IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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| ALCON RESEARCH, LTD.,<br><br>Plaintiff,<br><br>v.<br><br>WATSON LABS., INC.,<br><br>Defendant. | C.A. No. 15-1159-GMS<br>**CONSOLIDATED** |
| ALCON RESEARCH, LTD.,<br><br>Plaintiff,<br><br>v.<br><br>LUPIN LTD., &<br>LUPIN PHARMA., INC.,<br><br>Defendants. | |

**MEMORANDUM**

## I. INTRODUCTION

In this patent infringement action, Alcon Research, Ltd. alleges that Watson Labs., Inc., Lupin Ltd., and Lupin Pharma. Inc., (collectively, "the Defendants") infringes the asserted claims of the patents-in-suit. The court held a four-day bench trial in this matter beginning on October 2, 2017. 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, specifically whether the asserted claims are invalid as obvious under 35 U.S.C. § 103. (D.I. 149; D.I. 150.)

Pursuant to Federal Rule of Civil Procedure 52(a), having considered the entire record in this case and the applicable law, the court concludes that the asserted claims of the patents-in-suit

are not invalid due to obviousness. 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 Alcon Research, Ltd. ("Alcon") is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 6201 South Freeway, Fort Worth, Texas 76134.

2. Defendant Watson Laboratories, Inc. ("Watson") is a corporation organized and existing under the laws of the State of Nevada, having its principal place of business at 311 Bonnie Circle, Corona, California 92880, and a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054.

3. Defendant Lupin Ltd. ("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 €, Mumbai 400 051, India.

4. Lupin Pharmaceuticals, Inc. ("Lupin Pharms") is a corporation organized and existing under the laws of Delaware having a principal place of business at Harborplace Tower, 111 South Calbert Street, Baltimore, Maryland 21202.

5. Lupin Pharms is an indirectly wholly-owned subsidiary of Lupin Ltd. (collectively, "Lupin").

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

### B. Background

7. On January 30, 2015, Novartis Pharmaceuticals Corp., an affiliate of Alcon, received approval from the FDA to market olopatadine hydrochloride ophthalmic solution (0.7%) under the trade name Pazeo® for the treatment of ocular allergic conjunctivitis.

8. Alcon has asserted claims 4-6, 8-10, 12-14, and 20-27 of the '154 Patent.

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 131, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs 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 Part III this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

9. The Prescribing Information for Patanol® (Olopatadine Hydrochloride Opthalmic Solution) 0.1% (Revised August 2002) ("Patanol® Label") was publicly available before October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

10. Highlights of Prescribing Information for Pataday® (Olopatadine Hycdrochloride Opthalmic Solution) 0.2% (Revised August 2010) ("Pataday® Label") was publicly available before October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

11. Alcon Highlights of Prescribing Information and Labeling for Patanase® (Olopatadine Hydrochloride) Nasal Spray (Revised March 2008) ("Patanase® Label") was publicly available before October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

12. Each of Alcon's Patanol®, Pataday®, and Patanase® olopatadine products were commercially available in the United States prior to October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

**C. The Patents-in-Suit**

13. The '154 Patent may be referred to as the "Patent-in-suit."

14. United States Patent No. 8,791,154 ("the '154 Patent") issued on July 29, 2014 and is entitled "High Concentration Olopatadine Ophthalmic Composition." The '154 Patent names Daniel A. Gamache, Laman Alani, Malay Ghosh, Francisxo Javier Galán, Núria Carreras Perdiguer, and Onkar N. Singh as inventors.

15. The application that matured into the '154 Patent was filed on May 18, 2012 and claims priority to a provisional patent application (No. 61/487,789) that was filed on October 19, 2011.

16. The priority date for the asserted claims is October 19, 2011.

17. The '154 Patent is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") at the U.S. Food and Drug Administration ("FDA") in connection with Pazeo®.

18. Alcon is the assignee of and owns the '154 Patent.

19. It is stipulated that the products that are the subject of Defendants' Abbreviated New Drug Applications infringe asserted claims 8-9 and 21-24 of the '154 Patent. (D.I. 73); (D.I. 93); (D.I. 131-1, ¶ 96.)

## 1. The Asserted Claims

20. Alcon has asserted infringement of claims 8, 9, and 21-24 of the '154 Patent against Watson.

21. Alcon has asserted infringement of claims 8, 9, and 21-24 of the the '154 Patent against Lupin.

*i. '154 Patent, Claim 8*

22. Claim 8 of the '154 Patent claims:

"[a]n aqueous ophthalmic solution for treatment of allergic conjunctivitis, the solution comprising:
at least 0.67 w/v% but no greater than 1.0 w/v% olopatadine dissolved in the solution;
2.0 w/v% to 6.0 w/v% PEG having a molecular weight of 300 to 500;
2.0 w/v% to 6.0 w/v% polyvinylpyrrolidone;
at least 0.5% w/v% but no greater than 2.0 w/v% hydroxypropyl-γ-cyclodextrin; and
water."

*ii. '154 Patent, Claim 9*

23. Claim 9 of the '154 Patent claims: [a] solution as in claim 8 further comprising borate at a concentration of at least 0.18 w/v% but less than 0.5 w/v%."

*iii. '154 Patent, Claim 21*

24. Claim 21 of the '154 Patent claims: "[a]n aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:
At least 0.67 w/v% but no greater that 1.0 w/v% olopatadine dissolved in the silution;
2.0 w/v% to 6.0 w/v% PEG having a molecular weight of 300 to 500;
2.0 w/v% to 6.0 w/v% polyvinylpyrrolidone;
at least 0.5 w/v% but no greater than 2.0 w/v% hydroxypropyl-γ-cyclodextrin;
greater than 0.003 w/v% but less than 0.03 w/v% benzalkonium chloride; and
water.;
wherein the pH of the solution is 6.0 to 7.8 and the osmolality of the solution is 200 to 400 mOsm/kg."

*iv. '154 Patent, Claim 22*

25. Claim 22 of the '154 Patent claims: "[a] solution as in claim 21 further comprising at least 0.15 w/v% but no greater than 1.0 w/v% hydroxypropylinethyl cellulose."

*v. '154 Patent, Claim 23*

26. Claim 23 of the '154 Patent claims: "[a] solution as in claim 22 wherein:
i) the concentration of PEG is at least 3.0 w/v% but no greater than 5.0 w/v%;

ii) the concentration of polyvinylprrolidone is at least 3.0 w/v% but no greater than 5.0 w/v%; and
iii) the concentration of hydroxypropyl methylcellulose is at least 0.3 w/v% but no greater than 0.5 w//v%."

*vi. '154 Patent, Claim 24*

27. Claim 24 of the '154 Patent claims: "[a] solution as in claim 23 further comprising: at least 0.18 w/v% but less than 0.4 w/v% boric acid and at least 0.05 w/v% but no greater than 0.5 w/v% mannitol.

## 2. The Accused Products

*i. ANDA No. 20-8637 Submitted by Watson*

28. Watson submitted an Abbreviated New Drug Application ("ANDA") No. 208637 to the Food and Drug Administration ("FDA") under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, and sale of a generic olopatadine ophthalmic solution ("Watson's ANDA Product") prior to the expiration of the '154 Patent. .

29. Watson sent Alcon a letter dated November 3, 2015 ("Watson '154 Notice Letter"), stating that Watson had submitted an ANDA No. 208637 to the FDA seeking approval of the Watson's ANDA product.

30. Watson's '154 Notice Letter stated that the claims of the '154 patent are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 208637.

31. Alcon brought suit against Watson alleging infringement of the '154 patent under 35 U.S.C. § 100 et seq., including § 271(e)(2)(A), on December 16, 2015, within 45 days of receipt of Watson's '154 Notice Letter.

32. Watson had submitted an Abbreviated New Drug Application ("ANDA") No. 208637 to the Food and Drug Administration ("FDA") under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, and sale of a generic olopatadine ophthalmic solution ("Watson's ANDA Product") prior to the expiration of the '154 Patent.

33. Watson's '154 Notice Letter stated that the claims of the '154 patent are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 208637.

34. Alcon brought suit against Watson alleging infringement of the '154 patent under 35 U.S.C. § 100 et seq., including § 271(e)(2)(A), on December 16, 2015, within 45 days of receipt of Watson's '154 Notice Letter.

35. For purposes of this action only and only with respect to ANDA No. 208637, Watson's submission of ANDA No. 208637 constitutes an act of infringement of claims 4-6, 8-10, 12-14, 16-18, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided those claims are not found invalid or unenforceable. The commercial manufacture, use, sale, offer to sell, and/or importation into the United States of Watson's ANDA Product prior to the expiration of the '154 Patent would directly infringe, contribute to infringement of, and/or induce infringement of claims 4-6, 8-10, 12-14, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271, to the extent those claims are not found invalid or unenforceable.

*ii. ANDA No. 20-8896 Submitted by Lupin*

36. Lupin sent Alcon a letter dated March 11, 2016 ("Lupin's '154 Notice Letter"), stating that Lupin Ltd. had submitted an ANDA No. 208896 to the FDA under § 505(j) of the FFDCA § 355(j) seeking approval to engage in the commercial manufacture, use, and sale of a generic olopatiadine ophthalmic solution ("Lupin's ANDA Product") prior to the expiration of the '154 patent. Lupin's Ltd.'s '154 Notice Letter stated that the claims of the '154 patent are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 208886.

37. Alcon brought suit against Lupin alleging infringement of the '154 patent under 35 U.S.C. § 100 *et seq.*, including § 271(e)(2)(A), on March 28, 2016, within 45 days of receipt of Lupin Ltd.'s '154 Notice Letter.

38. For purposes of this action only and only with respect to ANDA No. 208896, Watson's submission of ANDA No. 208896 constitutes an act of infringement of claims 4-6, 8-10, 12-14, 16-18, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided those claims are not found invalid or unenforceable. The commercial manufacture, use, sale, offer to sell, and/or importation into the United States of Lupin's ANDA Product prior to the expiration of the '154 Patent would directly infringe, contribute to infringement of, and/or induce infringement of claims 4-6, 8-10, 12-14, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271, to the extent those claims are not found invalid or unenforceable.

39. Lupin sent Alcon a letter dated March 11, 2016 ("Lupin's '154 Notice Letter"), stating that Lupin Ltd. had submitted an ANDA No. 208896 to the FDA under § 505(j) of the FFDCA § 355(j) seeking approval to engage in the commercial manufacture, use, and sale of a generic olopatiadine ophthalmic solution ("Lupin's ANDA Product") prior to the expiration of the '154 patent. Lupin's Ltd.'s '154 Notice Letter stated that the claims of the '154 patent are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 208886.

34. Alcon brought suit against Watson alleging infringement of the '154 patent under 35 U.S.C. § 100 et seq., including § 271(e)(2)(A), on December 16, 2015, within 45 days of receipt of Watson's '154 Notice Letter.

35. For purposes of this action only and only with respect to ANDA No. 208637, Watson's submission of ANDA No. 208637 constitutes an act of infringement of claims 4-6, 8-10, 12-14, 16-18, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided those claims are not found invalid or unenforceable. The commercial manufacture, use, sale, offer to sell, and/or importation into the United States of Watson's ANDA Product prior to the expiration of the '154 Patent would directly infringe, contribute to infringement of, and/or induce infringement of claims 4-6, 8-10, 12-14, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271, to the extent those claims are not found invalid or unenforceable.

