UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. and APOTEX CORP.
Petitioner
v.

ALCON RESEARCH, LTD
Patent Owner

Patent No. 8,791,154
Issue Date: July 29, 2014
Title: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

Inter Partes Review No. IPR2016-01640

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,791,154 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.*

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1001	U.S. Patent No. 8,791,154 B2 ("'154 Patent")
1002	Declaration of Dr. Erning Xia
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1004	WO 2008/015695 A2 ("Bhowmick")
1005	YANNI *et al.*, "The *In Vitro* and *In Vivo* Ocular Pharmacology of Olopatadine (AL-4943A), an Effective Anti-Allergic/Antihistaminic Agent," Journal of Ocular Pharmacology and Therapeutics, Volume 12, Number 4, 1996, pp. 389-400 ("Yanni")
1006	U.S. Pat. No. 6,995,186 B2 ("Castillo")
1007	U.S. Pat. Pub. No. 2011/0082145 A1 ("Schneider")
1008	U.S. Pat. No. 5,641,805 B2("Hayakawa")
1009	Image File Wrapper for U.S. Patent No. 8,791,154 B2
1010	Image File Wrapper for U.S. Provisional Appl. No. 61/487,789
1011	Image File Wrapper for U.S. Provisional Appl. No. 61/548,957
1012	WO 1999/018963 ("Lisi")
1013	WO 2002/024116 A1 ("Shahinian")
1014	LOFTSSON *et al.,* "Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye," Acta Ophthamologica Scandinavica, 2002, pp. 144-150.
1015	NANDI *et al.*, "Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone," AAPS PharmSciTech 2003; 4 (1), pp 1-5.
1016	WO 2011/138801 A1 ("Khopade")
1017	JANSOOK *et al.*, "CDs as solubilizers: Effects of excipients and competing drugs," International Journal of Pharmaceutics, 379, 2009, pp. 32-40.
1018	HARADA, A., "Preparation and structures of supramolecules between cyclodextrins and polymers," Coordination Chemistry Reviews, 148, 1996, pp. 115-133.

1019	WO 2012/159064A1 ("Gamache")
1020	EP 0 799 044 B1 ("Yanni III")
1021	WO 2001/054687 A1 ("Yanni II")
1022	WO 2009/003199 A1 ("Pipkin")
1023	WO 2000/78396 A2 ("Graff")
1024	Curriculum Vitae for Dr. Erning Xia
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1029	EP 0214779 B1 ("Lever")
1030	Alcon Research, Ltd. v. Apotex Inc., 687 F.3d 1362 (Fed. Cir. 2012)
1031	Alcon Research, Ltd. v. Apotex Inc., 790 F. Supp. 2d 868 (S.D. Ind. 2011)
1032	EP 0 235 796 B2 ("Oshima")
1033	ABELSON *et al.*, "Combined Analysis of Two Studies Using the Conjunctival Allergen Challenge Model to Evaluate Olopatadine Hydrochloride, a New Ophthalmic Antiallergic Agent With Dual Activity," American Journal of Ophthalmology, Volume 126, No. 6, pp. 797-804.
1034	WO 2004/024126 A1 ("Thompson")
1035	CHAUDHARI *et al.,* "Solubility enhancement of hydrophobic drugs using synergistically interacting cyclodextrins and cosolvent," Current Science, 1586 Vol. 92, No. 11, 10 June 2007; pp. 1586-1591.
1036	ANSEL, Howard C., *Pharmaceutical Calculations*, 13th Ed., Wolters Kluwer, 2010, pp. 82-83
1037	PATANOL® Label
1038	PATADAY® Label
1039	PATANASE® Label
1040	GENNARO, Alfonso R., *Remington: The Science and Practice of*

	Pharmacy, Philadelphia College of Pharmacy and Science, 1995, Vol. 1., pp. 613-627
1041	GENNARO, Alfonso R., *Remington: The Science and Practice of Pharmacy*, Philadelphia College of Pharmacy and Science, 1995, Vol. 2., pp. 1563-1576
1042	LIDE, David R., *CRC Handbook of Chemistry and Physics*, CRC Press, 2006, pp. 6-4 – 6-5.
1043	ABELSON and ANDERSON, "Demystifying Dumulcents," Review of Ophthalmology, November 2006, pp. 122-125.
1044	LOFTSSON, *et al.*, "The effect of water-soluble polymers on the aqueous solubility and complexing abilities of β-cyclodextrin," International Journal of Pharmaceutics, 1998, Vol. 163, pp. 15-21
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1046	U.S. Pat. No. 5,985,310 ("Castillo III")
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1048	U.S. Pat. No. 8,399,508 B2 ("Singh II")
1049	U.S. Pat. No. 7,402,609 B2 ("Castillo II")
1050	WADE, *et al.*, "Ophthalmic antihistamines and H1–H4 receptors," Current Opinion in Allergy and Clinical Immunology, 2012, Vol. 12, No. 5, pp. 510–516
1051	CHOI, *et al.*, "Late-phase reaction in ocular allergy," Current Opinion in Allergy and Clinical Immunology, 2008, Vol 8, pp. 438–444.
1052	U.S. Pat. Pub. 2004/0198828 ("Abelson 2004")
1053	LEONARDI, *et al.*, "Double-masked, randomized, placebo-controlled clinical study of the mast cell-stabilizing effects of treatment with olopatadine in the conjunctival allergen challenge model in humans," Clin Ther 2003; 25, pp. 2539–2552.
1054	PROUD, *et al.*, "Inflammatory mediator release on conjunctival provocation of allergic subjects with allergent provocation of allergic subjects with allergen," Mediator generation in ocular allergy, 1989, Vol. 85. No. 5, pp. 896-905
1055	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, 1996, Vol. 278, No. 3, pp. 1252-1261
1056	LOFTSSON, *et al.*, "Pharmaceutical Applications of Cyclodextrins. 1. Drug Solubilization and Stabilization," Journal of Pharmaceutical Sciences, October 1996, Vol. 85, No. 10, pp. 1017-1025
1057	21 C.F.R. §349.12
1058	Polyvinylpyrrolidone K 30, http://www4.mpbio.com/ecom/docs/proddata.nsf/(webtds2)/102787
1059	SWEI, *et al.*, "Viscosity Correlation for Aqueous Polyvinylpyrrolidone (PVP) Solutions," Journal of Applied Polymer Science, 2003, Vol. 90, pp. 1153-1155
1060	68 Fed. Reg. 106, 32981-32983
1061	U.S. Pat. No. 6,316,483 B1 ("Haslwanter")
1062	U.S. Pat. Pub. No. 2010/0010082 A1 ("Chong")
1063	U.S. Pat. Pub. No. 2009/0136598 ("Chapin")

I. NOTICE OF LEAD AND BACKUP COUNSEL

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II. NOTICE OF SERVICE INFORMATION

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III. NOTICE OF EACH REAL-PARTY-IN-INTEREST

Petitioners Apotex Inc. and Apotex Corp. are the real parties-in-interest.

IV. NOTICE OF RELATED MATTERS

U.S. Patent No. 8,791,154 ("the '154 Patent") is the subject of the following litigations: *Alcon Research, Ltd. v. Watson Labs.*, 1-15-cv-01159 (D. Del.), filed

December 16, 2015; and *Alcon Research, Ltd. v. Lupin Ltd. et al*, 1-16-cv-00195 (D. Del.), filed March 28, 2016. U.S. Patent Appl. No. 14/304,124, is currently pending and claims priority to the '154 Patent.

V. GROUNDS FOR STANDING

Petitioners hereby certify that the patent for which review is sought is available for *inter partes* review, and that the Petitioners are not barred or estopped from requesting an *inter partes* review challenging the patent claims on the Grounds identified in the petition.

VI. STATEMENT OF PRECISE RELIEF REQUESTED

Petitioners respectfully request that claims 1-4, 8, 12, 13, 21, and 22 of U.S. Patent No. 8,791,154 (Ex. 1001) be canceled.

VII. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for *inter partes* review must demonstrate "a reasonable likelihood that the petitioners would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). The Petition meets this threshold. Each of the elements of claims 1-4, 8, 12, 13, 21, and 22 of the '154 patent are taught in the prior art as explained below in the proposed Grounds of unpatentability under 35 U.S.C. § 103(a). Also provided are motivations to combine those elements and an explanation of why a POSA would have had a reasonable expectation of success in achieving the benefits of the claimed compositions.

VIII. STATEMENT OF REASONS FOR RELIEF REQUESTED

A. Technical Introduction

The following technical introduction is supported by the Declaration of Dr. Erning Xia ("Xia Decl."), Ex. 1002 ¶¶ 22-51, and the Declaration of Dr. Leonard Bielory ("Bielory Decl."), Ex. 1003 ¶¶ 24-45, and as indicated.

1. Background

Well before the filing date of the '154 patent, topical ophthalmic compositions comprising aqueous solutions of the drug olopatadine were known to be useful for treating allergic eye diseases such as allergic conjunctivitis. Ex. 1002 ¶¶ 22-24. Olopatadine was understood to have antihistamine activity, as well as human conjunctival mast cell stabilizer activity. Ex. 1003 ¶ 29. Depending on olopatadine concentration, administration can be as infrequently as once or twice daily. *Id.*

It was also understood that, unlike some other antihistamine or mast cell stabilizer anti-allergy drugs, olopatadine did not exhibit a "biphasic effect," in which a drug can actually provoke histamine release at higher concentrations as compared to lower concentration where antihistaminic activity is observed. Ex. 1003 ¶57. The duration of olopatadine's anti-allergic activity was known to be dose dependent, with higher concentrations providing more prolonged effects. *Id*.

To provide long-term, shelf-stable solutions of olopatadine, especially those having olopatadine concentrations above 0.18 w/v% or so, solubilizing excipients have been widely used for years in olopatadine formulations, including in ophthalmic applications. *See* Ex. 1002, ¶¶ 25-50. Polyvinylpyrrolidone (PVP) has long been known to increase olopatadine solubility in aqueous solutions as well as increase the physical stability of such solutions. *Id.* ¶ 32. Complexes of olopatadine with cyclodextrins, such as hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, and sulfobutyl ether-β-cyclodextrin, have also been used to solubilize higher concentrations of olopatadine in aqueous solution and prevent precipitation or crystallization. *Id.* ¶¶ 38-40. Combinations of hydroxypropyl methylcellulose and cyclodextrin derivatives further enhance olopatadine solubility and the solution stability. *Id.* 34. Utilizing cyclodextrins provided other desirable benefits, such as increasing the effectiveness of drug delivery to the conjunctiva of the eye. *Id.* ¶ 82; Ex. 1014 at 149. Polyethylene glycols have also been long used to enhance olopatadine solublility and as viscosity enhancers with cyclodextrins. Ex. 1002 ¶¶ 27-28, 41-43.

