Hospira asserting infringement of the '190 patent, the '863 patent, the '270 patent, and the '756 patent. (Civil Action No. 1:13-cv-2094-GMS (D.I. 1); Civil Action No. 1:14-cv-1242-GMS (D.I. 1); Civil Action No. 1:15-179-GMS (D.I. 1); Civil Action No. 1:13-cv-02046-GMS (D.I. 277).)

56. In Complaints dated December 26, 2013, April 9, 2014, September 18, 2014, and February 23, 2015, Cephalon filed suit against Accord asserting infringement of the '524 patent, the '190 patent, the '863 patent, the '270 patent, the '279 patent, the '836 patent, and the '756 patent. (Civil Action No. 1:13-cv-2095-GMS (D.I. 1; D.I. 14; D.I. 28); Civil Action No. 1:15-cv-178-GMS (D.I. 1).)

57. In Complaints dated September 2, 2014; February 13, 2015; and February 23, 2015, Cephalon filed suit against Sagent Pharmaceuticals, Inc. ("Sagent"), asserting infringement of the '524 patent, the '190 patent, the '863 patent, the '270 patent, the '279 patent, the '836 patent, and the '756 patent. (Civil Action No. 1:14-cv-1116-UNA (D.I. 1); Civil Action No. 1:13-cv-2046-GMS (D.I. 188); Civil Action No. 1:15-179-GMS (D.I. 1).

58. On November 24, 2014, the court consolidated Civil Action Nos. 1:13-cv-2081-GMS, 1:14-cv-590-GMS, 1:14-cv-1238-GMS, 1:13-cv-2094-GMS, 1:14-cv-1242-GMS, 1:13-cv-2095-GMS, and 1:14-cv-1116-UNA, into Civil Action No. 1:13-cv-2046-GMS.

59. On November 24, 2015, the Defendants stipulated to infringement of the asserted claims for the purposes of this litigation. (D.I. 441.)

60. On April 8, 2015, the court consolidated Civil Action Nos. 1:15-cv-178-GMS and 1:15-cv-179-GMS with Civil Action No. 13-2046-GMS. (*See* Civ. Action No. 1:15-cv-178-GMS (D.I. 27); Civ. Action No. 1:15-cv-179-GMS (D.I. 25).)

61. The court held a six-day bench trial in this matter on December 1 through December 8, 2015. (D.I. 449–454.)

III. DISCUSSION AND CONCLUSIONS OF LAW

A. Defendants' Obviousness Challenge to All Asserted Claims

The Defendants challenge the validity of each of the asserted claims as obvious in light of the prior art. For the reasons that follow, the court finds that the Defendants have failed to establish a prima facie case of obviousness by clear and convincing evidence.

(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. *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"[4] 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 reliant on ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See KSR*, 550 U.S. at 415. The *KSR* Court acknowledged, however, the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in 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).

[4] "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)).

"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 pharmaceutics 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

The Plaintiff's experts testified that a person of ordinary skill in the art with respect to the patent-in-suit would have a bachelor's degree in pharmaceutical sciences or a related field and at least five years of experience, or an advanced degree in pharmaceutical sciences or a related field with at least three years of experience in formulating, characterizing or analyzing pharmaceutical products, and the ability to collaborate with individuals in other areas of science, including medicine and drug development. (D.I. 455 at 8.) The Defendants' experts testified that a person of ordinary skill in the art would have an advanced degree in pharmaceutics, pharmaceutical chemistry, medicinal chemistry or a related field, or would have less education but considerable professional experience in one or more of those fields, and experience with drug lyophilization, designing and preparing liquid drug formulations, designing and preparing formulations of drugs that are unstable in water, and the ability to understand work presented or published by others in

the field. (D.I. 459 at 4.) The court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.[5]

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

a. Motivation to Improve Ribomustin

The Defendants argue that a person of skill in the art would have started with Ribomustin, as did the inventors. They assert that a person of skill would have been motivated to improve Ribomustin in order to reduce degradants, reduce the vial size, and improve the reconstitution time. The prior art on the composition of Ribomustin is limited to the 2002 Ribomustin Product Monograph (DTX0576) and the 1996 Rote Liste (DTX0575). Neither discuss the pre-lyophilized solution of Ribomustin, but they disclose the marketed vial sizes, the amount of bendamustine hydrochloride and mannitol in each vial, the reconstitution volume, and the amount of time required to reconstitute (*i.e.* dissolve) the drug. (DTX0576 at 7–8, 55–56.)