*ii. ANDA No. 20-8896 Submitted by Lupin*

36. Lupin sent Alcon a letter dated March 11, 2016 ("Lupin's '154 Notice Letter"), stating that Lupin Ltd. had submitted an ANDA No. 208896 to the FDA under § 505(j) of the FFDCA § 355(j) seeking approval to engage in the commercial manufacture, use, and sale of a generic olopatadine ophthalmic solution ("Lupin's ANDA Product") prior to the expiration of the '154 patent.. Lupin's Ltd.'s '154 Notice Letter stated that the claims of the '154 patent are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 208886.

37. Alcon brought suit against Lupin alleging infringement of the '154 patent under 35 U.S.C. § 100 *et seq.*, including § 271(e)(2)(A), on March 28, 2016, within 45 days of receipt of Lupin Ltd.'s '154 Notice Letter.

38. For purposes of this action only and only with respect to ANDA No. 208896, Watson's submission of ANDA No. 208896 constitutes an act of infringement of claims 4-6, 8-10, 12-14, 16-18, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided those claims are not found invalid or unenforceable. The commercial manufacture, use, sale, offer to sell, and/or importation into the United States of Lupin's ANDA Product prior to the expiration of the '154 Patent would directly infringe, contribute to infringement of, and/or induce infringement of claims 4-6, 8-10, 12-14, and 20-27 of the '154 Patent pursuant to 35 U.S.C. § 271, to the extent those claims are not found invalid or unenforceable.

39. Lupin sent Alcon a letter dated March 11, 2016 ("Lupin's '154 Notice Letter"), stating that Lupin Ltd. had submitted an ANDA No. 208896 to the FDA under § 505(j) of the FFDCA § 355(j) seeking approval to engage in the commercial manufacture, use, and sale of a generic olopatadine ophthalmic solution ("Lupin's ANDA Product") prior to the expiration of the '154 patent. Lupin's Ltd.'s '154 Notice Letter stated that the claims of the '154 patent are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 208886.

40. Alcon brought suit against Lupin alleging infringement of the '154 patent under 35 U.S.C. § 100 *et seq.*, including § 271(e)(2)(A), on March 28, 2016, within 45 days of receipt of Lupin Ltd.'s '154 Nonce Letter.

### 3. State of the Art

41. U.S. Patent No. 5,641,805 ("Hayakawa"), entitled "Topical Ophthalmic Formulations for Treating Allergic Eye Diseases," issued on June 24, 1997 to Hayakawa et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

42. Vogelson et al., "Preclinical and clinical antiallergic effect of olopatadine 0.2% solution 24 hours after topical ocular administration." Allergy Asthma Proc. 2004 Jan.-Feb., 25(1):69-75 ("Vogelson") was published in 2004, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

43. Yanni et al., "The In Vitro and In Vivo Ocular Pharmacology of Olopatadine (AL- 4943A), an Effective Anti-Allergic/Antihistamine Agent," Journal of Ocular Pharmacology and Therapeutics, 12(4):389-400 (1996) ("Yanni 1996") was published in 1996, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

44. U.S. Patent No. 6,375,973 ("Yanni 2002") issued on April 23, 2002 to John Yanni, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

45. U.S. Patent Application Publication No. 2008/0139531 ("Yanni 2008") was published on June 12, 2008 to Yanni et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

46. U.S. Patent Publication No. 2011/0082145 ("Schneider") was published on April 7, 2011 to Schneider et al., and meets the requirements of 35 U.S.C. § 102(e) as prior art, but Alcon does not concede that it is relevant prior art.

47. U.S. Patent Application Publication No. 2010/0227917 ("Nakakura") was published on September 9, 2010 to Nakakura et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

48. Sharif et al., "Characterization of the Ocular Antiallergic and Antihistaminic Effects of Olopatadine (AL-4943A), a Novel Drug for Treating Ocular Allergic Diseases," The Journal of Pharmacology and Experimental Therapeutics, 278(3):1252-61 (1996) ("Sharif") was published in 1996, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

49. International Publication No. WO 2008/015695 ("Bhowmick") was published on February 7, 2008 to Bhowmick et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

50. Loftsson & Petersen, "Cyclodextrin solubilization of ETH-615, a zwitterionic drug," Drug Devel. Ind. Pharm., 24(4):365-70 (1998) ("Loftsson 1998") was published in 1998, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

51. U.S. Patent No. 6,995,186 ("Castillo") issued on February 7, 2006 to Castillo et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

52. U.S. Patent Application Publication No. 2007/0142458 ("Singh") was published on June 21, 2007 to Singh et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

53. PCT International Application Publication No. WO 97/010805 ("Kis") was published on March 27, 1997 to Kis et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

54. Loftsson et al., "Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye," Acta Ophthalmologica Scandinavica 144-150 (2002) ("Loftsson 2002") was published in 2002, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

55. Nandi et al., "Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye," Acta Ophthalmologica Scandinavica 144-150 (2002) ("Loftsson 2002") was published in 2002, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

56. Handbook of Pharmaceutical Excipients (5th Ed. 2006) ("Handbook") was published in in 2006, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

57. Thorsteinn Loftsson & Dominique Duchene, "Cyclodextrins and Their Pharmaceutical Applications," *International Journal of Pharmaceutics* 329:1-11 (2007) ("Loftsson 2007") was published in 2007, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

58. Marcus E. Brewster & Thorsteinn Loftsson, "Cyclodextrins as Pharmaceutical Solubilizers," Advanced Drug Delivery Reviews 59:645-66 (2007) ("Brewster") was published in 2007, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

59. Jansook et al., "CDs as solubilizers: Effects of excipients and competing drugs," International Journal of Pharmaceutics, 379:32-40 (2009) ("Jansook") was published in 2009, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

60. Ophthalmic Drug Facts, 20th ed. (Jimmy D. Bartlett, ed., 2009) ("Bartlett") was published in 2009, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

61. "Ophthalmic Drug Formulations," Clinical Ocular Pharmacology, 5th ed. (Jimmy D. Bartlett, ed., 2008) ("Bartlett II") was published in 2008, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

62. Joseph P. Remington, The Science and Practice of Pharmacy (21st Ed. 2006) ("Remington's") was published in in 2006, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

63. U.S. Patent No. 6,407,079 B1 ("Janssen Patent") issued on June 18, 2002 to Muller et al., and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

64. The Prescribing Information for Patanol® (Olopatadine Hydrochloride Opthalmic Solution) 0.1% (Revised August 2002) ("Patanol® Label") was publicly available before October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

65. Highlights of Prescribing Information for Pataday® (Olopatadine Hycdrochloride Opthalmic Solution) 0.2% (Revised August 2010) ("Pataday® Label") was publicly availavle before October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

66. Alcon Highlights of Prescribing Information and Labeling for Patanase® (Olopatadine Hydrochloride) Nasal Spray (Revised March 2008) ("Patanase® Label") was publicly available before October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

67. Each of Alcon's Patanol®, Pataday®, and Patanase® olopatadine products were commercially available in the United States prior to October 19, 2010, and meets the requirements of 35 U.S.C. § 102(b) as prior art, but Alcon does not concede that it is relevant prior art.

**D. Procedural History**

68. On December 16, 2015, Plaintiff filed patent infringement claims against Watson asserting infringement of the patents-in-suit, within 45 days of receipts of Watson's '154 Notice Letter under Civil Action No. 15-1159. (D.I. 1.)

69. On June 2, 2016, Plaintiff added Lupin Ltd., and Lupin Pharms., Inc. to Civil Action No. 15-1159 for infringement of the patents-in-suit. (D.I. 31.)

70. On December 9, 2016, it was stipulated that Watson's ANDA infringes claims 8-9 and 21-24 of the '154 Patent. (D.I. 71.)

71. On February 2, 2017, it was stipulated that Lupin's ANDA infringe claims 8-9 and 21-24 of the '154 Patent. (D.I. 90.)

72. On March 24, 2017, Alcon brought suit against Lupin alleging infringement of the '053 Patent within 45 days of receipt of Lupin's '053 Notice Letter.

73. On October 4, 2017, Plaintiff and Watson stipulated that Alcon's claims against Watson for infringement of the '053 Patent are dismissed with prejudice as applied to ANDA No. 208637 and that Defendants' counterclaims against Alcon regarding the '053 Patent are dismissed with prejudice. (D.I. 140.)

74. On October 4, 2017, Plaintiff and Lupin stipulated that Alcon's claims against Lupin for infringement of the '053 Patent are dismissed with prejudice as applied to ANDA No. 208896 and that Lupin's counterclaims against Alcon regarding the '053 Patent are dismissed with prejudice. (D.I. 140.)

75. In the Proposed Joint Pretrial Order, Defendants asserted obviousness, enablement, and written description defenses. (D.I. 131.)

76. The court held a bench trial on October 2, 2017 through October 5, 2017. After opening statements, Defendants dropped all written description arguments and all but one enablement argument. Tr. 56:4-25, 58:1-5. At trial, the court granted judgment rejecting Defendants' remaining enablement argument at the close of Defendants" case. Tr. 391:25-393:11. Thus, only Defendants' assertion of obviousness remains for decision.

77. On November 16, 2017, Defendants and Plaintiff submitted their Post-Trial Proposed Findings of Fact and Conclusions of Law. (D.I. 149); (D.I. 150).

78. On February 22, 2018, Plaintiff Alcon Research, Ltd. and Defendant Watson Laboratories, Inc. Stipulated to dismissal of all claims and defenses asserted by Alcon against Watson and all claims and defenses asserted by Watson against Alcon. Parties agreed to bear their own costs, disbursements and attorneys' fees. (D.I. 153.)

79. The only remaining issue for the court to decide is whether claims 8-9 and 21-24 of the '154 Patent are obvious.

## III. DISCUSSION AND CONCLUSIONS OF LAW

These consolidated cases arise under the patent laws of the United States. The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a). Venue is

proper in this court under 28 U.S.C. §§ 1391, and 1400(b). After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that the Defendants have failed to establish by clear and convincing evidence that the asserted claims of the '154 Patent would have been obvious to a person having ordinary skill in the art as of the October 19, 2011 priority date. The asserted claims of the '154 Patent are, therefore, valid under 35 U.S.C. § 103. The court's reasoning follows.

**A. Obviousness**

**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." Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). 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 patent shall be presumed valid." 35 U.S.C. § 282. A party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence[2] that the invention described in the patent would have been obvious to a person of ordinary skill in the

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

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 Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit teaching, suggestion, or motivation in the prior art, the "TSM test," in order to find obviousness. *See id.* at 415. The *KSR* Court acknowledged, however, the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *KSR*, 550 U.S. at 418-19; *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373-74 (Fed. Cir. 2008); *Endo Pharms. Inc. v. Actavis Labs UT, Inc.*, 660 F. App'x 959, 964-65 (Fed. Cir. 2016). The "mere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for

patentability." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1379-80 (Fed. Cir. 2006).