In the U.S., olopatadine-containing compositions have been commercially available under the brand names PATANOL® and PATADAY® as 0.1 % and 0.2% sterile ophthalmic solutions (respectively), both marketed by Alcon. *Id.* ¶ 24. PATANOL® is indicated for the treatment of signs and symptoms of allergic

conjunctivitis and PATADAY® for the treatment of ocular itching associated with eye allergy. *Id.* According to its labeling information, each mL of PATANOL® contains olopatadine hydrochloride (equivalent to 0.1% olopatadine), 0.01% benzalkonium chloride (BAC), and unspecified amounts of sodium chloride, dibasic sodium phosphate, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water. *Id.* Each mL of PATADAY® solution contains olopatadine hydrochloride (equivalent to 0.2% olopatadine), inactives such as 0.01% benzalkonium chloride, and unspecified amounts of polyvinylpyrrolidinone (*aka* povidone), dibasic sodium phosphate, sodium chloride, edentate disodium, hydrochloric acid/sodium hydroxide (to adjust pH) and purified water. *Id.*.

2. Alcon's Olopatadine Evergreening Strategy

Alcon has long attempted to control the market for olopatadine-containing compositions by obtaining new patents that cover trivial changes to the formulation, strength, and delivery system of the original olopatadine drug. The chart below illustrates Alcon's Orange Book listed patents that utilize olopatadine.

Alcon's Olopatadine Products				
Product Trade Name	**Olopatadine (free base) Conc.**	**Orange Book Patents**	**Publication or Issue Date**	**Patent Expiry (according to Orange Book)**
PATANOL	0.1%	5,641,805	6/24/1997	12/06/2015
PATADAY	0.2%	6,995,186	3/20/2003	5/12/2024
		7,402,609	7/21/2005	12/19/2022
PATANASE	0.6% (spray)	7,977,376	6/21/2007	8/02/2023
		8,399,508	12/15/2011	3/17/2023
PAZEO	0.7%	8,791,154	11/22/2012	5/19/2032

Hayakawa: The first Alcon patent directed to olapatadine compositions is U.S. Patent No. 5,641,805 (Ex.1008; "Hayakawa") covering PATANOL®, which published on June 24, 1997 and was assigned to Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co., Ltd. Hayakawa discloses and claims preparation of eye drops including olopatadine (*i.e.*, "Compound A") concentrations of **up to about 5 w/v%.** *Id.* at 6:30-44, Claims 2, 6. As discussed by Dr. Bielory and Dr. Xia in more detail in their declarations, Hayakawa indicates that formulations containing up to 5 wt% olopatadine are useful for treatment of allergic conjunctivitis. Ex. 1002 ¶ 72; Ex. 1003 ¶29. Across the claimed olopatadine concentration range of **0.0001 to 5 w/v%**, Hayakawa recommends the use of standard ophthalmic excipients such as glycerin, boric acid and polyvinylpyrrolidone among others, and

does not mention any solubility or stability issues at such concentrations. Ex. 1008 at 6:50-58, Claims 2, 6; Ex 1002 ¶¶ 72.

Hayakawa also discloses that olopatadine has both antihistamine activity, as well as human conjunctival mast cell stabilizing activity that allows it to be administered as infrequently as once or twice a day. Ex. 1008 at 3:18-23, Table 1; Ex. 1003 ¶ 29. The effects of olopatadine on histamine release from human conjunctival tissue mast cells upon anti-human IgE challenge were predictive of the *in vivo* effect of 0.1 %w/v olopatadine on passive conjunctival anaphylaxis in rats. Ex. 1008 at 5:57-6:29. The rat assay indicated that topically applied olopatadine effectively reduced local allergic response by 86% over control. Ex. 1003 ¶ 29.

When Alcon tried to enforce the Hayakawa patent, the Federal Circuit found all claims that were not limited to about 0.1 w/v% olopatadine to be invalid as obvious. *Alcon Research, Ltd. v. Apotex, Inc*., 687 F.3d 1362, 1366-70 (Fed. Cir. 2012). In its opinion, the Court found that the therapeutically effective amount of olopatadine recited by claim 1 encompassed the range of 0.0001–5 w/v%, as recited in dependent claims 2 and 6. *Id*. at 1367-68. Because the prior art disclosed olopatadine compositions overlapping with this range, claims having therapeutically effective amounts other than specifically about 0.1% were held obvious. *Id*. at 1368.

Yanni II: Alcon continued to pursue patents directed to olopatadine-containing solutions. WO 01/54687 (Ex. 1021, "Yanni II"; assigned to Alcon Universal Ltd.) was published August 2, 2001 and purports to claim an olopatadine-containing composition "suitable for use by patients wearing contact lenses." Ex. 1021 at 1:1-7, Claim 1. Yanni II also discloses using olopatadine up to 5 w/v% in the topically administrable compositions. *Id.* at 1:17-19; Claim 2. Like Hayakawa, Yanni II does not disclose any solubility or stability issues at any concentration of olopatadine, and recommends the use of standard ophthalmic components such as boric acid, hydroxypropylmethylcellulose, polyvinylpyrrolidone, mannitol, and many others. *Id.* at 4:30-5:24.

Castillo I and II: U.S. Pat. No. 6,995,186 (Ex. 1006, "Castillo"), which is listed as covering PATADAY®, issued February 7, 2006, to Alcon, Inc., and discloses topical solutions for treating allergic or inflammatory disorders of the eye that include approximately 0.2-0.6% olopatadine and an amount of PVP or polystyrene sulfonic acid sufficient to "enhance" the stability of the solutions. Ex. 1006 at 2:13-22, 3:42-46. Such solutions are taught to be effective as once-a-day products. *Id*. Castillo teaches that tonicity agents (*e.g*. mannitol) and buffering agents (*e.g*. borates) may be included in the solutions. *Id.* at 3:57–4:8.

PATADAY and the Castillo patent differ little from PATANOL and the Hayakawa patent. The primary difference is that PATADAY contains 0.2%

olopatadine rather than PATANOL's 0.1% (Ex. 1003 ¶31), and Castillo reports using solubilizing agents such as PVP to achieve clear solutions free of precipitates even at the highest tested olopatadine hydrochloride concentrations of 0.665%. Ex. 1006 at 2:64-65, Tables 12-13; Ex. 1002 ¶¶ 32, 56. Castillo's experiments also show that inclusion of PEG 400 can help promote olopatadine stability/solubility. Ex. 1006 at Tables 5-6 (compare formulations R and S); Ex. 1002 ¶¶ 28-29.

U.S. Patent No. 7,402,609 (Ex. 1049, "Castillo II") is a continuation of Castillo and contains the same disclosure.

Singh I and II: U.S. Pat. No. 7,977,376 (Ex. 1047, "Singh I") is a continuation-in-part of Castillo II. U.S. Pat. No 8,399,508 (Ex. 1048, "Singh II") is a continuation from both Singh I and Castillo II. Both cover PATANASE®, a nasal formulation of olopatadine. Ex. 1003 ¶40. The new disclosure over Castillo II teaches nasal compositions with approximately 0.6% olopatadine that do not rely on a polymeric ingredient, such as polyvinylpyrrolidone, as a "physical stability enhancing agent." Ex. 1047 at 2:15-22; 5:11-19. Instead, the nasal compositions use a phosphate salt to maintain a pH of 3.5-3.95 which aids in solubilizing olopatadine in the presence of sodium chloride. *Id.* at 2:22-25. Thus, the differences between PATANASE and PATADAY are the concentration of olopatadine (0.6 w/v% versus 0.2 w/v%) and the use of low pH to solubilize olopatadine rather than a polymeric agent, such as polyvinylpyrrolidone.

B. The '154 Patent

The '154 Patent (which is listed in the Orange Book as covering Alcon's PAZEO® product, containing 0.7 w/v% olopatadine) discloses ophthalmic compositions for treatment of allergic conjunctivitis that purportedly includes a "relatively high" concentration of olopatadine solubilized in aqueous solution. Ex. 1001 at 3:23-28; *see* Ex. 1002 ¶¶ 16-21; Ex. 1003 ¶¶ 17-23. "Relatively high" olopatadine concentrations are described as at least 0.50 w/v% to no greater than 1.5 w/v% olopatadine. *Id*. at 3:48-53. The ophthalmic compositions are purported to include a "unique set of excipients" for solubilizing olopatadine while maintaining comfort "and/or" efficacy such as symptoms associated with late phase allergic conjunctivitis. *Id.* at 3:28-35. The aqueous ophthalmic solutions claimed by the '154 Patent include one of three cyclodextrin derivatives: hydroxypropyl-β-cyclodextrin ("HP-β-CD"), hydroxypropyl-γ-cyclodextrin ("HP-γ-CD"), or a sulfoalkyl ether-β-cyclodextrin ("SAE- β-CD"). *Id.* at 4:45-52. The '154 Patent describes sulfobutyl ether-β-cyclodextrin ("SBE- β-CD") as a particular SAE- β-CD. *Id.*, 4:51-52. The claimed solutions further include polyvinylpyrrolidone ("PVP") as well as polyethylene glycol ("PEG") with a molecular weight of 300 to 500, where a PEG with a molecular weight of 400 ("PEG 400") is preferred. *Id.* at 6:8-40. Consistent with Castillo, PVP and PEG are each purported to aid in solubilizing olopatadine. *Id.* at 5:65-67; 6:22-24. The

'154 Patent further teaches that the solutions may include hydroxypropylmethyl-cellulose ("HPMC") to aid in solubilizing olopatadine. *Id.* at 6:48-50; 7:34-37.

The ophthalmic compositions of the '154 Patent are purported to "surprisingly" show significant reduction in late phase symptoms and early phase redness, to "surprisingly" solubilize the relatively high olopatadine concentration and be stable for extended periods of time, and to still exhibit efficacy despite inclusion of cyclodextrins such as HP-γ-CD. *Id.* at 11:17-50.

However, as shown herein, the claimed ophthalmic compositions of the '154 Patent and methods for using them would have been obvious to a person of ordinary skill in the art and do not provide any unexpected results or advantages.