The Defendants argue that the Olthoff patent (DTX0343), Mass publication (DTX0577) and Gust publication (DTX0149) would have motivated a person of skill to reduce the degradants in Ribomustin. Olthoff described bendamustine as a "relatively instable compound" that "almost completely hydrolyzed in aqueous solutions after a short period of time." (DTX0343.0011.) Maas studied the stability of Ribomustin after reconstitution in sterile water in sterile water and dilution in saline. Using HPLC analyses, Maas identified the degradant HP1 and disclosed the decomposition kinetics of bendamustine at room temperature. (DTX0577.0003–5; Tr. at 362:16–363:6 (Kamat).) Gust further studied bendamustine degradants and reported the same four impurities identified in the asserted claims: HP1, HP2, NP1, and BM1EE. (DTX0149.0008.)

[5] 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. (D.I. 459 at 4 n.4.)

Although Maas describes Ribomustin's degradants, it also states that "no stability problems can be expected" for Ribomustin "since there is a stability of 9 hours for these bendamustine preparations at room temperature." (DTX577.0004.) Based on Maas, a POSA would not have expected Ribomustin to degrade during reconstitution (which the Ribomustin Monograph disclosed as taking 5 to 10 minutes) or administration (which the Ribomustin Monograph disclosed as taking 30 to 60 minutes). (Tr. at 904:1–8 (Winter); DTX0567.008.) Furthermore, the prior art does not disclose the amounts of degradants in Ribomustin or its pre-lyophilization solution. A person of skill would need to know whether the impurities present in Ribomustin reached an unacceptable level before going through the effort to reduce them.[6] The court concludes that Maas and Gust would not have motivated a person of skill to improve Ribomustin.

The Defendants also argue that Ribomustin's large vial size and slow reconstitution times would motivate a person of skill in the art to improve its formulation. The Ribomustin Monograph disclosed a 40 mL dosage vial. (DTX0576.008.) The Defendants' expert, Dr. Kamat, explained that a smaller vial size would promote efficiency and cost-effectiveness. (Tr. at 378:9–14 (Kamat).) The Plaintiff's expert, Dr. Winter, agreed that a person of skill would consider the benefits of reducing vial size. The Ribomustin Monograph also disclosed that reconstitution of Ribomustin in water "usually takes 5 to 10 minutes." (DTX0576.008.) The 2003 textbook "Lyophilization—Introduction and Basic Principles" taught that "[i]f a product requires more than 5 min to reconstitute, then steps should be taken to decrease the reconstitution time." (DTX0438.0447.) The Plaintiff's expert, Dr. Ippoliti, testified that saving even a few minutes in

[6] Salmedix was aware that Ribomustin had unacceptably high levels of impurities, and stability and purity were among Mr. Brittain's motivations in creating an improved product. (Tr. at 66:5–67:7; 91:20–24; 92:15–19 (Kabakoff).) But although this may have motivated the inventor, it would not motivate a person of skill in the art who had no knowledge of what the levels of impurities were. For all the public knew, Ribomustin could have been an exceptionally pure product.

reconstitution time would provide significant benefits. (Tr. at 328:3–9 (Ippoliti).) In light of the potential benefits, the Plaintiff does not provide any convincing arguments why a person of skill would not have considered improving the vial size and reconstitution time of Ribomustin. Accordingly, the court concludes that vial size and reconstitution time would have motivated a person of skill to improve Ribomustin.