**2. The Level of Ordinary Skill in the Art**

A person having ordinary skill in the art ("POSA") with respect to the patent-in-suit would have the skills of an ophthalmic formulator who has a pharmacy degree, Pharm. D. or Ph.D. in various fields such as biochemistry, pharmaceutical sciences, or a related field, postgraduate experience developing and testing compositions for the treatment of ocular diseases, and familiarity in developing ophalmic formulations, as well as an understanding of ocular physiology, preservative efficacy testing, solubility testing and other aspects of ophthalmic formulation. Tr. 402:1-15. A POSA would also have the skills of a clinician with experience treating ophthalmic conditions, specifically allergic conjunctivitis, and conducting clinical trials of formulations for the treatment of allergic conjunctivitis. *Id.*; Tr. 650:1-10.[3]

**3. Obviousness of the '154 Patent**

The court will consider whether Defendants have established a *prima facie* case of obviousness in light of the evidence adduced at trial. Specifically, Defendants challenge the validity of asserted claims 8-9 and 21-24 of the '154 Patent. (D.I. 149 at 1.) The obviousness analysis hinges on the core elements of the independent claims asserted, 8 and 21 which require: (1) an aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis comprising; (2) at least 0.67 w/v% but no greater that 1.0 w/v % olopatadine dissolved in the solution; (3) 2.0 w/v% to 1.0 w/v% PEG having a molecular weight of 300 to 500; (4) 2.0 w/v% to 6.0 w/v% polyvinylpyrrolidone ("PVP") at least 0.5 w/v% but no greater than 2.0 w/v% hydroxypropyl-γ-

[3] The court's definition is drawn from the testimony of Dr. Orest Olejnik (Tr. 402:1-18.) While Defendants proposed slightly different definitions of a POSA, both parties' experts testified that their opinions would not change, regardless of whose definition of a POSA applied (Tr. 402:25-403:6 (Olejnik); Tr. 258:3-13 (Maurin)).

cyclodextrin ("HPγCD"); and (5) water. '154 Patent, Claim 8. Independent claim 21 of the '154 Patent further discloses that (1) greater than 0.003 w/v % but less than 0.03 w/v % benzalkonium chloride; and (2) water wherein the pH of the solution is 6.0 to 7.8 and the osmolality of the solution is 200 to 400 mOsm/kg. '154 Patent, Claim 21.[4] Defendants argue the asserted claims were obvious for six reasons: (1) that it would have been obvious to select a concentration of 0.67% to 1.0% w/v olopatadine; (2) a POSA would have been motivated to develop a solution; (3) a POSA would have known how to achieve a 0.67 to 1.0% olopatadine solution; (4) it was well within the level of ordinary skill to determine suitable amounts of the solubilizing agents for use with olopatadine; (5) Dr. Olejnik's opinions are conclusory and unsupported; and (6) claims 9 and 21-24 require only standard ophthalmic excipients and physical properties that would have been obvious to a POSA. The court addresses each of these arguments in turn.

Prior to addressing expert testimony on motivations to combine prior art references, the court will conduct a detailed analysis of the statutory prior art published before the earliest priority date of the patent-in-suit: October 19, 2011.

**a. The *Scope and Content of the Prior Art***

As of October 19, 2011, the priority date, the main allergic conjunctivitis treatments included Patanol® (0.1% olopatadine), and Pataday® (0.2% olopatadine), which were commercially available from Alcon Labs, Inc. JTX-1 at 1:29-31; JTX-64; JTX-65. Patanol® is approved for the treatment of the signs (redness) and symptoms (itching) associated with allergic conjunctivitis, and is dosed twice daily. Tr. 718:9-11; JTX-64. Pataday® is approved for once-daily treatment of itching associated with allergic conjunctivitis. Tr. 718:11-13; JTX-65. No higher concentration

[4] A solution is a drug homogenously dissolved throughout the vehicle (such as water). In contrast, in a suspension, some of the drug is dissolved in the vehicle and some of the drug exists as solid particulate matter. Tr. 416:20-417:4. As a result, a suspension may require shaking to dissolve the particulate prior to use.

of olopatadine other than that in Pataday® had been used in humans as of the priority date. Tr. 657:1-7; '154 Patent at 1:29-31. Olopatadine as an active ingredient in a drug was known to have advantages over other compounds tested to treat eye allergies. Tr. 157:8-16. Traditional antihistamines effectively reduced the itching, but did not effectively reduce the redness associated with ocular allergic conjunctivitis. Tr. 652:21-653:19. Olopatadine, by contrast, reduces both itching and redness because it is both an antihistamine and a mast cell stabilizer—it prevents mast cells from releasing mediators (mast cell stabilization) and prevents histamine from binding to receptors (antihistaminic activity). Tr. 653:11-16.[5]

In 1996, John M. Yanni, along with other researchers in the Allergy/Information Research Group at Alcon Labs., Inc., published the Yanni 1996 reference, entitled "The *In Vitro* and *In Vivo* Ocular Pharmacology of Olopatadine (AL-4943A), an Effective Anti-Allergic/Antihistaminic Agent." JTX-50. This study provided both *in vitro* and *in vivo* data showing the concentration-dependent efficacy of olopatadine in *suspensions* at concentrations up to 1.0%. JTX-50 at 6-9; Tr. 88:24-89:6, 103:20-104:13. Tables 1 and 2 show olopatadine's concentration-dependent efficacy in the guinea pig passive anaphylaxis model, which predominantly assesses olopatadine's mast-cell stabilization mechanism. JTX-50 at 7; Tr. 91:24-92:5, 94:8-15, 97:25-98:9. More specifically, Table 2 shows that 1.0 % w/v did not perform significantly better than a 0.1% concentration of olopatadine at the 30 minute mark. JTX-50 at 7, Table 2.[6] Table 3 shows olopatadine's concentration-dependent antihistaminic activity measured at time points ranging from 5 minutes to 24 hours of the *suspension*. JTX-50 at 8; Tr. 429:7-11. Importantly, Table 3 shows that while

[5] Eye allergies occur when an allergen—like pollen—enters the eye and triggers the release of mediators like histamine from eye mast cells, which bind to receptors on other tissues in the eye, causing itching and redness. Tr. 650:13-651:2. "Early phase" symptoms appear within minutes of allergen exposure and subside within about 30 minutes. Tr. 651:3-16.

[6] Specifically, the *r*-value of the regression model at the 30-minute mark was 0.542, which does not show a significant difference between the 0.1 and 1.0% w/v. JTX-50 at 7, Table 2.

the 0.1% and 1.0% olopatadine compositions achieved similar efficacy, the suspension containing 1.0% maintained its heightened response at later time points. Tr. 429:12-431:7, 432:22-435:11, 451:8-16. This means that 1.0% had a longer duration of effect, as the suspension's particulate matter retained in the eye dissolved over time. *Id.* Figures 1A and 1B describe concentrations well below 0.67%, with a maximum of about 0.34% (-2.0 log(M)). Tr. 440:2-441:14; (D.I. 150, ¶ 27.) However, no table or figure in the reference discloses a *solution* containing 0.67-1.0% olopatadine and no components in the study are shown to dissolve the olopatadine at 1.0% w/v. JTX-50 at 393, 395-96; Tr. 428:2-10.

The Hayakawa reference is one of Plaintiff's patents that issued in 1997 entitled "Topical Ophthalmic Formulations for Treating Allergic Eye Diseases." JTX-55; Tr. 15:7-10. The Hayakawa reference covers the commercial product Patanol® (0.1% w/v olopatadine). Tr. 12:10-11. Hayakawa states that olopatadine "may be administered to the eye by means of conventional topical ophthalmic formulations, such as solutions, suspensions, or gels. The preferred formulation for topical ophthalmic administration of [olopatadine] is a solution," which is "administered as eye drops." JTX-55 at 4. "The eye drops produced as a result need only be applied to the eyes a few times a day in an amount of one to several drops at a time." *Id.* The patent further discloses "[t]he concentration of [olopatadine] is 0.0001 to 5 w/v, preferably 0.001 to 0.2 w/v %, and most preferably about 0.1 w/v %, based on the sterilized purified water." *Id.*

Loftsson 1998, entitled "Cyclodextrin Solubilization of ETH-615, a Zwitterionic Drug," was published by Thorsteinn Loftsson and Dorte Seir Peterson, researchers at the University of Iceland, Department of Pharmacy. JTX-52. The study analyzes the effect of adding polymers to the following cyclodextrins: (1) CMbCDm CDSBE; (2) HPβCD; (3) MbCD; and (4) HTMAPCD. JTX-52 at 4. By comparing cationic cyclodextrins to *uncharged* cyclodesxtrins the study found

that uncharged cyclodextrins had a "much larger solubilizing effect on ETH-615 than the charged ones."

The Yanni 2002 reference is a patent issued to Plaintiff in 2002 entitled "Opthalmic Anti-Allergy Compositions Suitable for use with Contact Lenses." JTX-56. This reference discusses anti-allergy *compositions* comprising of olopatadine and a polymeric quaterny ammonium preservative suitable for use by patients wearing contact lenses. *Id.* This patent is directed towards multiple dosage forms of treatment including, but not limited to, solutions, suspensions, gels, and emulsions. *Id.* The description of the invention specifies that "[t]he concentration of olopatadine in the compositions of the present invention will range from about 0.0001 to 5%(w/v), preferably from about 0.001 to 0.25% (w/v), and most preferably from about 0.1 to 0.25% (w/v), based on the sterilized purified water." *Id.* at 2.

The Nandi reference, entitled "Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone," published in 2003. JTX-58. This study used progesterone, a neutral hydrophobic compound as the model compound with the goal of testing whether PEG-400 and cyclodextrins may have a synergistic effect on the solubility of progesterone. The results show that the solubility values were up to 96% higher than the theoretical values. The reference concluded that "[i]n general, the addition of polysorbate 80 to the PEG-400/water systems containing CDs affected synergism negatively." JTX-58 at 5.

The Vogelson reference, a 2004 study entitled "Preclinical and Clinical Antiallergic Effect of Olopatadine 0.2% Solution 24 Hours after Topical Ocular Administration," tested the efficacy of a topical ocular drop administration over the course of 24-hours on guinea pigs. JTX-53. The study explains that preclinical experiments conducted in guinea pigs indicated that olopatadine 0.2% w/v solution "was significantly effective 24 hours after dosing. This concentration of olopatadine

provided significantly more efficacy than Patanol[®] (olopatadine 0.1%) 24 hours after administration while being as effective as Patanol[®] (olopatadine 0.1%) 5 minutes after administration." JTX-53. Results from a Conjunctival Antigen Challenge ("CAC") confirmed clinical efficacy of olopatadine 0.2% over 24 hours. *Id.* Further, the reference states that "[i]ncerases in concentration between 0.175 and 0.30% were significantly more effective that 0.1%, but were not different within this range. Higher concentrations were more effective. From 0.5% to 1.0% olopatadine, however, essentially the same result occurred. The aqueous solubility of the drug limited formulations and the desire to maintain a comfortable solution formulation equivalent to Patanol® (olopatadine 0.1%) led to the selection of a 0.2% concentration for clinical evaluation." JTX-53 at 6.

The Castillo reference is a 2006 patent entitled "Olopatadine Formulations for Topical Administration," which discloses the Pataday® product as a topical formulations of olopatadine for treatment of allergic or inflammatory disorders of the eye and nose. JTX-54 at 1. This prior art reference discloses the highest concentration of olopatadine disclosed at a near-neutral pH at 0.33% w/v. JTX-54, Table 5. The solution formulations in this patent contain approximately 0.17-0.62% w/v olopatadine. JTX-54 at 2:38-39. The concentration for use in the eye is 0.17 to 0.25% and most preferably 0.18-0.22%. JTX-54 at 2:40-42. The reference does not disclose information for soluability of olopatdine at 0.67% w/v. JTX-54 at 7, Table 5. The highest amount of olopatadine disclosed at a near-neutral pH is at 0.33% w/v olopatadine. Tr. 51:18-25; JTX-54, Table 5.