C. Level of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") at the time of filing of the '154 Patent typically would have had: (i) an M.D., Pharm. D. or Ph.D. in chemistry, biochemistry, pharmaceutics, or in a related field in the biological or chemical sciences, and have at least about two years of experience in treatment of ocular diseases and developing formulations used to treat ocular diseases, including topical eye pharmaceuticals; (ii) a Master's degree in chemistry, biochemistry, pharmaceutics, or in a related field in the biological or chemical sciences, and have at least about five years of experience in treatment of ocular diseases and developing formulations used to treat ocular diseases, including

topical eye pharmaceuticals; or (iii) a bachelor's degree in pharmacy, chemistry, biochemistry or in a related field in the biological or chemical sciences, and have at least about ten years of experience in treatment of ocular diseases and developing formulations for treating ocular diseases, including topical eye pharmaceuticals. Ex. 1002 ¶¶ 12-13; Ex. 1003 ¶¶ 12-13. The descriptions are approximate, and a higher level of education or specific skill may make up for less experience, and vice-versa.

As evidenced by the art in this field (*see In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (noting that the level of ordinary skill can be evidenced by the prior art references themselves)), the POSA here would have an understanding of the basis of ocular allergy including knowledge of the structure and constitution of conjunctiva of the eye, IgE antigen stimulated histamine release, cell-based and animal models and assays for assessing effectiveness of ophthalmic treatments, and knowledge of ophthalmic formulation excipients. Furthermore, the '154 Patent and much of the prior art discussed herein involves the development of ophthalmic pharmaceutical compositions to treat ocular allergic conjunctivitis. Ex. 1001 at 2:41-42. Thus, the POSA will also have experience in developing ophthalmic pharmaceutical formulations for the treatment of ocular allergic conjunctivitis. Ex. 1002 ¶ 14; Ex. 1003 ¶14; *cf. Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007).

Lastly, a POSA typically would work as part of a multidisciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team to solve a given problem. Ex. 1002 ¶ 15; Ex. 1003 ¶15. For example, a clinician having experience in treating allergic disorders of the eye with topical pharmaceuticals would be part of the team. *Id*. A formulations chemist with knowledge of a wide array of excipients suitable for use in ophthalmic formulations and their properties would also be part of the team. *Id*. The hypothetical POSA will be aware of such specialized knowledge as applicable to various aspects of the claimed invention. *E.g*., *AVX Corp. v. Greatbatch, Ltd*., IPR2014-00697, Paper 60 at 3 (PTAB Jan. 11, 2016).

D. Claim Construction Under 37 C.F.R. § 42.104(b)(3)

Claim terms in *inter partes* review are given their "broadest reasonable construction in light of the specification." 37 C.F.R. § 42.100(b). Any claim term that lacks a definition in the specification is therefore given a broad interpretation. For the purposes of this proceeding, claim terms are presumed to take on their plain and ordinary meaning in view of the specification. Petitioners' discussion herein relies on the plain and ordinary meaning of the claim terms to a POSA in light of the specification at the time of the filing of the '154 Patent, and therefore Petitioners' analysis falls well within the standard set by 37 C.F.R. § 42.100(b),

and is consistent with *Phillips v. AWH Corp*., 415 F.3d 1303, 1313-14 (Fed. Cir. 2005)(*en banc*).

Solely for purposes of this proceeding, the following discussion proposes constructions of certain claim terms. Any claim terms not included below are to be interpreted in accordance with their plain and ordinary meaning in light of the specification, as understood by one of ordinary skill in the art.

1. Claims 1, 4, 8, and 21 -- Preamble

The preambles of claims 1, 4, 8 and 21 each recite "An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising …." The bodies of the claims (including the dependent claims) go on to define the compositional limitations of the solutions claimed, without any reference back to the preamble description. The '154 Patent nowhere teaches that the recited "intended use" imparts any structural differences to the claimed solutions, beyond the express compositional limitations in the claims.

Where, as here, the claim body fully sets forth all the limitations of the claimed invention, and the preamble merely states the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, the preamble is non-limiting. *Pitney Bowes, Inc. v. Hewlett-Packard Co*., 182 F.3d 1298, 1305 (Fed. Cir. 1999); *see also Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997) ("[W]here a patentee defines a structurally complete invention

in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"). In addition, neither the Patent Owner nor the Examiner relied on the preamble during prosecution to distinguish the claimed invention from the prior art (*see* Ex. 1009 at 56-65, 94-108, 126-143), which likewise confirms the preamble's non-limiting nature. *Catalina Mktg. Int'l v. Coolsavings.com, Inc*., 289 F.3d 801, 808-09 (Fed. Cir. 2002).

As such, the preambles of claims 1, 4, 8, and 21 (and the dependent claims therefrom) should be construed as non-limiting.

2. Claims 1, 4, 8, and 21 -- Construction of "solution comprising … at least 0.67 w/v % olopatadine … dissolved in the solution"

Claim 1 recites the term "solution comprising … at least 0.67 w/v% olopatadine dissolved in the solution." Claims 4, 8, and 21 recite "solution comprising … at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution." The '154 Patent states that:

> it is preferred that the entire concentration of olopatadine is dissolved in the composition …. However, it is contemplated that olopatadine could be only partially dissolved. For example, a portion of the olopatadine could be in solution with the remainder being in suspension.

Ex. 1001 at 4:24-29.

Thus, the use of "comprising" in claims 1, 4, 8 and 21, coupled with the above

discussion from the specification, make clear that solutions having additional olopatadine present in undissolved form (separate from the required amount of dissolved olopatadine) may fall within the scope of claims 1, 4, 8 and 21.

3. Claims 1, 4, 8, 21, and 22 -- Construction of "w/v %"

Claims 1, 4, 8, 21, and 22 each recite components in terms of "w/v %." While the '154 Patent states that this term means weight volume percent (*id*. at 3:41-43), it does not provide the *units* used in determining the weight volume percent. The expression "w/v %" is proposed to describe the mass of the component in grams per 100 milliliters of solution multiplied by 100, as this definition is the standard used in the formulations and topical eye pharmaceutical industries. Ex. 1002 ¶ 21.

E. None of the Claims Are Entitled to the Priority Date of Provisional Application 61/487,789

The '154 Patent claims priority to U.S. Provisional Appl. No. 61/487,789, filed on May 19, 2011 (Ex. 1010, "the '789 Provisional"). The Office never considered priority during prosecution of the '154 Patent, and no presumption of priority applies. *PowerOasis, Inc. v. T-Mobile USA*, 522 F.3d 1299, 1305 (Fed. Cir. 2008) (explaining that when neither the Office nor the Board has considered priority, there is no presumption that patent claims are entitled to the effective filing date of an earlier filed application). As shown below, none of claims 1-4, 8,

12, 13, 21, and 22 are entitled to the benefit of the filing date of the '789 Provisional.

Raising a priority issue involves "identifying, specifically, the features, claims, and ancestral applications allegedly lacking § 112, first paragraph, written description and enabling disclosure support for the claims based on the identified features." *Polaris Wireless, Inc. v. TruePosition, Inc.*, IPR2013-00323, Paper 9 at 29 (PTAB Nov. 15, 2013); *see also SAP America, Inc. v. Pi-Net Int'l., Inc.*, IPR2014-00414, Paper 11 at 13-14 (PTAB Aug. 8, 2014). The test for sufficiency under the written description requirement of 35 U.S.C. § 112 ¶1 is whether the application disclosure relied on reasonably conveys to a POSA that the inventors had possession of the claimed subject matter. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)(*en banc*).

None of the claims of the '154 Patent are supported by the '789 Provisional. Each independent claim of the '154 Patent recites a "**hydroxypropyl-γ-cyclodextrin**," and no dependent claim further limits the type of cyclodextrin employed. The '789 Provisional fails to even mention γ-cyclodextrins or derivatives of γ-cyclodextrins; instead, the '789 Provisional exclusively focuses on "includ[ing] a **β-cyclodextrin** derivative to aid in the solubility of the olopatadine" (Ex. 1010 at 3:2-7), with all examples relying on a β-cyclodextrin derivative (*id.*, Tables A-H). The '789 Provisional fails to reasonably convey the inclusion of

hydroxypropyl-γ-cyclodextrin in the compositions, and therefore fails to support that Patent Owner had possession of such compositions at the time of filing of the '789 Provisional.

Because the '789 Provisional fails to disclose or provide any examples utilizing γ-cyclodextrin derivatives, the claims of the '154 Patent find no support in the '789 Provisional and cannot benefit from the filing date of the '789 Provisional.

F. Claim-By-Claim Explanation of Grounds for Unpatentability

Claims 1-4, 8, 12, 13, 21, and 22 are unpatentable as shown in the detailed grounds for unpatentability below.

1. Ground 1: Claims 1-4, 8, 12, 13, 21, and 22 are unpatentable under 35 U.S.C. § 103(a) over Bhowmick, Yanni, and Castillo

Claims 1-4, 8, 12, 13, 21, and 22 are unpatentable under 35 U.S.C. § 103(a) over WO 2008/015695 (Ex. 1004, "Bhowmick"); Yanni, J.M. *et al.* "The *In Vitro* and *In Vivo* Ocular Pharmacology of Olopatadine (AL-4943A), an Effective Anti-Allergic/Antihistaminic Agent," *J. Ocular Pharmacol. Ther.* 1996, Vol. 12(4), 389-400 (Ex. 1005, "Yanni"); and U.S. Pat. No. 6,995,186 (Ex. 1006, "Castillo"). Bhowmick was published on February 7, 2008, Yanni was published in 1996, and Castillo was published February 7, 2006. Therefore each of Bhowmick, Yanni, and Castillo are prior art under 35 U.S.C. §102(b), pre-AIA.

Bhowmick describes stable aqueous topical solutions of olopatadine prepared by forming complexes of olopatadine and cyclodextrins. Ex. 1004, 2:24-27; 3:15-20; 4:16-17. Bhowmick teaches that cyclodextrins such as hydroxypropyl-β-cyclodextrin ("HP-β-CD"), hydroxypropyl-γ-cyclodextrin ("HP-γ-CD"), and sulfobutyl ether-β-cyclodextrin ("SBE- β-CD") may be used to prepare the stable aqueous topical solutions. *Id.* at 5:10-30. Bhowmick explains that such compositions keep olopatadine in solution and prevent its precipitation or crystallization. *Id.* at 3:25-28. Bhowmick also teaches use of hydroxypropyl methylcellulose ("HPMC") in the solutions to further stabilize the inclusion complex, and improve long-term stability. *Id.* at 2:26-27; 6:23-26; 7:10-13; Examples 1-2.