b. Motivation to create lyophilized product

Both parties' experts agreed that for a drug which degrades in water, a person of skill would prefer creating a liquid formulation over a lyophilized one, and would not attempt to develop a new lyophilized product unless the liquid formulation failed. (Tr. at 907:24–908:11 (Winter); Tr. at 394:7–19 (Kamat); Tr. at 564:25–565:12 (Kwan).) Indeed, the inventor, Mr. Brittain, began working on lyophilization only after initially failing to produce a liquid product. (Tr. at 139:11–140:16 (Brittain).) Dr. Winter testified that a person of skill formulating a lyophilized product would need to consider numerous interrelated factors, including solubility of the active compound and its bulking agents, the stability of the active compound in the pre-lyophilization solution, the lyophilization cycle, the vial size and fill volume, the quality of the lyophilized cake, the stability of the lyophilized product, the levels of residual solvents, reconstitution time, regulatory concerns, cost, and reconstitution diluent volume. (Tr. at 897:7–898:2 (Winter).) The interdependence of several of these factors means that a person of skill would need to perform many experiments to obtain the desired result. (Tr. at 898:3–900:6 (Winter).) In short, creating a new lyophilized product would not lead to predictable outcomes. Based on this, the court concludes a person of skill seeking to improve the formulation of Ribomustin would not have been motivated to start with lyophilization. This decreases the likelihood of the court finding the final lyophilized product is obvious.

c. Prior Art Regarding TBA/Water Co-Solvent Systems

Assuming a person of skill would have chosen to create an improved lyophilized formulation of bendamustine, the next step would be to choose a solvent for the pre-lyophilization solution. The prior art does not disclose which solvent was used in the lyophilization of Ribomustin. The Defendants contend the prior art publications from Teagarden (DTX0334) and Ni (JTX079) would have motivated a person of skill to use a mixture of tert-butyl alcohol (also known as TBA or tert-butanol) and water.

Dr. Kamat testified that because bendamustine is susceptible to degradation by hydrolysis, a person of skill would seek to reduce the amount of water in the lyophilization solution.[7] (Tr. at 373:17–25 (Kamat).) Teagarden taught that non-aqueous solvents could be used to improve a drug product's stability, reconstitution time, and solubility. (DTX0334.000.) Further, Teagarden stated that "the co-solvent system that has been most extensively evaluated was the tert-butanol/water combination." (DTX0334.0001.) Teagarden enumerated many advantages the TBA/water co-solvent system has over other co-solvent systems, and out of twenty-two compounds disclosed, it identified eight different drug preparations where TBA or TBA/water was used as the lyophilization solvent. (DTX0334.003 at Table 2.) The Defendants argue that from Teagarden, a person of skill would expect that the TBA/water co-solvent system would improve the stability of bendamustine. (Tr. at 494:23–496:12 (Kwan).) The Defendants also point to Ni, which studied TBA and TBA/water lyophilization solvent systems with SarCNU, a compound which is water soluble but highly unstable in water. (JTX079 at 39.) Ni taught that the greater concentration of

[7] The court notes that it has not accepted the Defendants' premise that impurity levels would have motivated a person of skill to improve Ribomustin in the first instance.

TBA in the lyophilization solution, the less a water sensitive drug will degrade. (Tr. at 370:15–371:25 (Kamat).)

The Plaintiff responds by first noting that water was the most commonly used lyophilization solvent in 2005. (Tr. at 900:7–10 (Winter); 432:14–17 (Kamat).) The Plaintiff's expert, Dr. Winter, testified that he had never used TBA as a solvent in any of the marketed pharmaceutical lyophilized products he developed in his nearly 30 years of experience. (Tr. at 900:11–23 (Winter).) Even Dr. Kamat admitted he was only aware of one commercialized pharmaceutical product made using TBA as a co-solvent as of 2005. (Tr. at 396:15–397:15 (Kamat).) The court finds this particularly telling. Dr. Winter testified that a person of skill working with a water-sensitive drug would still consider using water as the solvent because the drug is only dissolved in the pre-lyophilization solution for a limited period of time before it is freeze-dried. (Tr. at 901:6–15 (Winter).) He also explained that there were other methods to reduce degradation other than using a co-solvent, such as adjusting the pH value, using a different temperature, or considering alternative drying techniques. (Tr. at 901:16–902:4 (Winter).) The court found Dr. Winter's testimony persuasive.

The Plaintiff also notes that the Defendants did not present any references which studied using a TBA/water system with bendamustine hydrochloride, or even the same type of compound, a nitrogen mustard. Further, the Plaintiff argues that the Defendants ignored solvent effects, which describe the impact a solvent has on a reaction such as hydrolysis. (Tr. at 718:14–18 (Welton).) In this case, the solvent effects would impact the stability on the compound. Dr. Welton testified that a person of skill would need to understand the reaction mechanism in order to predict how a particular solvent would affect the reaction. (Tr. at 722:24–723:8 (Welton).) According to Dr.