Marcus E. Brewster and Thorsteinn Loftsson published the Brewster reference, entitled "Cyclodextrins as pharmaceutical solubilizers" in 2007. JTX-59. The reference is a review intended to provide a general background to the use of cyclodextrin as solubilizers while

highlighting the kinetic and thermodynamic tools and parameters useful in the study of drug solubilization by cycloxextrins. *Id.*

Yanni 2008 is a patent application assigned to Plaintiff published on June 12, 2008. JTX-60. The invention relates generally to the field of mast cell stabilizers, pharmaceutics, and the treatment and prevention of wounds. JTX-60 at 2. More specifically, the reference specifies that the invention concerns methods of treating or preventing wounds in a subject that involve administering a pharmaceutically effective amount of a composition comprising one or more mast cell stabilizers to the wound of the subject. *Id.*[7] Exemplary mast cell stabilizers include "olopatadine, derivatives of olopatadine, alcaftidine, derivatives of alcaftadine, spleen tyrosine kinase inhibitors, and dihydropyridines. JTX-60 at 3. The reference additionally lists as non-exclusive examples hundreds of derivatives of the mast cell stabilizer olopatadine that an inventor could choose from. JTX-60 at 3-5. The reference further discloses that the "compositions of the present invention will range from 0.01% to 0.8%, and is preferably from 0.1-0.8%." JTX-60 at 8.

The Bhowmick reference, published in 2008, is an international patent published pursuant to the Patent Cooperation Treaty administered by the World Intellectual Property Organization. JTX-70. This invention relates to an inclusion complex of olopatadine or its pharmaceutically equivalent salt and hydroxypropyl-β-cyclodextrin ("HPβCD"). The problem the reference purports to solve is getting enough olopatadine into the solution, having a neutral pH, and having osmolality. JTX-70. The reference discloses that "[p]referably, the solution formulations intended for use in the eye contain about 0.17% to about 0.25% olopatadine and the solution

[7] "A 'mast cell stabilizer' is defined herein to refer to an agent that inhibits the degranulation of sensitized and/or nonsenstitized mast cells. A mast cell stabilizer thus inhibits the release of inflammatory mediators, such as histamine, SRS-A, and chymase from mast cells. A wide variety of mast cell stabalizzers are known in the art. These agents are known in the art as antiasthmatic and antiallergic agents. However, only mast cell stabilizers effective in human tryptase-and chymase-containing mast cells (connective tissue type) are effective in the methods of the present invention. One of ordinary skill in the art would be familiar with this class of agents. Exemplary mast cell stabilizers include olopatadine, derivatives of olopatadine, alcaftidine. . . ." JTX-60 at 3.

formulations intended for the nose contain about 0.35% to about 0.62% olopatadine." JTX-70 at 5. The reference further lists preferred cyclodextrins for use in the "present invention as alkyl cyclodextrins, hydroxyl alkyl cyclodeztrin, such as hydroxyl propyl beta-cyclodextrin, carboxy alkyl cyclodextrins and sulfoalkyl ether cyclodesctrin, such as sulfo butyl ether beta-cyclodextrin." JTX-70 at 6. The patent lists about fifty other cyclodextrins that are "suitable cyclodextrins." *Id.* The reference then states that "[t]he most preferred cyclodextrin for use in the pharmaceutical composition of the present invention is hydroxyl propyl beta-cyclodextrin . . . [which] may be used in concentrations from about 0.1 % to about 20%w/v of the concentration and more preferably used in concentrations ranging from about 1.0% to about 10% w/v of the composition. Generally, for solutions meant for ophthalmic administration[,] [the] preferable concentration of hydroxypropyl beta-cyclodextrin is in the range from about 1.0% to about 5%; for solutions meant for nasal administration, the concentration of hydroxypropyl beta-cyclodextrin is in the range from about 1.0% to 10%." JTX-70 at 5-6.

The 2009 Jansook reference entitled "CDs as Solubulizers: Effects of Excipients and Competing Drugs" was published by Phatsawee Jansook and Thorsteinn Loftsson at the University of Iceland. JTX-63. The reference concludes that "[c]ommon pharmaceutical excipients like various salts, preservatives, and water-soluble polymers can have a significant effect on cyclodextrins and the drug bioavailability from aqueous drug formulations." Tr. 501:20-25; JTX-63 at 39.

***b. Selecting a Concentration of 0.67 to 1.0% Olopatadine at a Near-Neutral pH***

As is clear after a recitation of the prior art, a 0.67-1.0% w/v olopatadine concentration at a near-neutral pH was not disclosed in the references that pre-date the patent-in-suit. In arguing that the concentration of 0.67 to 1.0% w/v olopatadine would have been obvious to a POSA,

Defendants assert two combinations of prior art references: (1) a combination of Hayakawa (JTX-55), Yanni 2002 (JTX-56), and Yanni 2008 (JTX-60); and (2) Yanni 1996 (JTX-50) and Vogelson (JTX-53). Tr. 308:24-309:1, 331:8-12. The court finds that neither combination renders the selection of the olopatadine concentration obvious. Tr. 502:23-503:10.

*i. Hayakawa, Yanni 2002, and Yanni 2008 did not teach the use of solutions containing 0.67-1.0% w/v olopatadine.*

Defendants first argue that a combination of Hayakawa, Yanni 2002, and Yanni 2008 would make the selection of 0.67 to 1.0 % w/v olopatadine at a near neutral pH obvious to a POSA. (D.I. 149, ¶¶ 4-10.) Defendants make three primary arguments to support their position. First, Defendants assert that the Hayakawa reference disclosed the use of ophthalmic solutions containing up to 5% olopatadine and identified solutions as the preferred ophthalmic dosage form. Tr. 86:14-22; JTX-55 at 6:32-35.[8] Second, Defendants assert that Yanni 2002 taught "compositions" containing up to 5% olopatadine. (D.I. 149, ¶ 7); Tr. 269:20-270:14; 420:14-23. Third, Defendants assert Yanni 2008 taught that compositions containing up to 0.8% olopatadine are "preferred." Tr. 334:13-16; (D.I. 149, ¶ 9.) The court disagrees.

The court finds that persons having ordinary skill in the art would not have selected a concentration of 0.67 to 1.0% w/v olopatatdine to treat allergic conjunctivitis in light of the asserted prior art. While Hayakawa discloses a concentration range of olopatadine from 0.0001 to 5%, it does not disclose an ophthalmic *solution* containing 0.67-1.0 w/v% olopatadine at a near-neutral pH. JTX-55; Tr. 407:5-8, 408:14-17. Instead, Hayakawa states that in solutions, 0.1% olopatadine (Patanol®) is the preferred amount. JTX-55 at 6:43-45. That disclosure alone would

[8] Defendants state that "[h]aving embraced the enablement of claim 2 in an effort to prevent companies from marketing ophthalmic solutions of olopatadine, Alcon should be estopped from now disclaiming its enablement. (D.I. 149, ¶ 6.) Defendants, however, provide no evidence or any citations to support their position. The court, therefore, finds no need to address this issue.

not have taught the POSA that one could make an ophthalmic solution containing 0.67 to 1.0% olopatadine because it only discloses examples testing up to the preferred amount of 0.1 w/v % as a solution or a gel. Tr. 405:5-8, 408:14-17.[9] In Hayakawa, all solutions described contained well below 0.67% olopatadine and all tested contained below 0.1% olopatadine. JTX-55 at 4:46-6:30, 7:1-15; Tr. 125:17-126:4, 407:15-19, 408:24-410:9.

The court finds that Yanni 2002 does not disclose an ophthalmic solution within the range specified in the claims at issue. JTX-56. Dr. Olejnik testified that Yanni 2002 simply provides a long list of excipients to choose from and that it does not teach one how to solubilize olopatadine or even disclose the solubility limit. Tr. 422:4-423:23. While the range for all types of compositions is from 0.0001 to 5% w/v olopatadine, Yanni 2002 discloses that the preferred range of olopatadine for ophthalmic solutions is 0.1 to 0.25% w/v olopatadine. Tr. 422:10-423:22.

Lastly, Yanni 2008 discloses a concentration of olopatadine ranging from 0.01-0.8% for all types of compositions. JTX-60. Dr. Olejnik, a person having ordinary skill in the art, testified that the compositions disclosed in the patent, include nonsolution dosage forms—suspensions, gels, ointments, emulsions, and bioerodible implants—as well as compositions not intended for ophthalmic use, and those directed toward non-human use. JTX-60; Tr. 424:7-25, 378:18-380:4, 382:2-383:19. While the parties agree that the broad term "compositions" include solutions, all compositions are not solutions and the reference does not teach an ophthalmic solution with at least 0.67% olopatadine. Tr. 424:3-6. The POSA would understand that Example 1, which recites a concentration range of 0.0025-1.0% of a "[h]uman connective tissue mast cell stabilizer," is

[9] Defendants do not address whether a POSA would combine these references. Instead, Defendants simply state that they "do not rely on Hayakawa, Yanni 2002, or Yanni 2008 alone to make a 0.67-1.0% olopatadine solution, as other prior art expressly taught how to prepare such solutions." (D.I. 149, ¶ 10.)

directed generally toward the entire class of mast cell stabilizers described in the patent; not about olopatadine specifically. JTX-60, ¶¶ 20-23, 99; Tr. 425:1-426:10, 380:5-382:1.

*ii. Effectiveness of 0.67 to 1.0% w/v olopatadine in the Prior Art.*

Defendants assert that Yanni 1996 and Vogelson would have motivated a POSA to select olopatadine concentrations of 0.7 to 1.0%. Tr. 108:25-109:7; (D.I. 149, ¶ 12.) Dr. Modi, an expert qualified to discuss dose selection, testified that Yanni 1996 provided both *in vitro* and *in vivo* data showing the concentration-dependent efficacy of olopatadine at concentrations up to 1.0%. JTX-50 at 6-9; (D.I. 149, ¶ 12.)[10] For example, Table 3 shows olopatadine's concentration-dependent antihistaminic activity measured at time points ranging from 5 minutes to 24 hours and shows that 0.1% has a continuous decline in efficacy while 1.0% olopatadine maintains maximal efficacy at 4, 8, and 24 hours. JTX-50, Table 3; Tr. 102:21-103:19. Dr. Modi further testified that the Vogelson reference demonstrates that a POSA would not have expected a concentration of 0.7 to 1.0% olopatadine to improve efficacy at all points because there were "concentrations in the middle time points that were fairly reaching maximal efficacy. But at early times and at later time points you would have closer to maximal efficacy at higher concentrations." Tr. 110:13-20; JTX-53, Table 2. In Vogelson, efficacy at 24-hours reached a plateau at a concentration of 0.75 to 1.0% olopatadine. Tr. 106:7-14. There was, however, no difference in efficacy among the three highest olopatadine concentrations, 0.5, 0.75, and 1.0%, nor was there data showing what happened during the interval between 0.5-0.75%. Tr. 447:5-24. Dr. Modi stated that a clinician would place the greatest weight on human clinical data in evaluating the expected efficacy of a particular concentration even though no human clinical data were available for 0.67-1.0% olopatadine. Tr.

[10] *In vitro* studies occur outside of the living organism in a controlled environment. This may lead to results that do not correspond to circumstances in living organisms. Tr. 174: 17-23, 698:5-8. *In vivo* studies occur on living organisms and are trials tested on living organisms such as animals or humans. Tr. 698:5-8, 701:10-15.

121:9-15. Dr. Modi further explained that the POSA would consider that there was no evidence of dose-limiting toxicity in humans with Patanol® (0.1%) and Pataday® (0.2%), despite a doubling in the concentration of olopatadine. Tr. 110:24-111:25.