Bhowmick does not suggest an upper limit to the amount of olopatadine and simply calls for a therapeutically effective amount (*see id.*, Claim 6), although Bhowmick recites a preferred range of about 0.17% w/v to about 0.62% w/v of olopatadine (*id.* at 4:9-12 (reporting free base concentrations)). Ex. 1002 ¶ 54. Antimicrobial preservatives such as benzalkonium chloride may be included in amounts ranging from about 0.005% w/v to about 1% w/v. Ex. 1004 at 7:15-22. The osmolality of such aqueous topical compositions may be adjusted to between 150 mOsm to 450 mOsm, and preferably adjusted to between 250 and 350 mOsm.

Id. at 8:11-12; Ex. 1002 ¶ 51. Finally, Bhowmick teaches the beneficial inclusion of tonicity agents as well as buffering agents such as borates. Ex. 1004 at 8:4-21.

Well before the '154 Patent, a POSA would have appreciated the desirability of including olopatadine at "relatively high" concentrations, because the art recognized the benefits of including higher olopatadine concentrations. In particular, Yanni reports studies performed with olopatadine characterizing the topical ocular pharmacological profile. Ex. 1005, Abstract. Upon assessing the histamine release from human conjunctival mast cells after treatment with varying concentrations of olopatadine (referenced as "AL-4943A" (*id.*)), Yanni found histamine release was significantly reduced in a concentration dependent fashion. *Id.* at 393, Fig. 1B; Ex. 1003 ¶ 34. Yanni also studied the effects of topically applying 20 μL drops of aqueous solutions of varying olopatadine concentrations to the eyes of guinea pigs or rats.[1] Ex. 1005 at 391-392.

In all cases reported by Yanni, 1 wt% olopatadine was superior to 0.1 wt% after dosing in passive anaphylaxis and histamine-induced vascular permeability models. Ex. 1005 at 394-396,Tables 2 & 3; *see also* Ex. 1003 ¶¶ 35, 49.

[1] While Petitioner does not believe the preambles to be limiting in the claims at issue here, the intended use recited in the claims does not defeat the relevance of Yanni's animal testing. *See Alcon*, 687 F.3d at 1369 ("Here, the motivation to adapt [the prior art's olopatadine] formulation for human use is that it is an effective antihistamine in guinea pigs and that animal models are [] predictive of antihistaminic efficacy in humans.").

Moreover, in eyes pretreated 24 hours beforehand with the drops, 1 wt% olopatadine provided 96% inhibition, while drops with 0.1 wt% olopatadine only provided 33% inhibition. Ex. 1005, Table 3; *see* Ex. 1003 ¶ 35.

Castillo likewise discloses topical solutions for treating allergic or inflammatory disorders of the eye, and teaches that solutions containing approximately 0.2-0.6% olopatadine and are effective as once-a-day products. Ex. 1006 at 2:13-19. Castillo teaches the inclusion of 0.1% to 3% PVP to enhance the storage stability of the solutions. *Id.* at 2:19-22; 3:17-25; Example 11. Similar to Bhowmick, Castillo also teaches tonicity agents such as mannitol, preservatives such as benzalkonium chloride, and buffering agents such as borates may each be included in the solutions. *Id.* at 3:57–4:8.

Castillo also provides test results from an example with 2% w/w PEG 400 (Formulation M), along with formulations including both PVP with a MW of 58,000 and PEG 400 (Formulations L and R). Ex. 1006, Example 7, Table 5. Each of these formulations exhibited enhanced stability when subjected to freeze-thaw testing. *Id.*, Table 6; *see* Ex. 1002 ¶ 59. While Castillo states that its solutions do not contain HPMC, Castillo does recognize HPMC as a "polymeric physical stability enhancing ingredient." Ex. 1006 at 3:46-50. Castillo also provides a working example with HPMC that illustrates the same enhanced stability provided by PVP. *Compare* Ex. 1006, Example 6, Tables 3 & 4

(Formulation H) *with id.*, Example 7, Tables 5 & 6 (Formulations K & Q); Ex. 1002 ¶ 34. Thus, Castillo does not disparage or recommend avoiding HPMC, but instead confirms HPMC's known role as a "physical stability enhancing ingredient" that provides enhanced stability along with PVP. Ex. 1002 ¶ 34.

Together, Bhowmick, Yanni, and Castillo teach all of the limitations of claims 1-4, 8, 12, 13, 21, and 22 of the '154 Patent, as shown in detail in the claim chart at the end of this section. As further discussed below, these claims would have been obvious to one of skill in the art.

a. Claims 1-3

All of the challenged claims of the '154 Patent require an olopatadine concentration (free base) of at least 0.67 w/v% dissolved in the solution. While Bhowmick and Castillo teach olopatadine concentrations of "about 0.62% w/v" and "approximately" 0.6 w/v%, respectively (*see* Ex. 1004 at 4:9-12; Ex. 1006 at 2:13-19; 2:32-34), Yanni clearly discloses solutions with 1 w/v% olopatadine (Ex. 1005 at Tables 1-3 (reporting various experiments using 1% olopatadine); *see also id*. at 393 (noting that the reported concentrations are free base w/v%).

Motivation to use higher levels of olopatadine: A POSA would have been motivated to utilize higher concentrations of olopatadine than those reported in Bhowmick and Castillo based on Yanni's teachings that solutions with 1 w/v% olopatadine exhibited superior reductions in symptoms of allergic conjunctivitis

and provided significantly longer durations of action than lower concentrations of olopatadine. *See* Ex. 1003 ¶¶ 47-52. A POSA would not have been dissuaded from pursuing such high concentrations, knowing that olopatadine does not exhibit biphasic behavior, and further appreciating Yanni's reported effectiveness in human mast cells. *Id*. ¶¶ 42, 57; *see also Alcon*, 687 F.3d at 1369 ("Here, the motivation to adapt [the prior art's olopatadine] formulation for human use is that it is an effective antihistamine in guinea pigs and that animal models are [] predictive of antihistaminic efficacy in humans.").

Motivation to include PEG, PVP, HP-γ-CD, BAC, and water: Claim 1 further calls for the inclusion of PEG, PVP, HP-γ-CD, BAC, and water in the composition. As discussed below, all of these components are well-known excipients for ophthalmic solutions, including those containing olopatadine.

While Yanni does not state whether all of the olopatadine is dissolved in solution versus being suspended (*see* Ex. 1005 at 393 (referring to solutions and suspensions)), Yanni reveals that the studies reported therein were the basis for successful human trials that led to the filing of a New Drug Application with the FDA. *Id*. at 398; Ex. 1003 ¶ 48. It is well-known in that art that such ophthalmic pharmaceutical compositions preferably maintain the active ingredient in solution and are substantially free of precipitates and crystallites, as taught, for example, by Bhowmick. *See* Ex. 1004 at 1:31–2:5; 3:25-28; Ex. 1002 ¶¶ 27-28, 32, 34, 38-43,

59. This is further consistent with a POSA's understanding based upon the general teachings in the art. *See* Ex. 1007 at ¶[0007] ("In general, it is more desirable for active ingredients to be in solution rather than suspension in a pharmaceutical composition."); Ex. 1003 ¶ 36.

To achieve high solubility of olopatadine in a stable, precipitate-free solution, a POSA would have relied on the teachings in the art regarding useful excipients for solubilizing olopatadine and maintaining long-term storage stability. Ex. 1002 ¶ 59. As discussed previously, both Bhowmick and Castillo are directed to these very issues.

Specifically, Bhowmick teaches the use of cyclodextrins (including HP-β-CD, HP-γ-CD, and SBE- β-CD) to prepare stable aqueous topical solutions of olopatadine. *Id.* at 5:17-18, 5:28. Bhowmick also teaches use of HPMC to further stabilize the solutions. *Id.* at 2:26-27; 6:23-26; 7:10-13; Examples 1-2.

Similarly, Castillo teaches the use of PVP as a solubility and stability enhancer in olopatadine-containing ophthalmic solutions. Ex. 1006 at 2:19-22; Example 10. A POSA also appreciated PVP's role in increasing the solubility of cyclodextrin-drug complexes. *See* Ex. 1044, Fig. 5; Ex. 1002 ¶¶ 41, 59-61. Based on this, Castillo would motivate inclusion of PVP with Bhowmick's cyclodextrin-olopatadine combination. Ex. 1002 ¶ 59.

Castillo also discloses that PEG 400, both alone and with PVP, provides olopatadine solutions with enhanced stability. Ex. 1006, Example 7, Tables 5 and 6 (Formulations L, M, & R); Ex. 1002 ¶ 59. PEG 400 was also known to increase the solubility of cyclodextrin-drug complexes. Ex. 1002 ¶¶ 41-43. A POSA would therefore be motivated to include PEG 400 with PVP to further increase the solubility of Bhowmick's cyclodextrin-olopatadine combination.

In addition to solubility/stability issues, additional motivations were known for including components such as PVP and PEG into ophthalmic pharmaceutical compositions such as those of Bhowmick. For example, PEG is not only a solvent (solubilizer), but is also an FDA-approved demulcent, which protects and lubricates mucous membrane surfaces and relieving dryness and irritation. Ex. 1002 ¶¶ 25-26. PEG is also used as a viscosity agent. *Id*. ¶ 29. PVP is likewise a recognized demulcent, and is known to be generally beneficial in ophthalmic anti-allergy compositions. *Id*. ¶¶ 30-32.

Thus, the desire to solubilize the higher olopatadine concentrations of Yanni and achieve long-term solution stability, as well as the general motivation to provide an FDA-approved ophthalmic formulation for human use, would have motivated a POSA to include excipients such as HP-γ-CD, PEG 400, and PVP into the ophthalmic composition, as called for in Claim 1. Ex. 1002 ¶ 55.

Lastly, a POSA would also have known and been motivated to include a preservative such as benzalkonium chloride (*see* Ex. 1004, 7:20-22; Ex. 1006, 3:66-4:1), and water (see Ex. 1004, Abstract; Ex. 1006, Claim 1), given that these are aqueous ophthalmic solutions. Ex. 1002 ¶¶ 44-46.