Welton, a person of skill would need to understand *how* a compound degrades to predict whether a particular solvent would have a stabilizing effect on that compound.

In this case, bendamustine hydrochloride is a nitrogen mustard that undergoes hydrolysis through a neighboring group participation reaction. (Tr. at 726:15–727:9, 728:23–733:9 (Welton).) As of 2005, "almost nothing" was known in the prior art about the solvent effects on neighboring group participation reactions. (Tr. at 732:22–24 (Welton).) The Defendants' references do not disclose analogous reaction mechanisms. Dr. Welton explained that Ni studied a nitrosourea compound, which has a different degradation reaction mechanism than a nitrogen mustard. (Tr. at 744:6-745:13 (Welton).) Therefore, a person of skill reading Ni could not predict a favorable outcome using TBA with bendamustine hydrochloride. Further, Ni concludes that anhydrous TBA best stabilized SarCNU, rather than a co-solvent mixture with water. (Tr. at 747:13–748:16 (Welton).) This would not suggest to a person of skill in the art that a TBA/water co-solvent system would be the best option. In Dr. Welton's opinion, the claims are not obvious because the prior art did not provide "a sufficient predictive capacity or likelihood of success of using TBA." (Tr. at 714:10-15 (Welton).)

Like Ni, Teagarden did not discuss bendamustine or analogous compounds. (Tr. at 914:25–915:1 (Winter); Tr. at 750:2–14 (Welton).) Teagarden highlighted the disadvantages involved in selecting a co-solvent system. Teagarden noted that co-solvent systems "can cause a multitude of problems" such as "toxicity concerns, operator safety concerns due to a high degree of flammability or explosion potential, . . . high cost to use, . . . and lack of regulatory familiarity." (DTX999.0002.) Therefore, the "advantages and disadvantages of their use must be carefully weighed before they are chosen to be used in the manufacture of a pharmaceutical product." (*Id.*) Further, because the impact of a co-solvent on reconstitution is "dependent on several factors,"

Teagarden explained that "one will need to evaluate this property on a case by case basis." (DTX999.0009.) Teagarden did not offer enough information from which a person of skill could obtain a reasonable expectation of success in using a TBA/water co-solvent system with bendamustine hydrochloride. To the contrary, Teagarden showed that the process of selecting a co-solvent system is complex and would have required substantial experimentation.

Based on the court's determination that a person of skill would not have been motivated by a need to reduce an unknown level of impurities, the prevalence of water as a lyophilization solvent, and the unpredictability and disadvantages in choosing a co-solvent system, the court concludes that a person of skill would not have been motivated to use a TBA/water co-solvent system.

d. Routine Experimentation and Reasonable Expectation of Success

The limitations of the eleven asserted claims can fall into three major categories: 1) claimed concentrations and ratios of TBA and mannitol (claim 5 of the '190 patent and claim 1 of the '863 patent); 2) 20 mL vial size and reconstitution volume (claim 4 of the '756 patent and claim 1 of the '756 patent); and 3) impurity levels (claim 8 of the '190 patent and claims 1, 3, 5, and 19–21 of the '270 patent). The crux of the Defendants' obviousness argument is that after a person of skill chose to develop an improved lyophilized bendamustine hydrochloride product using a TBA/water co-solvent system and mannitol as a bulking agent,[8] that person would arrive at the claimed limitations through routine experimentation.

Dr. Kwan testified that the lyophilization process involves 1) determining the solubility of the drug in water and co-solvent systems; 2) identifying a suitable bulking agent and determining

[8] The Plaintiff does not seem to dispute that mannitol was an obvious choice for a bulking agent. Mannitol was used in the Ribomustin formulation and was the preferred bulking agent in pharmaceutical formulations at the time. (DTX0576.0007; DTX0370.0004; Tr. at 355:4–7 (Kamat).) The Plaintiff does, however, argue that the claimed ratios and concentrations of mannitol were not obvious.

an optimum range of the bulking agent in the pre-lyophilization solution; 3) evaluating lyophilization factors such as fill volume, cake quality, and reconstitution time; and 4) optimizing the final composition. (Tr. at 467:13–469:12 (Kwan).) Dr. Kamat testified that a person of skill would have a reasonable expectation of success following this process. (Tr. at 390:8–11 (Kamat).)