In contrast, Dr. Torkildsen, a POSA and clinician who has performed hundreds of clinical research studies, testified that the available clinical data showed concentrations of olopatadine well below 0.67% were effective. Tr. 664:14-665:13.[11] Dr. Torkildsen explained that the POSA would be concerned that increasing the concentration would increase adverse effects that are problematic for patients. Tr. 667:10-668:25; JTX-65 at 2. Dr. Torkildsen explained that Pataday® is dosed once per day, which the POSA would consider to be the ideal dosing frequency. Tr. 660:6-13. As Dr. Olejnik explained, the high potency shown in olopatadine's $ED_{50}$ and $IC_{50}$ values provide no reason to select an olopatadine concentration of 0.67-1.0%.[12] JTX-50 at 8-9; Tr. 435:12-436:21, 441:19-443:2. Dr. Olejnik testified that the POSA would expect that ample olopatadine was available at lower concentrations to achieve maximum effect because a low value indicates a drug is more potent. Tr. 661:20-665:14; JTX-1 at 23:46-56. According to Plaintiff, the POSA would not have motivation to increase the concentration of olopatadine to improve duration of effect from 16 to 24 hours. Tr. 763:9-764:2. In addition, Dr. Torkildsen explained that products seeking approval for once-daily dosing are assessed 16 hours after administration, which is sufficient

[11] An initial clinical trial found concentrations of 0.05 and 0.1%—not the 0.15% concentration—to be "the most effective," and a second trial confirmed both were effective. Tr. 679:21-681:21; JTX-145 at 2, 8. Doubling the concentration did not increase efficacy. Tr. 680:23-681:18. This is consistent with clinical observations for the commercial olopatadine products, where the efficacy of Pataday® (0.2%) is similar to that of Patanol® (0.1%); it merely has less frequent dosing. Tr. 658:11-660:5; JTX-102A at 115.

[12] According to Dr. Olejnik, a POSA would not automatically correlate the $IC_{50}$ value with a specific dose. He explained that whether using $ED_{50}$ or $IC_{50}$, they are just values that enable pharmacologists and others as part of a team to understand the potency of the drug. Dr. Olejnik testified that it is not something that will finalize the way you are going to proceed down the road in drug development and select the final system; it is just one of many data points a POSA would have on the road of drug development. Tr. 436:4-21.

because patients generally are exposed to ocular allergens only while awake, *i.e.*, about 16 hours per day. Tr. 702:22-703:11.

While Defendants suggest that the POSA would have been motivated to formulate such a solution in order to improve upon the efficacy of Pataday® between 16 and 24 hours, they presented no evidence that the POSA recognized such a need. Tr. 763:9-13.[13] Where, as here, the problem solved by the invention was unrecognized in the art, a POSA would not have been motivated to solve the problem and the invention would not be obvious, or even obvious to try. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (holding no reason to improve upon the prior art when it was not "recognized or disclosed" in the prior art). The court therefore, is persuaded that the POSA would not have been motivated to select 0.67 to 1.0% w/v olopatadine or combine any of the cited references because the prior art asserted would not teach the POSA what concentration of olopatadine to select. While olopatadine was effective in the prior art, it was not tested at the dosage that was used in the asserted claims.

*iii. Motivation to Develop a 0.67% to 1.0% Olopatadine Solution*

By the priority date, persons having ordinary skill in the art knew that little is routine in ophthalmic formulation. Tr. 499:4-500:2. Specifically, they knew ophthalmic formulation has nuances that can lead to interactions and unpredictable results. *Id.* The prior art references listing olopatadine products on the market as of the priority date and those likely to be on the market in the next few years did not list any ophthalmic solutions for the treatment of allergic conjunctivitis with a concentation of 0.67 to 1.0 % w/v olopatadine at a near-neutral pH.

[13] In fact, the only evidence Defendants cite are letters written three years after the priority date discussing results of clinical trials involving 0.7% olopatadine, and in at least one clinical trial Pataday® was more effective at 24 hours than 16. Tr. 702:22-703:11.

Defendants argue that a POSA would have been motivated to develop a solution because it is the most comfortable composition and Plaintiff's previous two olopatadine formulations were solutions. (D.I. 149, ¶ 31.) Plaintiff avers that even assuming that a POSA were motivated to develop a solution for eye treatment, a POSA would not be motivated to make one containing the specific ingredients claimed. (D.I. 150, ¶¶ 47, 79.) Dr. Olejnik explained, in the absence of teachings directed towards the problem of solubilizing at least 0.67% olopatadine, given the unpredictability of the field, the POSA could not have had a reasonable expectation of success that any particular approach, let alone the claimed invention, would work. Tr. 514:4-12, 516:6-11, 570:3-7, 577:1-4. With only general teachings and no disclosures in the art of the claimed ternary system, the POSA would have had no guidance to choose the correct combination of excipients, at the proper concentrations, to solubilize 0.67-1.0% olopatadine at near-neutral pH. Tr. 523:4-23, 545:23-546:16, 581:2-18.[14] Plaintiff, therefore, argues that routine experimentation would not allow the POSA to arrive at the claimed concentrations. Tr. 499:4-500:2, 501:20-502:15. The court finds Plaintiff's position persuasive and concludes that routine optimization would not lead a POSA to develop the claimed solution given the complexity of ophthalmic formulation.

[14] Defendants argue a POSA would have known how to determine suitable amounts of solubilizing agents for use with olopatadine. (D.I. 149 at 19.) First, Defendants argue that the claimed ranges of concentrations for each of the solubilizers are not directed to specific amounts but rather to quite broad ranges, covering a three to four-fold range of each excipient. JTX-1 at Claim 1; Tr. 305:5-20. Second, Defendants assert the determination of an appropriate amount of each excipient is a necessary and fundamental step in all formulation development projects. Tr. 307:3-20. The FDA requires drug companies to provide the basis for the selection of the amount of each excipient. Tr. 626:2-7. This determination requires nothing more than routine optimization efforts. Tr. 307:3-20. Third, the amounts of each excipient required by the claims were known and consistent with the prior art. Lastly, Defendants assert that claim 8 would have also been obvious over Yanni 2002 in view of Bhowmick, Nandi, and Loftsson 1998. Tr. 331:8-22. A POSA would have considered these references in combination because Yanni 2002 and Bhowmick both teach olopatadine solutions for treatment of ocular allergic conjunctivitis, and Nandi and Loftsson 1998 expand upon the disclosure of Bhowmick by teaching how to enhance solubilizing efficacy of cyclodextrins with zwitterionic drugs like olopatadine. Tr. 332:12-21.

The court disagrees for the reasons stated previously. On cross-examination, Dr. Oljenik testified that the ranges of the excipients must be viewed in light of the solubility of the excipient. Tr. 569:8-23; 469:2-12. The court heard, and finds credible, testimony that while the combination of excipients is logically necessary in a formulation, that creating a solution with even just four excipients is very complex. Tr. 501:7-14.

Defendants suggest that Plaintiff had a motive to "evergreen" or extend patent protection on olopatadine because it had other patents expiring is nothing more then attorney argument. (D.I. 149, ¶¶ 26-31.) Given the dearth of direct or circumstantial evidence advanced at trial to support this contention, Defendants assertion devolves to nothing more than attorney argument.[15] Both parties presented evidence that a solution is the most comfortable to the eye. Nevertheless, the POSA is not Alcon, and the POSA had no olopatadine franchise to extend. Rather, the POSA is presumed to be motivated by "a design need or market pressure to solve a problem," not by a desire to obtain a patent or avoid infringement. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013). A person of ordinary skill is not a lawyer or legal strategist. *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (factors determining ordinary skill do not include legal training).

***c. Selecting HPγCD to Solubulize Olopatadine***

All of the asserted claims require HPγCD to solubilize and improve the solubility of olopatadine. Defendants argue that a POSA would have considered the solubilizers taught in the prior art for use with olopatadine and would have selected excipients based on the known physiochemical properties of both olopatadine and the excipients commonly used to solubilize

[15] Defendants argue that Dr. Olejnik offered a conclusory opinion that a POSA would never consider blocking patents when choosing excipients for a commercial product. Tr. 479:4-15; (D.I. 149, ¶ 47.) When asked about HPγCD and HPβCD, Dr. Ghosh explained that after Janssen would not license the HPβCD patent to Alcon. As a result, they had to go back to figuring out how to develop a formulation, not find a different solubulizer. Tr. 636:1-637:5; JTX-46 at 1-3. Defendants mischaracterize Dr. Ghosh's testimony. Dr. Ghosh explained that using HPγCD was not their first choice after Janssen would not license HPβCD. Tr. 637:6-15. He further explained that they did have a proof of concept for HPγCD. Tr. 638:6-17. Defendants incorrectly assert that Alcon proceeded directly to clinical trials with this new formulation, without performing a proof of concept study like it did for the HPβCD formulation, indicating that Alcon did not expect the switch to negatively impact the solution. JTX-46 at 1-5; Tr. 633:10-12, 634:19-635:14, 635:22-637:5.

The court finds that, though the Janssen patent covered HPβCD, it would not discourage the POSA from pursuing HPβCD, and any unavailability of HPβCD would provide no reason at all for the POSA to select HPγCD instead. Tr. 478:25-479:21. Were Defendants' logic correct, the POSA would have been discouraged from pursuing any high concentration olopatadine composition because Hayakawa's claims cover a method of treating allergic eye disease using a composition containing 0.67-1.0% olopatadine. JTX-55 at 7:35-39; Tr. 348:19-349:25.

drugs. (D.I. 149, ¶ 41); (D.I. 150, ¶ 56.) It is undisputed that the physiochemical properties of olopatadine were known, including that olopatadine is a zwitterion at a neutral pH. *Id.* Defendants, therefore, argue that a POSA would have preferred the uncharged zwitterionic properties of olopatadine to avoid potential interactions between the charge of the excipients and olopatadine. *Id.*

Defendants seek to discredit the Bhowmick reference by pointing out that out of the hundreds of cyclodextrins identified in Bhowmick, only HPγCD and HPβCD are used in commercialized eye solutions. JTX-70 at 6; (D.I. 149, ¶ 42.) Defendants explain that a POSA would have been motivated to use these cyclodextrins to avoid the hurdles of using a new excipient. Defendants assert cyclodextrins—HPγCD and HPβCD in particular—were known to be solubilizers suitable for use in ophthalmic formulations, including with zwitterionic drugs like olopatadine. JTX-70 at 3-4; JTX-59, Table 1. According to Defendants, a POSA would have been motivated to select HPγCD over the *beta* cyclodextrins found in commercial solutions because it has a slightly larger cavity to accommodate a larger portion of the olopatadine molecule. Tr. 279:21-280:20, 282:21-283:17.