Reasonable expectation of success: The claims call for at least 0.67 w/v% olopatadine, which is a level only slightly higher than the "about 0.62% w/v" of Bhowmick's preferred range and the up to "0.62% (w/v)" claimed in Castillo. Given that Castillo is an issued U.S. patent that is presumptively enabled up to 0.62% (w/v) olopatadine in solution (*see Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1355 (Fed. Cir. 2003)), and because the claims require only a small amount more of olopatadine, a POSA would reasonably have expected aqueous solutions including a HP-γ-CD, PVP and PEG 400 to solubilize at least 0.67 w/v% olopatadine. Ex. 1002 ¶ 59. Indeed, even as early as 1997, a POSA would have been presumptively able to make an olopatadine solution with a concentration of dissolved olopatadine as high as 5% (w/v). Ex. 1008 at 6:40-44, Claim 2; *see Amgen*, 314 F.3d at 1355.

Moreover, Bhowmick taught using cyclodextrins to increase the solubility of olopatadine, and nowhere suggests an upper limit to the amount of olopatadine that can be included in such stable solutions. Ex. 1002 ¶¶ 53-54.

Given that HP-γ-CD, PVP and PEG were known to have a beneficial effect (both individually and collectively) on olopatadine solubility and stability, choosing the correct excipients and in appropriate concentrations would have been a matter of routine experimentation and optimization. *Id*., ¶ 61; *see In re Woodruff,* 919 F.2d at 1577 (Fed. Cir. 1990); *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980).

Claims 2 and 3: Claim 2 calls for inclusion of a borate. Borates are known buffering agents useful for ophthalmic compositions (Ex. 1002 ¶¶ 47-48), and both Bhowmick and Castillo disclose the inclusion of borates. Ex. 1004 at 8:14-21; Ex. 1006 at 4:2-4.

Claim 3 calls for a polyol. Polyols are known to be useful in ophthalmic compositions as, *e.g.*, tonicity agents. Ex. 1002 ¶¶ 49-50. Both Bhowmick and Castillo call for the inclusion of tonicity agents, and Castillo expressly discloses mannitol as an exemplary polyol. Ex. 1004 at 8:4-12; Ex. 1006 at 3:64-65.

Because borates and polyols and well-known additives in ophthalmic compositions that merely perform the functions they are intended for in the claimed compositions, Claims 2 and 3 do not add any patentably distinct limitations over Claim 1. *See* Ex. 1002 ¶¶ 56, 58-61.

b. Claims 4, 8, 21, and 22

Claims 4, 8, 21, and 22 require that both the PEG and PVP be present at 2-6 w/v%. Claim 4 further calls for 0.5-2 w/v% of one or more of HP-β-CD, HP-γ-CD, or SAE- β-CD, while Claims 8 and 21-22 specify HP-γ-CD. Claim 21 further calls for a pH of 6-7.8 and an osmolality of 200-400 mOsm/kg, while Claim 22 further calls for 0.15-1 w/v% of HPMC. None of these additional limitations render the claims patentably distinct over the prior art. Ex. 1002 ¶¶ 60-62.

PEG and PVP: Regarding PEG and PVP, Castillo expressly discloses the use of 2% PEG 400 in its olopatadine solutions, both alone and with 2% PVP. Ex. 1006, Example 7, Tables 5 & 6 (Formulations L, M, & R); Ex. 1002 ¶ 59. While Castillo reports these concentrations in terms of % w/w, in effect this means that the 2% levels reported for PEG and PVP are above 2% on a w/v basis, as required for the claims of the '154 Patent. Ex. 1003 ¶¶ 43-45. Thus, the PEG and PVP concentrations required by Claims 4, 8, 21, and 22 are disclosed in the art.

Cyclodextrin: Regarding the required cyclodextrin, Bhowmick expressly teaches that HP-β-CD, HP-γ-CD, and SBE- β-CD may be used to prepare stable aqueous topical solutions of olopatadine. Ex. 1004 at 5:17-18, 5:28. Bhowmick teaches preferably including HP-β-CD from about 1.0% w/v to about 5% w/v for solutions meant for ophthalmic administration. *Id*. at 6:1-6. Thus, the cyclodextrin limitation of Claim 4 is disclosed by Bhowmick.

Regarding the requirement in Claims 8 and 21-22 for 2-6% HP-γ-CD, this would have been obvious based on Bhowmick's teachings, and the knowledge of a person of ordinary skill in the art. Bhowmick suggests that HP-β-CD, HP-γ-CD, and SBE- β-CD may be used interchangeably to prepare stable aqueous topical solutions. *Id.* at 5:10-30; Ex. 1002 ¶ 40. This is consistent with the prior art, which likewise suggests that these three CD varieties can be used interchangeably in ophthalmic pharmaceutical compositions. *See, e.g.*, Ex. 1045 at ¶[0018]. It is also noteworthy that nowhere does the '154 Patent teach a special distinction between HP-β-CD and HP-γ-CD, but instead treats them as interchangeable for the purpose of stabilizing aqueous topical solutions. Ex. 1001 at 5:30-47.

Where, as here, two known alternatives are interchangeable for a desired function, an express suggestion to substitute one for the other is not needed to render a substitution obvious. *In re Fout*, 675 F.2d 297, 301 (C.C.P.A. 1982); *In re Siebentritt*, 372 F.2d 566, 568 (C.C.P.A. 1967); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007) (indicating that a claim is obvious if it is no "more than the predictable use of prior art elements according to their established functions," even without an express suggestion to combine). Thus, Bhowmick's teachings as to CDs would give a POSA a reason to use HP-γ-CD at a concentration of 1-5%. Ex. 1002 ¶¶ 40, 60. Indeed, the prior art provides consistent teachings of

concentrations of HP-γ-CD in ophthalmic solutions within the range of 0.05-10%. Ex. 1045 at ¶[0163], Table 1; Ex. 1002 ¶¶ 38-40, 60.

BAC, pH and osmolality: Claim 21 calls for 0.003-0.03 w/v% of BAC, water, a pH of 6-7.8, and an osmolality of 200-400 mOsm. Bhowmick teaches that the aqueous solutions preferably contain 0.005-l w/v% BAC, have a pH of 6.5 to 7.5, and an osmolality between 250-350 mOsm. Ex. 1004 at 7:20-22; 8:11-24. These are standard conditions for topical ophthalmic pharmaceutical compositions (Ex. 1002 ¶¶ 44-45, 51, 62), and do not add any patentably distinct limitations.

HPMC: Claim 22 calls for between 0.15 and 1% HPMC. Bhowmick teaches the inclusion of HPMC at a preferred range about 0.01 to 1%. Ex. 1004 at 7:10-13.

Motivation to Combine: The motivation to incorporate PEG, PVP, HP-γ-CD, BAC, and water was discussed previously as to Claim 1, which discussion is equally applicable here. Along those same lines, a POSA would also have been motivated to include HPMC, given Bhowmick's teachings that HPMC further enhances both solubility and stability. *Id*. at 6:23-26; Examples 1-2; Ex. 1002 ¶¶ 34, 41, 63. HPMC is also an FDA-approved demulcent at 0.2-2.5% for protecting and lubricating mucous membrane surfaces and relieving dryness and irritation. Ex. 1002 ¶¶ 33-34.

Bhowmick and Castillo teach ranges and provide examples both within and overlapping with the claimed PEG, PVP, cyclodextrin, and HPMC ranges. Moreover, no criticality of these ranges (either alone or combined) is disclosed in the '154 Patent. Therefore, it would have been obvious to select ranges within Bhowmick and Castillo that fall within the claimed ranges. Ex. 1002 ¶¶ 60-63. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)(prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness); *Woodruff*, 919 F.2d at 1578.

In addition, because the beneficial effects of the recited PEG, PVP, cyclodextrin, and HPMC components were well-known in the art (Ex. 1002 ¶¶ 61, 63), as were studies directed at optimizing the solubility of drugs with these components (*see id*.¶¶ 27-28, 32, 34, 38-43), the recited ranges of claims 4, 8, 21, and 22 would arise from routine optimization due to the natural desire to maximize known, beneficial properties. *In re Applied Materials*, 692 F.3d 1289, 1297-98 (Fed. Cir. 2012); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997).

Claim 21's recitation of particular ranges for benzalkonium chloride, pH, and osmolarity is likewise obvious. Bhowmick teaches that benzalkonium chloride is a preferred preservative for ophthalmic solutions that may be used in concentrations of 0.005-1 w/v% (Ex.1004 at 7:20-22) and that the aqueous solutions preferably have a pH of 6.5 to 7.5 and an osmolarity between 250-350

mOsm (*id.* at 8:11-12, 22-24). Ex. 1002 ¶ 62. The '154 Patent recites ranges for benzalkonium chloride, pH, and osmolarity that falls within the recited ranges of Bhowmick, yet the '154 Patent fails to show the criticality of such ranges. Moreover, a POSA understood inclusion of benzalkonium chloride within the claimed range was known to further increase the solubility of cyclodextrin-drug complexes. Ex. 1002 ¶¶ 46, 62. It therefore would have been obvious to select the ranges for benzalkonium chloride, pH, and osmolarity within Bhowmick's teachings that fall within the claimed ranges. *Peterson*, 315 F.3d at 1330.

Finally, given that the prior art discloses all of the claimed components in ranges that overlap with the claimed ranges, a POSA would have had a reasonable expectation of success in arriving at the claimed compositions through such routine optimization. *See In re Sasse*, 629 F.2d 675 (C.C.P.A. 1980) (noting that the prior art is presumed operable). Moreover, the fact that Bhowmick discloses many cyclodextrin compounds does not render a formulation having the specific HP-γ-CD compound any less obvious. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

c. Claims 12 and 13

Claim 12 calls for the topical application of the composition of Claim 4 sufficient to treat at least one ocular allergy symptom. Claim 13 specifies that the step of applying the composition includes dispensing at least one drop of the

solution to the eye. Bhowmick, Castillo amd Yanni each discloses topical olopatadine compositions that were recognized to treat ocular allergy symptoms, such as ocular itching. Ex. 1004 at 1:16-27; Ex. 1005 at 398; Ex. 1006 at 2:13-19, 4:16-19; Ex. 1003 ¶¶ 63-66. A POSA would appreciate that higher olopatadine concentrations would provide superior antihistamine effects and for longer durations based on Yanni. Ex. 1003 ¶¶ 48-49, 61.