Although this process may be routine, the court is not convinced that it is as straightforward as the Defendants profess. As discussed above, a person of skill would not have started with lyophilization precisely because of its complexity. The Defendants point out the fact that Mr. Brittain followed this exact process and obtained the claimed composition of bendamustine hydrochloride after two and a half months. (D.I. 459 at 14–15.) But the Defendants' analysis discounts the fact that Mr. Brittain was actually in a position superior to the theoretical person of skill in the art. Mr. Brittain worked for the pharmaceutical company Salmedix, which entered into a License Agreement with the maker of Ribomustin, Fujisawa Deutschland GmbH ("Fujisawa"), in order to develop a bendamustine hydrochloride product for the United States market. (Tr. at 63:12–64:15 (Kabakoff).) This License Agreement gave Mr. Brittain access to a wealth of confidential information on the formulation of Ribomustin. He therefore could make the informed choices necessary to obtain his final product with less experimentation than an outsider would have to conduct.

Thus, the biggest flaw in the Defendants' defense is the scant level of publicly available information. In the words of the defendant's own expert, bendamustine "was a very unknown kind of compound." (Tr. at 374:9–10 (Kamat).) A person of skill could have followed precisely in Mr. Brittain's footsteps, but the court finds that it would not have been obvious to do so. Because the court concludes that a person of skill would not have chosen to create a lyophilized product using a TBA/water co-solvent system, the court cannot find that these numerous claim limitations would

have been obvious. Because the Defendants have failed to meet their burden to present a prima facie case of obviousness, the court does not consider the parties' secondary considerations.

B. Defendants' § 102 Challenges to Asserted Claims of the '270 Patent

(1) Anticipation

"[I]nvalidity by anticipation requires that the four corners of a single[] prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1271, 1282 (Fed. Cir. 2000). 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)).

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. *See Advanced Display Sys.*, 212 F.3d at 1281.

The Defendants contend that claims 1, 3, and 5 of the '270 patent are anticipated by Maas. These claims cover a pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine hydrochloride containing not more than 0.9%, 0.5%, and 0.4% of the HP1 impurity, respectively. Maas studied the degradation of a reconstituted pharmaceutical composition of Ribomustin and characterized the amount of degradants, including HP1. (DTX0577.0001; DTX0577.0003.) The Defendants' expert, Dr. Jarosz, testified that even though Maas did not calculate the overall amount of HP1 in the studied samples, the reaction rate Maas computed can be used to obtain the impurity levels. (Tr. at 653:2–20 (Jarosz).) According to Dr. Jarosz, the Maas study inherently disclosed that 0.4% HP1 formed in 20 minutes from reconstituted Ribomustin. (Tr. at 651:8–11 (Jarosz). Maas normalized the data such that the initial purity reading after dilution was 100%. (DTX146.0005–6; Tr. at 693:20–694:11 (Jarosz).) This means that Maas only reported the relative purity of Ribomustin, and did not disclose the amount of HP1 in Ribomustin before reconstitution. (Tr. at 653:17–20; 693:20–694:11 (Jarosz).) Without knowing the absolute concentration of impurities, the court cannot conclude that Maas anticipates the claimed impurity levels.

The Defendants also point to a Ribomustin photostability study which observed 0.48% HP1. (DTX0090.0150.) Unfortunately for the Defendants, this study is irrelevant. It does not corroborate Maas because it did not analyze the same batch of Ribomustin as used in the Maas reference. (Tr. at 675:13–16 (Jarosz).) Further, there is no evidence about how the batches used for the photostability study were dissolved, so the court cannot find that the study met the limitation of a "pharmaceutical composition that has been reconstituted." (Tr. at 675:4–12 (Jarosz).) Claims 1, 3, and 5 of the '270 patent are not invalid as anticipated by Maas.

(4) On-Sale Bar

Section 102(b) of the Patent Act prohibits granting a patent for an invention that was "on sale" in the U.S. more than one year before the patent application date. 35 U.S.C. § 102(b). The "critical date" in a Section 102(b) inquiry is defined as exactly one year before a patent application is filed. *Id.* The on-sale bar applies when two conditions are satisfied before the critical date of one year before the filing date of the application: 1) a product embodying the claimed invention is the subject of a commercial offer for sale; and 2) the claimed invention is ready for patenting. *See Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 67 (1998). A claimed invention is ready for patenting if it is reduced to practice or if there is "proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention." *Id.* Whether an invention was on sale more than one year before the patent's application date is a question of law for the court to decide based on underlying factual determinations. *See Abbot Lab. v. Geneva Pharm., Inc.*, 182 F.3d 1315, 1317 (Fed. Cir. 1999); *Ferag AG v. Quipp Inc.*, 45 F.3d 1562, 1566 (Fed. Cir. 1995).