The court disagrees and finds that a POSA would not have selected HPγCD through routine experimentation. *In re Stepan Co.*, 868 F.3d 1342, 1346 (Fed. Cir. 2017); (D.I. 149, ¶ 36.) First, Bhowmick would not have motivated a POSA to select a cyclodextrin to solubilize olopatadine because it did not disclose any formulation with such a high olopatadine concentration, let alone a *solution* at a near-neutral pH. JTX-70; Tr. 471:15-474:12, 353:24-354:2. In fact, Bhowmick does not disclose any *compositions* containing greater than 0.62% olopatadine. *Id.* The high-concentration exemplars—which were at concentrations of no more than 5%—were not at near-neutral pH. *Id.* Further, Bhowmick does not teach an ophalmic solution containing more than

0.25% olopatadine. Tr. 471:23-472:20. While it teaches compositions for use in the eye and nose, it teaches that those intended for use in the eye should contain only about 0.17-0.25% olopatadine. *Id.* The only example in Bhowmick at neutral pH contains 0.2% olopatadine. JTX-70, Table 11. Dr. Olejnik, a person having ordinary skill in the art, explained that the POSA would understand the compositions containing 0.35 to 0.62% olopatadine to be nasal, not ophthalmic solutions because you have (1) a higher concentration of olopatadine, which Bhomick suggests is nasal; and (2) an acidic pH of 3.5-5.0 which would be uncomfortable in the eye. Tr. 473:17-474:12.[16]

First, the court finds that to the extent that Bhowmick motivated the POSA to select a cyclodextrin at all, it would have motivated the POSA to select HPβCD, which it identifies as the most preferred cyclodextrin. JTX-70 at 5:30-6:1. Prior art demonstrated that a POSA would have had a large number of different cyclodextrins and cyclodextrin derivatives available to choose from, each with different properties and characteristics. JTX-70 at 5:3-30; Tr. 463:13-464:14. For example, Bhowmick itself provides an extensive list, some of which are individual cyclodextrins and others of which are entire families of cyclodextrins. JTX-70 at 5:3-6:1; Tr. 475:1-25. HPγCD is only one among the hundreds of cyclodextrins recited in this list. *Id.*; Tr. 476:1-21. This universe a POSA has to choose from would include both charged (and "ionic") and uncharged (or "non-ionic") cyclodextrins. JTX-52 at 365 (Abstract); Tr. 485:9-14, 357:20-358:4. HPγCD is not listed as the most preferred cyclodextrin, used in any example, and no data shows the ability of HPγCD to solubilize olopatadine. JTX-70 at 5:3-6:1; Tr. 476:17-24, 478:4-7. As of the priority date, HPγCD was not widely used and not compendial like other cyclodextrins. Tr. 467:4-6; Tr. 373:4-13, 375:3-10; JTX-61, Table 3.[17] At the time, only one commercial ophthalmic product

[16] Bhowmick also reports no efficacy data for 0.67 to 1.0% olopatadine, nor does it teach how to improve the solubility of olopatadine at a near-neutral pH. Tr. 410:10-13.

[17] Compendial means related to a compendium that serves as a standard, such as the British Pharmacopoeia, or the US Pharmacopeia.

used HPγCD—Voltaren—but it was not approved in the United States, and in that product, HPγCD was not used to improve solubility. Tr. 467:7-19, 612:2-13; (D.I. 150, ¶ 60.)

Second, the court finds that because of its structure, the POSA would expect HPγCD to exacerbate the known disadvantages associated with cyclodextrins. Tr. 464:15-466:13. It is undisputed that HPγCD has an eight-glucose center ring, which gives the molecule a larger central cavity than the beta and alpha cyclodextrins. Tr. 464:19-25. According to Plaintiff, that larger cavity would heighten the risk of diminished bioavailability, as a larger cavity would trap more olopatadine in the cavity. Tr. 465:8-22. HPγCD's larger cavity would also increase the likelihood of trapping more preservative in the cavity, which would diminish preservative effectiveness. Tr. 465:23-466:13. Because of these known concerns with HPγCD, the POSA would not have formed a reasonable expectation as to the solubilizing effect of HPγCD on olopatadine without testing it. Tr. 564:24-565:11, 519:7-22, 612:14-613:4. The evidence demonstrates that a particular cyclodextrin can have drastically different solubilizing effects on different drugs, and thus, the POSA would not merely assume that the solubilizing effect of a given cyclodextrin on one drug would be the same as to a different drug. Tr. 467:23-25. For example, Table 5 of Brewster shows that HPβCD, for example, caused a 1.5-fold solubility improvement on Bupivacaine, a ten-fold impact on Hesperetin, and a 30-to-50-fold impact on Camptothecin. JTX-59, Table 5; Tr. 468:7-469:12. Dr. Olejnik further explained that different cyclodextrins have a different solubilizing effect on the same drug, and thus, the POSA would not merely assume that different cyclodextrins will solubilize a given compound to the same degree. Tr. 469:13-470:4. Again, Table 5 of Brewster shows that depending on the cyclodextrin used, the progesterone showed from a 4-fold to a 3600-fold solubility increase; the prednisolone showed from a 10 to 90-fold solubility increase; and risperidone showed, at times, no solubility improvement at all, while at other times,

a 70- fold increase. JTX-59, Table 5; Tr. 469:13-470:4. There was, however, no teaching in the prior art as to how or whether HPγCD would solubilize 0.67-1.0% olopatadine at near-neutral pH. The court, therefore, finds that a POSA would have no expectation that HPγCD would solubilize such a high olopatadine concentration and no motivation to select HPγCD from among the available cyclodextrins.

***d. Selecting PVP and PEG-400 in Combination with HPγCD***

*i. Castillo, Nandi, and Loftsson 1998*

All of the asserted claims further require the use of PEG-400 and PVP in combination with HPγCD. Defendants contend that because Loftsson 1998 teaches that PVP enhances the complexation efficiency of cyclodextrin, such as HPβCD, with zwitterionic drugs it would have been obvious to a POSA to select HPγCD. JTX-52; (D.I. 149, ¶ 53.) Much of the prior art, however, including Loftsson 1998 and Nandi, does not involve olopatadine, and thus, would not teach the POSA how to formulate a solution containing a high concentration of olopatadine at near-neutral pH in combination with the claimed ternary system. JTX-52; JTX-58; Tr. 480:13-14, 495:7-12, 361:5-10, 369:9-13. Moreover, the references describe only generic formulation principles, often with long lists of excipients, for a variety of dosage forms, at different concentrations and pH levels. Tr. 417:19-419:2, 423:9-23, 426:11-15, 474:18-20, 497:18-23, 126:9-12, 344:7-346:2; JTX-54 at 3:57-4:26; JTX-56 at 3:25-4:14. The POSA would not understand how to overcome the formulation challenges inherent in developing an ophthalmic solution containing 0.67-1.0% olopatadine at near-neutral pH. *Id.*

Turning to the references, Loftsson 1998 specifically discusses ETH-615; not olopatadine or HPγCD. Tr. 480:13-14, 361:5-10; 485:18-23; (D.I. 150, ¶ 68.) Even Dr. Maurin, Defendants' expert, testified that ETH-615 is not comparable to olopatadine, as the two molecules have very

different structures, properties, and solubility profiles. JTX-52 at 367-68; Tr. 365:11-368:1, 480:15-482:1, 569:8-14. As such, the POSA would not expect that the effects of cyclodextrins on the solubility of ETH-615 would be at all similar to their solubilizing effects on olopatadine. Tr. 482:2-10. Further, Loftsson 1998 reported the use of 10% cyclodextrin to solubilize ETH-615, which is much higher than the 0.67 to 1.0% recited in the claims. JTX-52, Table 1; Tr. 483:23-484:8, 361:19-21. Because there is no data on lower cyclodextrin concentrations, Loftsson 1998 provides no expectation that a lower concentration would have had similar solubilizing effects as the higher concentration. Indeed, using a lower concentration of a cyclodextrin may well have worsened solubility according to Dr. Oljenik. Tr. 484:9-23. Moreover, Loftsson 1998 does not have any data that mitigates the POSA's concern that bioavailability and preservative efficacy would diminish with the introduction of a cyclodextrin. Tr. 484:24-485:4. The court finds that like Bhowmick, Loftsson provided no reason to select HPγCD and had no reason to do so.

Similarly, Nandi did not mention olopatadine, did not test HPγCD at all, and did not disclose the claimed ternary system. JTX-58; Tr. 495:7-15. Rather, Nandi discloses the hormonal drug progesterone, which Dr. Olejnik testified is nothing like olopatadine. Tr. 495:10-12. According to Dr. Olejnik, because Nandi does not mention olopatadine, the POSA would have found Nandi completely irrelevant to the challenge of solubilizing 0.67-1.0% olopatadine at near-neutral pH. Tr. 495:7-496:5. Lastly, the Castillo reference discloses formulations intended for use in the eye containing only 0.17 to 0.25% olopatadine. JTX-54; Tr. 496:15-18. In Table 5 of Castillo, both PEG-400 and PVP are contained in the same formulation, but, there is no information from the formulations provided about the ability of PVP and PEG together to solubilize 0.67 % olopatadine. JTX-54; Tr. 497: 11-24. The court, therefore, finds that there was no motivation to combine any of these references.

### *e. Selecting Benzalkonium Chloride, Hydroxypropyl Methylcellulose, Boric Acid and Mannitol*

Claims 9 and 21-24 each recite a precise concentration of PEG, PVP, and HPγCD—the ternary system found in claim 8—as well as the excipients benzalkonium chloride ("BAK"), boric acid,[18] mannitol, and hydroxypropyl methylcellulose ("HPMC"). JTX-1 at 27:1-2 (claim 9), 27:32-28-23 (claims 21-24). As Plaintiff's experts indicated at trial, ophthalmic formulation is highly complex: to arrive at the claimed formulation, the POSA would have had to make a series of specific decisions, amongst countless choices. Tr. 454:23-455:3. The POSA would not have had a reason to do so, nor had a reasonable expectation that doing so would be successful. Tr. 403:12-22. The court heard testimony that there can be unpredictable interactions among the excipients of a complex formulation such as the one claimed, and that the POSA would not have a reasonable expectation that the required concentrations of these particular excipients would achieve their purpose in the claimed formulation. Tr. 491:18-492:6, 500:20-501:6. Defendants present no evidence to show the prior art would have motivated the POSA to select the specific concentrations of these excipients in the context of the claimed solutions.[19]

#### *i. Benzalkonium Chloride ("BAK")*

Claims 21-24 require 0.003 to 0.03 % Benzalkonium Chloride ("BAK").[20] According to Defendants, BAK is the most commonly used preservative agent for ophthalmic solutions, and preservatives are necessary for all multi-dose ophthalmic formulations. Tr. 320:17-321:23, 322:3-10, 529:5-9, 550:11-12. Dr. Maurin testified that BAK was a compendial excipient, and was the most widely-used preservative in ophthalmic formulations. *Id.*; JTX-56 at 1:19-21; JTX-46 at 7;

[18] It is undisputed that borate and boric acid are equivalent. Tr. 330:3-17; (D.I. 150, ¶ 79); (D.I. 149, n.2.)

[19] Dr. Maurin has never tried to formulate olopatadine in a lab. Tr. 338:1-3. Dr. Maurin also admitted on cross-examination that Hayakawa's preferred range is 0.1%, which is narrow. Tr. 339:12-15, 343:5-14.

[20] Defendants make no argument as to the pH and osmolality requirements aside from asserting that is undisputed that those elements were known. JTX-70 at 9. Because these elements were undisputedly known in the prior art, the court need not address this in its obviousness analysis.

Tr. 321:4-15. According to Defendants, numerous prior art references taught the use of BAK in ophthalmic solutions of olopatadine at concentrations within those covered by the claims. JTX-70 at 8; JTX-54, Exs. 1-3; JTX-56 at 1:19-21; JTX-55 at 6:50-2; JTX-57 at [0051]; Tr. 321:4-322:2. Patanol® and Pataday® each contain 0.01% BAK. JTX-64 at 1; JTX-65 at 3; Tr. 321:16-322:2, 526:19-23. Dr. Ghosh, the named inventor on the Patent, testified that his objective is a BAK free olopatadine formulation. Tr. 615:14-17.