Given that the composition of Claim 4 would have been both obvious and known to provide antihistamine effects as discussed above, the topical administration of such a composition for its known purpose according to Claims 12 and 13 is likewise obvious in view of Bhowmick, Castillo, and Yanni. *See Alcon*, 687 F.3d at 1369 ("A person of ordinary skill in the art at the time of invention would have been motivated to use olopatadine to treat human eye allergies as claimed for its established antihistaminic efficacy."). Claims 12 and 13 are therefore unpatentable in view of these references.

d. Claim Chart

As shown in the following claim chart, the combination of Bhowmick, Yanni, and Castillo teaches or suggests each and every limitation to a POSA, and thus renders claims 1-4, 8, 12, 13, 21, and 22 obvious.

'154 Patent Claims	**Bhowmick, Yanni, and Castillo**
1. An aqueous ophthalmic solution for	"The present invention also relates to an **aqueous topical solution** comprising a therapeutically effective

treatment of ocular allergic conjunctivitis, the solution comprising:	amount of olopatadine or its pharmaceutically acceptable salt; hydroxyalkyl-ß-cylcodextrin, preferably hydroxypropyl-ß-cylcodextrin and hydroxypropyl methylcellulose in an amount sufficient to enhance the physical stability of the solution." Bhowmick, Abstract. "The present invention provides **topical** olopatadine formulations that are effective as once-a-day products for treating **allergic or inflammatory disorders of the eye** and are effective for treating allergic or inflammatory disorders of the nose. The formulations of the present invention are **aqueous** solutions that comprise approximately 0.2-0.6% olopatadine. " Castillo, 2:13-19.
at least 0.67 w/v % olopatadine dissolved in the solution;	"In a most preferred embodiment of the present invention, the olopatadine hydrochloride salt may be used in concentrations such that it is equivalent to the olopatadine free base in amount ranging from about 0.17% to **about 0.62%.** Bhowmick, 4:9-12. "Among other factors, the present invention is based on the finding that polyvinylpyrrolidone and polystyrene sulfonic acid … enhance the physical stability of solutions containing **approximately 0.2-0.6% olopatadine**." Castillo, 2:23-27. Yanni studies the effects of 20 µL drops of an aqueous solution of olopatadine topically applied to eyes of guinea pigs or rats in passive anaphylaxis and histamine-induced vascular permeability models where the olopatadine concentrations ranged from 0.001 to **1.0 %w/v**. Yanni, 391-392; 394-396,Tables 2 & 3.
PEG having a molecular weight of 300 to 500;	Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R)
polyvinylpyrrolidone;	"Among other factors, the present invention is based on the finding that **polyvinylpyrrolidone** and polystyrene sulfonic acid … **enhance the physical stability of solutions containing approximately 0.2-0.6% olopatadine**." Castillo, 2:23-27.

hydroxypropyl-γ-cyclodextrin	"According to one embodiment of the present invention, the aqueous topical solution comprises cyclodextrin to enhance the physical stability of the solution. … Examples of cyclodextrin derivatives that may be used in the pharmaceutical compositions of present invention include the **hydroxypropyl derivatives of** alpha-, beta- and **gamma-cyclodextrin** ...." Bhowmick, 4:16-17 and 5:3-8. "Examples of suitable cyclodextrins for use in the present invention non-exclusively include …**2-hydroxypropyl gamma-cyclodextrin**…" Bhowmick, 5:12-18.
benzalkonium chloride; and	"The **preferred preservative for the aqueous topical solution of the present invention is benzalkonium chloride**. It may be used in an amount ranging from about 0.005% to about l %w/v." Bhowmick, 7:20-22. "**Suitable preservatives** include p-hydroxybenzoic acid ester, **benzalkonium chloride**, benzododecinium bromide, polyquaternium-1 and the like." Castillo, 3:66-4:1.
water.	The present invention also relates to an **aqueous** topical solution ..." Bhowmick, Abstract. "A topically administrable solution composition for treating allergic or inflammatory disorders of the eye and nose, wherein the solution has … **water**." Castillo, claim 1.

2. A solution as in claim 1 further comprising borate.	"The aqueous topical solution of the present invention may include an effective amount of buffering agent. The buffering agents are included to minimize any change in pH during shelf life of the aqueous topical solution. Examples of buffering agents include, but are not limited to … **sodium borate,** and the like and mixtures thereof." Bhowmick, 8:14-21. "**Suitable buffering agents** include phosphates, **borates,** citrates, acetates and the like." Castillo, 4:2-4.

3. A solution as in claim 2 further comprising a polyol.	"**Suitable tonicity-adjusting agents include mannitol,** sodium chloride, **glycerin, sorbitol** and the like." Castillo, 3:64-65.

4. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:	See claim 1 above.
at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution;	"In a most preferred embodiment of the present invention, the olopatadine hydrochloride salt may be used in concentrations such that it is equivalent to the olopatadine free base in amount ranging from about 0.17% to **about 0.62%.** Bhowmick, 4:9-12. "Among other factors, the present invention is based on the finding that polyvinylpyrrolidone and polystyrene sulfonic acid … enhance the physical stability of solutions containing **approximately 0.2-0.6% olopatadine**." Castillo, 2:23-27. Yanni studies the effects of 20 µL drops of an aqueous solution of olopatadine topically applied to eyes of guinea pigs or rats in passive anaphylaxis and histamine-induced vascular permeability models where the olopatadine concentrations ranged from 0.001 to **1.0 %w/v**. Yanni, 391-392; 394-396,Tables 2 & 3.
2.0 w/v % to 6.0 w/v % PEG having a molecular weight of 300 to 500;	Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R).
2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone;	"In addition to olopatadine, the aqueous solution compositions of the present invention comprise **polyvinylpyrrolidone** or polystyrene sulfonic acid in an amount sufficient to enhance the physical stability of the composition." Castillo, 2:66-3:2. "In general, the **amount of polyvinylpyrrolidone** contained in the compositions of the present invention

	will be **0.1-3%, preferably 0.2-2%, and most preferably 1.5-2%**." Castillo, 3:22-25.
at least 0.5 w/v % but no greater than 2.0 w/v % cyclodextrin derivative selected from the group consisting of SAE-β-cyclodextrin, HP-γ-cyclodextrin, HP-β-cyclodextrin and combinations thereof; and	"The preferred cyclodextrins for use in the present invention include alkyl cyclodextrins, hydroxy alkyl cyclodextrin, such as **hydroxy propyl beta-cyclodextrin**, carboxy alky1 cyclodextrins and **sulfoalkyl ether cyclodextrin**, such as **sulfobutyl ether beta-cyclodextrin**. Examples of suitable cyclodextrins for use in the present invention non-exclusively include … **2-hydroxypropyl beta-cyclodextrin; 2-hydroxypropyl gamma-cyclodextrin**; … In a preferred embodiment of the present invention, hydroxypropyl beta-cyclodextrin may be used in concentrations ranging from about 0.1% to about 20% w/v of the composition, 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 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 about 10%." Bhowmick at 5:10-18, 6:1-8. "The ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cyclodextrin in the inclusion complex is from about **1:1.65 to about 1:50 by weight**. The amount of hydroxypropyl β-cylcodextrin present in the inclusion complex is sufficient to enhance the physical stability of the olopatadine solution." Bhowmick at 6:18-21.
water	"The present invention also relates to an **aqueous** topical solution ..." Bhowmick, Abstract. "A topically administrable solution composition for treating allergic or inflammatory disorders of the eye and nose, wherein the solution has … **water**." Castillo, claim 1.

8. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:	See claim 1 above.
at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution;	See claim 4 above.
2.0 w/v % to 6.0 w/v % PEG having a molecular weight of 300 to 500;	Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R).
2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone;	See claim 4 above.
at least 0.5 w/v % but no greater than 2.0 w/v % of hydroxypropyl-γ-cyclodextrin, and	"The preferred cyclodextrins for use in the present invention include alkyl cyclodextrins, hydroxy alkyl cyclodextrin …. Examples of suitable cyclodextrins for use in the present invention non-exclusively include … 2-hydroxypropyl beta-cyclodextrin; **2-hydroxypropyl gamma-cyclodextrin**; … In a preferred embodiment of the present invention, hydroxypropyl beta-cyclodextrin may be used in concentrations ranging from about 0.1% to about 20% w/v of the composition, 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 preferable concentration of hydroxypropyl beta-cyclodextrin is in the range from **about 1.0% to about 5%** ..." Bhowmick at 5:10-18, 6:1-8. "The ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cyclodextrin in the inclusion complex is from about **1:1.65 to about 1:50 by weight**." Bhowmick at 6:18-21.

water	See claim 4 above.

12. A method of treating at least one ocular allergy symptom in humans, the method comprising: topically applying to an eye of a human an amount of the solution of claim 4 sufficient to treat the at least one ocular allergy symptom.	"Olopatadine hydrochloride is commercially available in the U.S. as 0.1 % and 0.2% sterile ophthalmic solutions under the brand names PATANOL® and PATADAY® respectively, both marketed by Alcon. PATANOL® is indicated for the treatment of signs and symptoms of allergic conjunctivitis." Bhowmick, 1:16-19. "The present invention provides **topical** olopatadine formulations that are effective as once-a-day products for treating **allergic or inflammatory disorders of the eye** and are effective for treating allergic or inflammatory disorders of the nose." Castillo, 2:13-19.

13. A method as in claim 12 wherein the step of topically applying the solution includes dispensing at least one drop of the solution to the eye.	"The aqueous topical solution is intended to be **administered as** nasal solution or **eye drops**." Bhowmick, 8:10-11. "Particularly for compositions intended to be **administered as eye drops** …" Castillo, 4:16-19."

21. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:	See claim 1 above.
at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution;	See claim 4 above.
2.0 w/v % to 6.0 w/v % PEG having a molecular weight of	Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R).