The court concludes the Defendants have failed to meet their burden under *Pfaff*. To satisfy the first condition stated in *Pfaff*, the Defendants must show that the patented formulation of bendamustine hydrochloride was commercially offered for sale in the United States. Because Ribomustin was never marketed in the U.S., the Defendants rely on the License Agreement between Salmedix and Fujisawa. (JTX37.) Under the License Agreement, Fujisawa granted Salmedix "an exclusive right and license . . . to develop, manufacture, have manufactured, market, sell, import, distribute, and promote" a product for the U.S. market. (*Id.* at 2.) Fujisawa also provided Salmedix with batches of bulk bendamustine hydrochloride and unlabeled vials of Ribomustin to allow them to "conduct development work." (*Id.* at 8.) In exchange, Salmedix

agreed to pay Fujisawa up to $2.5 million in license fees and royalties if Salmedix launched a product in the U.S. (*Id.* at 10.) The language of the License Agreement clearly indicates that it did not contemplate commercial sale, but was instead a development license.

The actions of the scientists at Salmedix corroborate the fact that no commercial sale took place here. Salmedix used the batches of Ribomustin it obtained to conduct phase 2 clinical trials and laboratory research. Mr. Brittain used the unlabeled vials of Ribomustin to develop the formulation claimed in the asserted patents. (Tr. at 165:16–166:17 (Brittain).) Salmedix only used the product obtained from Fujisawa for experimental, development purposes. This does not satisfy the "commercial" sale requirement for the on-sale bar. Accordingly, the court concludes that the '270 patent is not invalid based on Section 102(b).

(5) Derivation

Section 102(f) prohibits the issuance of a patent to a person who derives the conception of an invention from any other source. See *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993). To prove derivation under § 102(f), the patent challenger must establish prior conception of the invention by another and communication of that conception to the patentee. *Id.*

The Defendants argue that the inventors derived claims 19–21 of the '270 patent from Fujisawa. Claim 19 covers a pharmaceutical composition of bendamustine hydrochloride containing less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants, and not more than 0.5% of degradant BM1EE. Claims 20 and 21 cover the method of using that composition to treat various forms of cancer. As part of their License Agreement, Fujisawa provided Salmedix with several batches of Ribomustin and the Common Technical Specification, which reported degradant levels for several batches of Ribomustin. JTX-128A at CEPH-_01680813–01680820. Each Ribomustin batch had total degradant levels of less than 4.0% and

total BM1EE levels of less than 0.5% (area percent of bendamustine). *Id.* This falls within the patent claims.

The Plaintiff argues that the Defendants have failed to prove conception or enablement because the Ribomustin Technical Specification specified a product with no more than 5.0% total impurities and no more than 0.6% BM1EE. The fact that some batches of Ribomustin may have contained higher levels of degradants is, however, not dispositive. The eight batches analyzed by Fujisawa contained impurities which fell well below the patented levels, so it is unreasonable to presume that scientists at Fujisawa did not conceive of these levels of impurities. Mr. Brittian also testified that he received the "soup to nuts" concerning manufacturing Ribomustin from Fujisawa. (Tr. at 119:1–8 (Brittain).) The court concludes that claims 19–21 of the '270 patent were derived from Fujisawa and are therefore invalid.

IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) the asserted claims of the patents-in-suit are not invalid as obvious under 35 U.S.C. § 103; (2) claims 1, 3, and 5 of the '270 patent are not invalid as anticipated under 35 U.S.C. § 102(b); (3) claims 1 and 19 of the '270 patent are not invalid due to the on-sale bar under 35 U.S.C. § 102(b); (4) claims 19–21 of the '270 patent are invalid as derived under 35 U.S.C. § 102(f); and (5) each of the parties' 52(c) motions are granted in part and denied in part. An appropriate order will follow.

Date: June 10, 2016

UNITED STATES DISTRICT JUDGE