Loftsson 1992 illustrates the preservative efficacy problem, explaining that "the complexation of the preservatives [with cyclodextrins] reduces, or even abolishes, their antimicrobial activity." JTX-132 at 8; Tr. 461:18-462:7. Table 2 shows that when there is no cyclodextrin present, a small amount of BAK can prevent microbial growth. *Id.* As the concentration of cyclodextrin is increased to 5%, however, more than a ten-fold increase in the amount of preservative is needed to eliminate microbes such as *E. coli* and *Ps. Aeruginosa*. JTX-132, Table 2; Tr.462:8-463:12. The court finds the use of BAK as a preservative in ophthalmic formulations was known in the art at the time of the invention, but not in combination with the claimed ternary system.

*ii. Hydroxypropyl Methylcellulose ("HPMC")*

Claim 22-24 require specific amounts of HPMC. (D.I. 149, ¶ 99); Tr. 307:3-20, 324:8-325:3.[21] The court finds that the use of HPMC in the claimed formulation would not have been obvious. Prior art demonstrated that ophthalmic solutions should have a viscosity that produces a suitable drop size and enables the solutions to reside on the surface of the eye for a longer period of time. Tr. 309:23-310:21. At the time, HPMC was one of the most common viscosity-increasing agents used in ophthalmic solutions, the function for which it is used in the claimed invention. JTX-56

[21] Claim 22 requires 0.15 to 1.0 % hydroxypropylmethyl cellulose ("HPMC") and claims 23 and 24 require 0.3 to 0.3 to 0.5% HPMC.

at 3:38-45; JTX-70 at 3; JTX-57; Tr. 310:22-311:19; 525:15-24. Dr. Ghosh, a named inventor on the patent, confirmed that HPMC was a safe and widely-used viscosity increasing agent. Tr. 631:4-12. Defendants argue that the prior art taught the use of HPMC in ophthalmic solutions of olopatadine and that it enhances the solubilizing effect of cyclodextrins. Tr. 311:20-313:23. Bhowmick taught the use of HPMC to enhance the solubility and stability of olopatadine solutions when used in combination with a cyclodextrin. JTX-70 at 3-4; Tr. 312:7-23. The prior art taught the use of HPMC in olopatadine solutions at concentrations of 0.01-1.0 %. JTX-70 at 8; Tr. 313:19-23. Defendants argue that a POSA would have determined the claimed concentrations of HPMC through routine development efforts to arrive at a suitable viscosity. Tr. 313:4-15. However, Dr. Olejnik testified that while HPMC used with olopatadine was published in the prior art, routine optimization would not lead a POSA to select the specific concentrations required by the claims because HPMC is just one of the many components that a POSA in ophthalmic formulation would use. Tr. 525:15-24, 499:4-25. The court, therefore, finds that while it may have been obvious to select HPMC, the specific concentrations of HMPC would not have been obvious for a POSA to select.

*iii. Boric Acid (or Borate) & Mannitol*

Claims 9 and 24 both require the excipients borate and mannitol. Defendants argue that choosing boric acid and mannitol would have been obvious to a POSA as a POSA would have considered boric acid the most logical choice to use as a buffer in the olopatadine solution. Tr. 314:16-316:9; (D.I. 149.) Both parties' experts testified that boric acid was a compendial buffering agent used in ophthalmic formulations in the prior art. Tr. 314:16-315:5, 526:15-18. According to Defendants, the prior art also disclosed the use of boric acid at concentrations of 0.3 to 0.5 % in solutions of olopatadine. JTX-56 at 3:15-24; JTX-54, Ex. 2; Tr. 319:19-320:10, 325:16-21.

Defendants' expert, Dr. Maurin, testified that a POSA would not have wanted to use a phosphate buffer commonly used in ophthalmic solutions in 2011 with a borate. Tr. 363:7-21.

Next Defendants argue that a POSA would have understood the need to include a tonicity adjusting agent in the formulation. Tr. 316:12-317:16. It is undisputed that mannitol was a compendial and commonly-used tonicity agent in ophthalmic solutions. Tr. 317:17-318:13, 325:4-8, 325:16-21, 526:4-14, 587:7-11. Numerous prior art references taught its use as a tonicity agent in ophthalmic solutions of olopatadine. *Id.*

Defendants argue that not only were boric acid and mannitol known to be used to achieve and maintain suitable pH and tonicity values, the prior art taught the use of them together in eye formulations with olopatadine. JTX-56 at 3:15-24; Tr. 315:6-316:11, 319:19-320:10; JTX-46 at 6-7; 310:22-311:19, 528:3-529:9, 631:4-632:18. Specifically, the prior art taught that use of boric acid and a polyol, such as mannitol, would both maintain pH and tonicity and provide enhanced preservative efficacy. *Id.* According to Defendants, this added benefit would have further motivated a POSA to select these excipients. Tr. 315:15-316:11.

In response, Plaintiff argues that nothing in the prior art would motivate the POSA to select the specific concentrations of the claimed excipients in the context of the claimed solutions. Plaintiff's experts explained that there can be unpredictable interactions among the excipients of a complex formulation such as the claimed one, and the POSA would not have a reasonable expectation of what concentrations of these particular excipients would be required to achieve their purpose in the claimed formulation. Tr. 491:18-492:6, 500:20-501:6. Plaintiff also argues that the POSA would not have had a reasonable expectation of what effect the addition of BAK, HPMC, boric acid, and mannitol would have on the ternary system and its ability to solubilize 0.67-1.0% olopatadine at near-neutral pH. A formulation with just four excipients was already considered in

the prior art to be a "very complex" formulation. JTX-58 at 4. The prior art teaches that formulation studies "should always be performed in media that closely resembles the final drug formulation" because adding four more excipients to an already complex formulation of olopatadine and the ternary system would only heighten the complexity of an already complex formulation. JTX-63 at 39; Tr. 502:1-3. Here, the prior art did not teach the ternary system with 0.67-1.0% olopatadine at near-neutral pH, with BAK, HPMC, boric acid, and mannitol. As such, the POSA could not have predicted that the claimed formulation—with all of its elements—would have been successful. Tr. 501:7-502:15.

The court finds that a POSA would be concerned that a more than three-fold increase in the concentration from 0.2% (as in Pataday®) to at least 0.67% would increase redness. Tr. 671:7-22. Trial evidence showed that at some point, as the concentration increases, an antihistamine will cause the mast cell to release all of its different mediators—including those that lead to redness—thereby causing an increase in ocular redness. Tr. 652:21-653:10. According to Plaintiff, a POSA would reasonably expect that increased redness would accompany an increase in concentration to at least 0.67%. Tr. 672:22-673:2; JTX-50, Fig. 1B. "[Olopatadine] . . . and the like are added to the solution and dissolved therein. . . . after dissolution . . . ." Tr. 86:19-22. The court is persuaded that the prior art would not motivate a POSA to develop the claimed aqueous ophthalmic solution for treating allergic. JTX-1, Claim 8. In *KSR*, the Supreme Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co.*, 550 U.S. at 418; *see Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). Here the court finds that there was no such reason. More specifically, the POSA would not have been motivated, based on what was known in the prior art, to make the claimed solution

by combining all of the elements of the claims in the particular way they are recited, and have a reasonable expectation of success in doing so.

***f. Dr. Olejnik's Opinions are Valid and Supported***

Defendants assert that Plaintiff's expert, Dr. Olejnik, provided no support for his "conclusory" scientific assertions that a POSA would not have reasonably expected to achieve a 0.7% olopatadine solution. (D.I. 149 at 21.) The court disagrees with Defendants' characterization of Dr. Olejnik's testimony as conclusory. With more than 35 years of experience formulating ophthalmic compositions, Dr. Orest Olejnik testified as to how the POSA would understand the issues related to ophthalmic formulation. Tr. 402:16-17, 412:14-21.[22] It is unclear to the court why Dr. Olejnik would need to support the statements at issue with more than the record and his expertise in ophthalmic formulation. There is, however, record evidence that does provide the support Defendants seek.

First, Defendants take issue with Dr. Olejnik's opinion that it is not routine to see improvements in solubility of 100-fold in ophthalmic formulations. Tr. 454:8-15; (D.I. 149, ¶ 80.) Defendants argue that data in Brewster listing drugs for which cyclodextrins improved solubility by 100-fold or more contradicts Dr. Olejnik's opinion. JTX-59 at 14; Tr. 575:13-23. Brewster, however, discusses Prednisolone, not Pataday®. Tr. 575:17-576:5. The court previously heard testimony on this subject matter about the different solubilizing effects cyclodextrins can have on different drugs and found that a POSA would have no expectation that HPγCD would solubilize such a high olopatadine concentration. *See supra* Part III.A.3.c.[23] Defendants argue that unlike

[22] Dr. Olejnik was formerly the senior vice president of global pharmaceutical sciences at Allergan, where he was involved with ophthalmic formulation development. Tr. 394:17-395:17. He holds a Ph.D from the University of Nottingham in pharmaceutics, with a dissertation focused on ion association species and drug transport. *Id.*; JTX-208. He has developed, or assisted in developing, more than 20 products for the treatment of allergic eye disease, is a member of several professional societies, and has served as visiting professor at two universities. Tr. 397:18-401:11.

[23] Defendants assert that a 100-fold increase is nowhere near the level required to achieve a 0.7 % w/v olopatadine solution. Defendants, however, fail to provide any citation for this proposition.

Dr. Maurin's prior-art based analysis, Dr. Olejnik never considered whether any prior art had suggested the use of these excipients with olopatadine, whether they were suitable for use with a zwitterionic drug, whether they were compendial, or whether they had been previously used in commercial ophthalmic dosage forms, particularly solutions. The court disagrees. Dr. Olejnik testified about zwitterionic drugs on multiple occasions throughout his direct. Tr. 405:9-16, 482:11-485:23. Regardless, Dr. Maurin testified on cross-examination that, based on Loftsson 2007, HPγCD was not compendial in the United States, while HPβCD was. Tr. 372:19-373:13.

In addition, Defendants take issue with Dr. Olejnik's explanation of the possibility that the cyclodextrin could trap the drug, thereby reducing bioavailability. Tr. 458:2-459:11. According to Defendants, Dr. Olejnik ignored statements in the Kaur and Kanwar reference, which explains that the "optimum bioavailability would be expected when there is just enough cyclodextrin (<15%)" and "too much cyclodextrin will decrease the bioavailability." JTX-154 at 6; JTX-178 at 4; Tr. 459:18-460:6. Dr. Olejnik, however, testified on cross-examination that the asserted claims can have less than 15% cyclodextrin, but that a POSA understands the generalizations in the field and that nothing is routine in formulation. Tr. 514:2-12. Defendants assert that the prior art teaches the opposite of what Dr. Olejnik claims because Loftsson 2002 shows that cyclodextrins make it "possible to increase the drug concentration and bioavailability and create formulations that offer more effective and less frequent treatment schedules for patients with ocular inflammation." JTX-178 at 6. The court disagrees. Nothing in Dr. Olejnik's testimony ignores that too much cyclodextrin reduces bioavailability. According to the testimony at trial and the Kaur and Kanwar reference, cyclodextrins were known to decrease bioavailability. Tr. 458:10-459:11. Further, Loftsson 2002 addresses the effect of cyclodextrin concentration on flux, not solubility, and its teachings concern dexamethasone, not olopatadine. Tr. 514:13-516:14, 519:7-24.