300 to 500;	
2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone;	See claim 4 above.
at least 0.5 w/v % but no greater than 2.0 w/v % of hydroxypropyl-γ-cyclodextrin;	"The preferred cyclodextrins for use in the present invention include alkyl cyclodextrins, hydroxy alkyl cyclodextrin…. Examples of suitable cyclodextrins for use in the present invention non-exclusively include … 2-hydroxypropyl beta-cyclodextrin **;2-hydroxypropyl gamma-cyclodextrin**; … Generally, for solutions meant for ophthalmic administration preferable concentration of hydroxypropyl beta-cyclodextrin is in the range from **about 1.0% to about 5%** …" Bhowmick at 5:10-18, 6:1-8. "The ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cyclodextrin in the inclusion complex is from about **1:1.65 to about 1:50 by weight**. The amount of hydroxypropyl β-cylcodextrin present in the inclusion complex is sufficient to enhance the physical stability of the olopatadine solution." Bhowmick at 6:18-21.
greater than 0.003 w/v % but less than 0.03 w/v % benzalkonium chloride; and	"The **preferred preservative for the aqueous topical solution of the present invention is benzalkonium chloride**. It may be used in an amount ranging from **about 0.005% to about l %w/v**." Bhowmick, 7:20-22. "**Suitable preservatives** include p-hydroxybenzoic acid ester, **benzalkonium chloride**, benzododecinium bromide, polyquaternium-1 and the like." Castillo, 3:66-4:1.
water	See claim 4 above.
wherein the pH of the solution is 6.0 to 7.8 and the osmolality of the solution is 200 to 400 mOsm/kg.	"The aqueous topical solution intended for ophthalmic administration has a pH 4 to 8, preferably **pH of 6.5 to 7.5**, and most preferably a **pH of 6.8 to 7.2**." Bhowmick, 8:22-24. "The aqueous topical solution is intended to be administered as nasal solution or eye drops. The osmolality may be adjusted preferably between 150 to

	450 mOsm, and more preferably between **250 to 350 mOsm**." Bhowmick, 8:11-12. "Particularly for compositions intended to be administered as eye drops, the compositions preferably contain a tonicity-adjusting agent in an amount sufficient to cause the final composition to have an **ophthalmically acceptable osmolality (generally 150-450 mOsm, preferably 250-350 mOsm).**" Castillo, 4:16-19."

22. A solution as in claim 21 further comprising at least 0.15 w/v % but no greater than 1.0 w/v % hydroxypropylmethyl cellulose.	"In preferred embodiments of the present invention, **hydroxypropyl methylcellulose** may be used concentrations ranging from about 0.001 % to about 5%, and more preferably in concentrations ranging from **about 0.01 % to about 1 % w/v**." Bhowmick, 7:10-13.

2. Ground 2: Claims 1-4, 8, 12, 13, 21, and 22 are unpatentable under 35 U.S.C. § 103(a) over Schneider in view of Hayakawa, Bhowmick, and Castillo

Claims 1-4, 8, 12, 13, 21, and 22 are unpatentable under 35 U.S.C. § 103(a) over U.S. Pat. Publ. No. 2011/0082145 ("Schneider") in view of U.S. Pat. No. 5,641,805 ("Hayakawa"), Bhowmick, and Castillo. Schneider was filed October 1, 2010 and published April 7, 2011; Hayakawa issued June 24, 1997; Bhowmick published February 7, 2008, and Castillo published February 7, 2006. Thus, Schneider is prior art at least under 35 U.S.C. §§102(a) & (e), pre-AIA, and Hayakawa, Bhowmick, and Castillo are prior art under §102(b), pre-AIA.

Schneider provides solutions that include olopatadine, as well as a genus of phosphodiesterase type-IV ("PDE4") inhibitors, that are useful in treating allergic

conjunctivitis. Ex. 1007, [0006], [0050]. Treatment may involve administering 1-2 drops of the aqueous solution to the eye. *Id.* Schneider explicitly provides for concentrations of olopatadine in solution of "about 0.05%, …. **0.60% w/v, or higher.**" *Id.,* [0045] (emphasis added). Schneider explains that while there are solubility enhancing components for olopatadine, PDE4 itself increases the solubility of olopatadine in aqueous solutions. *Id.*, [0042]. *See* Ex. 1002 ¶ 65.

Schneider also teaches that, in general, it is more desirable for active ingredients to be in solution rather than in suspension in a pharmaceutical composition. *Id.*, [0007]. The compositions of Schneider are disclosed as optionally including one or more polymers as lubricants or viscosity agents. *Id.*, [0052]. Examples include HPMC, PEG, and PVP. *Id*. Schneider further teaches that the olopatadine-containing solutions desirably comprise a variety of other components, such as tonicity agents (*e.g.*, mannitol), preservatives (*e.g.*, benzalkonium chloride), chelating agents, buffering agents (*e.g.*, borates), surfactants, and antioxidants. *Id*. In particular, polyols such as mannitol, sorbitol, propylene glycol, or glycerol are tonicity agents that may be added in amounts sufficient to provide a solution with an osmolality of 250-350 mOsm. *Id.*, [0053].

Hayakawa likewise discloses aqueous topical ophthalmic solutions containing olopatadine for treating allergic eye diseases such as allergic conjunctivitis. Ex. 1008 at 1:7-10; 6:40-43. The concentration of olopatadine

(referenced as "Compound A" (*id*. at 2:67–3:3)) dissolved in the aqueous solutions may be from 0.0001 w/v % to 5 w/v %. *Id.* at 6:40-49 ("Compound A and an isotonic agent are added to sterilized purified water … and dissolved therein."), Claims 2, 6. The olopatadine solutions may further contain viscous vehicles (*e.g.*, PVP), buffering agents (*e.g.*, boric acid), and preservatives (*e.g.*, BAC). *Id.*, 6:40-43, 50-58.

Hayakawa demonstrates olopatadine's inhibitory effects on human conjunctivial mast cells (*id.* at 3:43-4:40), and discusses benefits of including higher concentrations of olopatadine, such as olopatadine having prophylactic effects as well therapeutic effects (*id.* at 3:18-23). Hayakawa discloses that olopatadine produces concentration-dependent inhibition of mast cell degranulation (*id.* at 4:43-45, Table 1), confirming what was known in the prior art at the time. Ex. 1005 at 394-396,Tables 2 & 3; Ex. 1003 ¶¶ 49-50.

A POSA would understand Schneider admits there are other agents in the art for increasing olopatadine solubility, and that PDE4 itself is just one such agent. Ex. 1007, [0042]; Ex. 1002 ¶ 68. Bhowmick and Castillo each disclose solubility- and stability-enhancing agents for olopatadine solutions.

As discussed above in Ground 1, Bhowmick describes preparing stable aqueous topical solutions of olopatadine by including cyclodextrins in the solution. Ex. 1004 at 2:24-27; 3:15-20; 4:16-17; Ex. 1002 ¶ 69. Bhowmick does not suggest

an upper limit to the amount of olopatadine and simply calls for a therapeutically effective amount. *See id.*, Claim 6; Ex. 1002 ¶ 38. Bhowmick teaches that HP-β-CD, HP-γ-CD, and SBE-β-CD may be used to prepare such solutions (*id.* at 5:10-30) and keep olopatadine in solution, preventing precipitation or crystallization (*id.* at 3:25-28). Ex. 1002 ¶ 69. Bhowmick teaches that inclusion of HPMC further stabilizes the solutions. *Id.* at 2:26-27; 6:23-26.

Castillo similarly discloses topical solutions for treating allergic or inflammatory disorders of the eye, and teaches that PVP enhances the stability of olopatadine in solution. Ex. 1006 at 2:13-22; Example 10; Ex. 1002 ¶ 70. Castillo teaches inclusion of 0.1% to 3% PVP, most preferably with a weight average molecular weight from 50,000 to 60,000. *Id.* at 3:17-25; Ex. 1002, ¶ 56. Castillo shows that utilizing 2% w/w (*i.e.*, slightly more than 2% w/v; Ex. 1003, ¶ 43) PEG 400, both alone and with PVP, provides olopatadine solutions with enhanced stability. *Id.*, Example 7, Tables 5 & 6 (Formulations L, M, & R); Ex. 1002, ¶ 57. Castillo further illustrates that HMPC, like PVP, provides enhanced stability. *Compare* Ex. 1006, Example 6, Tables 3 & 4 (Formulation H) *with* Example 7, Tables 5 & 6 (Formulations K & Q); *see* Ex. 1002, ¶ 57.

Together, Schneider, Hayakawa, Bhowmick, and Castillo teach all of the limitations of claims 1-4, 8, 12, 13, 21, and 22 of the ’154 Patent, as shown in

detail in the claim chart at the end of this section. As further discussed below, these claims would have been obvious to one of skill in the art.

a. Claims 1-4, 8, 21, and 22

All of the challenged claims of the '154 Patent require an olopatadine concentration (free base) of at least 0.67 w/v% dissolved in the solution. While Schneider teaches olopatadine concentrations "in solution" of "0.60% w/v, or higher" (Ex. 1007, [0045]), Hayakawa teaches dissolved olopatadine concentrations as high as 5 w/v% (Ex. 1008 at 6:40-49). Ex. 1003 ¶ 67. In addition, a POSA was well-aware of excipients useful for achieving solubility and stability at high olopatadine concentration ranges such as those taught by Hayakawa. *See* Ex. 1002 ¶¶ 27-28, 32, 34, 38-43, 82.

While Schneider discloses one such agent, Schneider also admits there are other agents in the art for increasing the solubility of olopatadine. Ex. 1007, [0042]; Ex. 1002 ¶ 74. For example, as discussed previously, Bhowmick teaches the use of cyclodextrins (*e.g.,* HP-β-CD, HP-γ-CD, and SBE- β-CD) and HPMC to stabilize aqueous topical solutions of olopatadine. Ex. 1004 at 2:26-27; 5:17-18, 5:28; 6:23-26; 7:10-13. Similarly, Castillo teaches the use of PVP as a solubility- and stability-enhancer in olopatadine-containing ophthalmic solutions. Ex. 1006 at 2:19-22; Example 10. Castillo also discloses that PEG 400, both alone and with PVP, provides olopatadine solutions with enhanced stability. *Id*., Example 7,

Tables 5 and 6 (Formulations L, M, & R); Ex. 1002 ¶¶ 28, 74. Schneider further teaches the beneficial inclusion of HPMC, PEG, and PVP as lubricants or viscosity agents. Ex. 1007, [0052].

In fact, as explained in the discussion above with respect to Ground 1 (which is likewise included here), and is as shown by the claim chart at the end of this section, Bhowmick and Castillo together disclose not only all of the components called for in Claim 1, but all of the claimed ranges for PEG, PVP, HP-γ-CD, HPMC, BAC called for in Claims 4, 8, 21, and 22 as well.