Defendants attempt to discredit Dr. Olejnik because he filed a Patent Cooperation Treaty ("PCT") application in 2004 entitled "Drug Delivery to the Back of the Eye" describing and claiming the use of formulations containing HPγCD to solubilize different drugs, including "mast cell stabilizers" and "antihistamines." DTX-316 at 8-12, 14; Tr. 582.[24] The reference, however, specifically refers to a formulation of Prednisolone, which is for use at the back of the eye, specifically the steric chamber. Tr. 584:8-12, 586:7-17. The patent provides a non-exclusive list of hundreds of "examples of therapeutically active agents." DTX-316 at 8-12, 17, 25-28, claim 19; Tr. 586:19-587:16. According to Defendants, a POSA would have been motivated to select HPγCD to solubilize olopatadine based on Dr. Olejnik's 2004 application teaching the use of HPγCD as a solubilizer for an ophthalmic solution. DTX-316 at 8-12. Defendants assert Dr. Olejnik's 2004 patent application, in which he informs the POSA that HPγCD can be used with BAK contradicts his opinion. DTX-316 at 17. In his patent, the reference he cites in support of this proposition demonstrated that BAK remained an effective preservative when used with a cyclodextrin. JTX-132 at 7; Tr. 522:5-17.

The court disagrees with Defendants. First, Dr. Modi, one of Defendants' experts, testified that treating diseases in the back of the eye is *different* and has different concerns than treating diseases in the front of the eye like conjunctivitis. Tr. 147:5-25, 583:7-10, 584:11-12, 586:7-17. Second, Dr. Maurin testified that there is no evidence as of 2011 that the cyclodextrins and olopatadine were compendial. Tr. 375:3-19. Third, while, Dr. Olejnik agreed that all of the claimed excipients had been used for their claimed purpose, he explained that a POSA would "understand the various excipients [and] what they do" and that a POSA would not know how the components "when put together with the drug compound itself" would react. Tr. 504:17-505:8,

[24] While Olejnik filed a PCT, this patent application was not asserted as prior art against the patent at issue. Dr. Oleknik further testified that he does not list the cyclodextrins, but it "all comes down to how you put it together.

523:24-524:17, 525:15-526:23, 528:3-529:8, 586:19-587:16. Thus, the claims do not "simply arrange old elements with each performing the same function. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). Lastly, at the close of evidence, the court remarked that this case turned on the testimony of the parties' two lead experts: Alcon's expert Dr. Orest Olejnik, and Defendants' expert Dr. Michael Maurin. In questioning counsel for Defendants, the court instructed Defendants to assume that the court "found Dr. Olejnik more credible [than] Dr. Maurin" and, accordingly, would "credit Dr. Olejnik's testimony over Dr. Maurin's." Tr. 797:16-24, 798:18-20. The court has not changed its opinion, and finds Dr. Oljenik's opinions have the more persuasive force, particularly when taken in context with the testimony as a whole.

***g. Obvious to Try***

An invention is "obvious to try" only if the number of alternatives available to the POSA was "finite" and "small in the context of the art," *KSR*, 550 U.S. at 421. Here, the number of alternatives available was neither "finite" nor "small." The prior art disclosed hundreds of different cyclodextrins, polymers, cosolvents, and other potential solubilizing agents, yet provided no teaching to select the ternary system from what was an exponential number of possibilities. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (finding claims non-obvious; expert "discounted the number and complexity of the alternatives").

Rather than offer a reason why the POSA "would have combined these particular references to produce the claimed invention," Defendants rely on hindsight, beginning with the claimed invention and looking backwards to piece together the elements of the claimed solution from the scattered disclosures in the prior art. *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017); *see Ortho-McNeil*, 520 F.3d at 1364; *Procter & Gamble Co. v.*

*Teva Pharm. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009); *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371-72 (Fed. Cir. 2000).

Merely asserting, as Defendants do, that the POSA "would have arrived at the claimed invention through routine optimization" does not demonstrate obviousness. *In re Stepan Co.*, 868 F.3d 1342, 1346 (Fed. Cir. 2017). Defendants have not explained "why it would have been routine optimization to arrive at the claimed invention," suggesting instead that the inventions would have been little more than "common sense." *Id.*; *see also Genetics Inst., LLC v. Novartis Vaccines & Diagn., Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011). There is no teaching in the prior art that predicts that the combination of HPγCD, PEG 400, and PVP, at the particular concentrations, with the other claimed excipients, would solve the challenge of how to solubilize 0.67-1.0% olopatadine in an ophthalmic solution at near-neutral pH. Put simply, the prior art gave "no direction as to which of many possible choices [was] likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Moreover, when dealing with complex and unpredictable fields like ophthalmic formulation, courts are quick to reject the simplistic assertion that the invention is the obvious result of "routine" pharmaceutical development. *See, In re Armodafinil Patent Litig.*, 939 F. Supp. 2d 456, 501 (D. Del. 2013).

Obviousness requires "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). Defendants failed to establish by clear and convincing evidence that a POSA would have made the many necessary modifications to obtain a 0.67 to 1.0 w/v % olopatadine solution. Far from a clear path, a POSA developing the claimed invention would face an array of decisions. For the foregoing reasons,

Defendants have not met its burden to establish a *prima facie* case that the asserted claims are invalid for obviousness.

**4. Secondary Considerations**

Under relevant law, once a *prima facie* case of obviousness has been established, the burden then shifts to the applicant to present evidence of secondary considerations of non-obviousness to overcome this *prima facie* showing. *See, e.g., In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). The Supreme Court has made clear that secondary considerations can include, among other things, evidence of commercial success, long-felt but unsolved needs, and/or the failure of others. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1996). A plaintiff may also rebut an obviousness contention by demonstrating that there were unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and/or skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998).

"Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Moreover, "[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) (quoting *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir .2000)), *abrogated on other grounds by Travel Sentry, Inc. v. Tropp*, 877 F.3d 1370 (Fed. Cir. 2017) (alteration in original). In other words, the secondary considerations, must be commensurate in scope—"coextensive"—with the

claimed features of the invention. *Id.*; *MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264–65 (Fed. Cir. 2013).

Here, Plaintiff argues that even should the court determine that Defendants established *prima facie* case on the issue, the secondary consideration of unexpected results and long-felt but unmet need rebut this *prima facie* case. (D.I. 151, ¶16); *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). The court will address each secondary consideration in turn.

***a. Unexpected Results***

Unexpected results may be demonstrated by showing "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). This comparison is made to the closest prior art. *Kao Corp. v. Unilever U.S. Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Plaintiff adduced evidence that its invention unexpectedly showed that the claimed 0.7% olopatadine solution decreased redness at the onset of action as compared to Pataday®. Specifically, Plaintiff avers that a POSA would have found the further reduction of redness caused by 0.7% olopatadine to be surprising and unexpected because it would believe that lower concentrations achieved maximum efficacy, and thus further increasing the concentration would not further improve redness. Tr. 688:15-17. Further, a POSA would have recognized that increasing the concentration of olopatadine to such a high concentration could trigger mediator release and increase redness compared to Pataday®. (D.I. 150, ¶ 88.)

Olopatadine reduces itching through mast cell stabilization and its antihistaminic effect, but reduces redness primarily through mast cell stabilization. Tr. 653:17-656:13; JTX-123 at 4; JTX-125 at 2. Prior to 2011, Alcon obtained FDA approval for two eye drops for the treatment of

allergic conjunctivitis containing olopatadine: Patanol® (0.1% olopatadine dosed twice daily) and Pataday® (0.2% olopatadine dosed once daily). Tr. 508:24-509:17, 658:15-18; JTX-64; JTX-65. The POSA would be concerned that a more than three-fold increase in the concentration from 0.2% (as in Pataday®) to at least 0.67% would increase redness. Tr. 671:7- 22.

At some point, as the concentration increases, an antihistamine will cause the mast cell to release all of its different mediators—including those that lead to redness—thereby causing an increase in ocular redness. Tr. 652:21-653:10, 670:4-671:2; JTX-102A, Fig. 2; JTX-50, Fig. 1B. The POSA, therefore, would have reasonably expected that increased redness would accompany an increase in concentration to at least 0.67%, particularly since, as of the priority date, the highest concentration tested in a human mast cell stabilization model, which measures potential for biphasic activity, was 0.34%. Tr. 672:22-673:2; JTX-50, Fig. 1B. Surprisingly and unexpectedly, human clinical trial data showed that the claimed 0.7% olopatadine solution decreased redness at the onset of action as compared to Pataday®. Eye drops intended for the treatment of allergic conjunctivitis are tested using the Conjunctival Antigen Challenge ("CAC") model. Tr. 649:7-10. In the CAC, pollen is applied to the eye to trigger an allergic reaction and the resulting redness is graded by investigators, who receive redness-grading training using the FDA-accepted scale. Tr. 673:8-678:7, 737:1-11; JTX-207. Two Phase III CAC trials used the 0.7% olopatadine formulation now marketed as Pazeo® and the results were combined into an "integrated analysis." Tr. 682:25-684:7-11, 613:22-614:8; JTX-169; JTX-180; JTX-194; JTX-199 at 4. The integrated analysis showed that the 0.7% formulation was better, by a statistically significant margin, than Pataday® at reducing redness at onset of action. JTX-194, Tables 13-15; Tr. 685:25-688:14.

The POSA would find the further reduction of redness caused by 0.7% olopatadine to be surprising and unexpected. Tr. 688:15-17. The POSA would believe that lower concentrations

achieved maximum efficacy, and thus further increasing the concentration would not further improve redness. Moreover, the POSA would have recognized that increasing the concentration of olopatadine to such a high concentration could trigger mediator release and increase redness compared to Pataday®. This further reduction in redness is a clinically meaningful benefit for patients. Tr. 688:18-689:1. Patients are very concerned about redness, particularly the social stigma associated with eye redness. Tr. 689:3-12. Patients are able to notice even small changes in redness in other people's eyes. Tr. 689:9-12.

***b. Long-felt Need***

Second, the court finds that substantial evidence on the record supports a finding that the claimed solution serves an unmet need. While Patanol® treats redness and itching associated with allergic conjunctivitis, it requires a dosing of twice a day. Tr. 718:9-11. Pataday® has once-daily dosing, but does not treat the associated redness. *Id.* at 11-13. Pazeo®, by contrast, has been shown to treat both the redness and itching associated with allergic conjunctivitis and is only dosed once-daily. The evidence showed that a further reduction in redness is a clinically meaningful health benefit for patients who are concerned about redness. Tr. 688:18-689:1. The evidence showed that Pazeo® was coextensive with the asserted claims of the '154 Patent and Defendants presented insufficient evidence to rebut the presumption of a nexus. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed.Cir.2000) ("If the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus.").

In sum, Defendants have failed to present a *prima facie* case that the asserted claims of the patents-in-suit are invalid as obvious. Additionally, the court finds that the secondary, objective

indicia point towards a finding of non-obviousness. Thus, the asserted claims are not invalid as obvious.

## IV. CONCLUSION

For the reasons stated above, the court concludes that the asserted claims of the patent-in-suit are not invalid as obvious under 35 U.S.C. § 103.

Dated: March 1, 2018

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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|---|---|
| ALCON RESEARCH, LTD.,<br><br>Plaintiff,<br><br>v.<br><br>WATSON LABS., INC.,<br><br>Defendant. | C.A. No. 15-1159-GMS<br>**CONSOLIDATED** |
| ALCON RESEARCH, LTD.,<br><br>Plaintiff,<br><br>v.<br><br>LUPIN LTD., &<br>LUPIN PHARMA., INC.,<br><br>Defendants. | |

**ORDER**

At Wilmington this 1st day of March, 2018, IT IS HEREBY ORDERED THAT:

1. The asserted claims of the patent-in-suit is not invalid due to obviousness; and

2. The Clerk of Court is directed to enter final judgment in favor of the Plaintiff.

UNITED STATES DISTRICT JUDGE