Motivation to combine: A POSA would have appreciated the higher concentrations of olopatadine reported by Hayakawa would provide superior antihistamine effects. Ex. 1008, Table 1; Ex. 1003 ¶¶ 47-57. Hayakawa's teaching that olopatadine exhibited prophylactic effects as well therapeutic effects (*id*. at 3:18-23) would have further encouraged a POSA to test the full range of olopatadine concentrations disclosed therein. Ex. 1003 ¶¶ 58-60, 69.

In addition, as Schneider teaches, "it is more desirable for active ingredients to be in solution rather than suspension in a pharmaceutical composition." Ex. 1007, ¶[0007]. Because the components required by Claims 1-3 are all taught in the art for olopatadine-containing ophthalmic solutions, it would have been obvious for a POSA to include those components when developing formulations at

the relatively high olopatadine concentrations called for by Hayakawa (*i.e.*, up to 5% w/v). Ex. 1002 ¶¶ 64-74.

In addition, just as described with respect to Ground 1 above (which discussion is likewise included here), because the beneficial effects of the recited PEG, PVP, cyclodextrin, and HPMC components were well-known in the art (Ex. 1002 ¶¶ 69-70), as were studies directed at optimizing the solubility and stability of drugs with these components (*see id*.¶¶ 27-28, 32, 34, 38-43), choosing the correct excipients and in appropriate concentrations would have been a matter of routine experimentation and optimization (*id.* ¶ 75). *In re Woodruff,* 919 F.2d at 1577. That is, given that these components were known to have a beneficial effect (both individually and collectively) on olopatadine solubility and long-term storage stability, the recited ranges of claims 4, 8, 21, and 22 would arise from routine optimization due to the natural desire to maximize known, beneficial properties. *Geisler*, 116 F.3d at 1470; *Applied Materials*, 692 F.3d at 1297-98.

The same conclusion applies to Claim 21's recitation of a particular ranges for benzalkonium chloride, pH, and osmolarity, which ranges are all taught by Bhowmick, for example (Ex. 1004 at 7:20-22; 8:11-12, 22-24). Ex. 1002 ¶ 76. In additional to the importance of these parameters for obtaining a viable ophthalmic composition for human use, a POSA also understood inclusion of benzalkonium chloride within the claimed range was known to further increase the solubility of

cyclodextrin-drug complexes. *Id.*, ¶¶ 46, 76. Because the '154 Patent fails to show the criticality of such ranges, it would have been obvious to arrive at the claimed ranges for benzalkonium chloride, pH, and osmolarity based on Bhowmick's teachings. *See Woodruff*, 919 F.2d at 1578; *Peterson*, 315 F.3d at 1330.

Expectation of success: Where the prior art discloses all of the claimed components in ranges that overlap with the claimed ranges, a POSA presumptively has a reasonable expectation of success in arriving at the claimed compositions through routine optimization. *Applied Materials*, 692 F.3d at 1297-98. Moreover, the fact that the prior art discloses numerous excipients for stabilizing formulations with high levels of olopatadine (*e.g.*, Bhowmick disclosure of many cyclodextrin compounds in addition to the specific the specific HP-γ-CD compound called for in some of the claims) does not render a formulation having the claimed components any less obvious. *Merck & Co.*, 874 F.2d at 807.

To the contrary, that a POSA could reasonably expect to be able to develop suitably solubilized and stable compositions at the olopatadine concentrations given by Hayakawa is confirmed by the Federal Circuit's opinion in the prior case involving that reference. *See Alcon*, 687 F.3d at 1367-68 (rejecting the argument that claims calling for 0.0001-5% w/v are not enabled). As such, a POSA, having the teachings of not only Hayakawa, but also Schneider, Bhowmick, and Castillo at

hand, would have had a reasonable expectation of success in arriving at compositions falling with the claims at issue here. Ex. 1002 ¶¶ 76-77.

b. Claims 12 and 13

The methods of claims 12 and 13 which employ the composition of Claim 4 would have been obvious. Ex. 1002 ¶ 78; Ex. 1003 ¶ 67. In addition to the teachings of Bhowmick and Castillo as discussed above in Ground 1 (which is likewise included here), Hayakawa similarly teaches high-concentration olopatadine solutions as beneficially providing concentration-dependent inhibition of mast cell degranulation and antihistamine activity (*e.g.*, Ex. 1004 at 4:43-45, Table 1). Ex. 1003 ¶ 69. Hayakawa further teaches that the formulations can be provided as solutions for eye drops (*id*. at 6:31-39), which necessarily suggests dispensing at least one drop of the solution to the eye (*see id*. at 6:63-67). Ex. 1003 ¶70.

Given that the composition of Claim 4 is obvious as discussed above, the topical administration of such a composition according to Claims 12 and 13 was likewise well within the public domain pursuant to Schneider, Hayakawa, Bhowmick, and Castillo. Claims 12 and 13 are therefore unpatentable in view of these references.

c. Claim chart

As shown in the following claim chart, the combination of Schneider, Hayakawa, Bhowmick, and Castillo teaches or suggests each and every limitation to a POSA, and thus renders claims 1-4, 8, 12, 13, 21, and 22 obvious.

'154 Patent Claims	**Schneider, Hayakawa, Bhowmick, and Castillo**
1. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:	"The invention provides pharmaceutical **aqueous solution** compositions comprising olopatadine and a PDE4 inhibitor compound of Formula I, as provided herein." Schneider, [0009]. "In certain embodiments, an **ophthalmic formulation** is administered to the eye of a patient in need thereof to treat an ocular disorder. …In certain embodiments, the compounds of the present invention are used to treat an allergic eye disease selected from the group consisting of **allergic conjunctivitis** ..." Schneider, [0048].
at least 0.67 w/v % olopatadine dissolved in the solution;	"In certain embodiments, the concentration of olopatadine in a solution composition of the invention is at least 0.05% w/v. For example, the concentration of olopatadine can be about 0.05%, … **or 0.60% w/v, or higher**." Schneider, [0045] "[Olopatadine] and an isotonic agent are added to sterilized purified water, and if required, a preservative, a buffering agent, a stabilizer, a viscous vehicle and the like are added to the solution **and dissolved therein**. The **concentration of [olopatadine] is 0.0001 to 5 w/v %** …" Hayakawa, 6: 40-49.
PEG having a molecular weight of 300 to 500;	"The compositions of the present invention [which include olopatadine] may contain one or more nonionic, anionic, or cationic polymers as lubricants or as viscosity agents, including but not limited to … **polyethylene glycols** (PEGS)…" Schneider, [0052]. Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R).

polyvinylpyrrolidone;	"The compositions of the present invention [which include olopatadine] may contain one or more nonionic, anionic, or cationic polymers as lubricants or as viscosity agents, including but not limited to … **polyvinylpyrrolidones (PVPs)**…." Schneider, [0052].
hydroxypropyl-γ-cyclodextrin	"According to one embodiment of the present invention, the aqueous topical solution comprises cyclodextrin to enhance the physical stability of the solution. … Examples of cyclodextrin derivatives that may be used in the pharmaceutical compositions of present invention include the **hydroxypropyl derivatives of** alpha-, beta- and **gamma-cyclodextrin** …" Bhowmick, 4:16-17 and 5:3-8. "Examples of suitable cyclodextrins for use in the present invention non-exclusively include …**2-hydroxypropyl gamma-cyclodextrin**…" Bhowmick, 5:12-18.
benzalkonium chloride; and	"Topical ophthalmic products may also be packaged in multidose form. Preservatives may thus be required to prevent microbial contamination during use. Suitable preservatives include: **benzalkonium chloride**…" Schneider, [0051].
water.	"The solution composition may comprise … **water** to form an aqueous, sterile ophthalmic solution, suspension, or emulsion." Schneider, [0049].

2. A solution as in claim 1 further comprising borate.	"An appropriate buffer system (e.g., sodium phosphate, sodium acetate, sodium citrate, **sodium borate or boric acid**) may be added to the compositions to prevent pH drift under storage conditions." Schneider, [0044]

3. A solution as in claim 2 further comprising a polyol.	"Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example,… **dextrose, mannitol, sorbitol, propylene glycol,** or **glycerol** may be added to the composition to approximate physiological tonicity." Schneider, [0053].

4. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:	See claim 1 above.
at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution;	"In certain embodiments, the concentration of olopatadine in a solution composition of the invention is at least 0.05% w/v. For example, the concentration of olopatadine can be about 0.05%, … , **or 0.60% w/v, or higher**." Schneider, [0045] "[Olopatadine] and an isotonic agent are added to sterilized purified water, and if required, a preservative, a buffering agent, a stabilizer, a viscous vehicle and the like are added to the solution **and dissolved therein**. The **concentration of [olopatadine] is 0.0001 to 5 w/v %** …" Hayakawa, 6:40-49.
2.0 w/v % to 6.0 w/v % PEG having a molecular weight of 300 to 500;	"The compositions of the present invention [which include olopatadine] may contain one or more nonionic, anionic, or cationic polymers as lubricants or as viscosity agents, including but not limited to hydroxypropylmethylcelluloses (HPMCs), methylcelluloses, carboxymethylcelluloses (CMCs), **polyethylene glycols** (PEGS) …" Schneider, [0052]. Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R).
2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone;	"The compositions of the present invention [which include olopatadine] may contain one or more nonionic, anionic, or cationic polymers as lubricants or as viscosity agents, including but not limited to … **polyvinylpyrrolidones (PVPs),** alginic acids and salts, gellan gums, carrageenans, and chitosans." Schneider at ¶[0052]. "In general, the amount of **polyvinylpyrrolidone** contained in the compositions of the present invention will be **0.1-3%, preferably 0.2-2%, and most preferably 1.5-2%.**" Castillo, 3:22-25.

at least 0.5 w/v % but no greater than 2.0 w/v % cyclodextrin derivative selected from the group consisting of SAE-β-cyclodextrin, HP-γ-cyclodextrin, HP-β-cyclodextrin and combinations thereof; and	"The preferred cyclodextrins for use in the present invention include alkyl cyclodextrins, hydroxy alkyl cyclodextrin, such as **hydroxy propyl beta-cyclodextrin**, carboxy alky1 cyclodextrins and **sulfoalkyl ether cyclodextrin**, such as **sulfobutyl ether beta-cyclodextrin**. Examples of suitable cyclodextrins for use in the present invention non-exclusively include … **2-hydroxypropyl beta-cyclodextrin; 2-hydroxypropyl gamma-cyclodextrin**; … In a preferred embodiment of the present invention, hydroxypropyl beta-cyclodextrin may be used in concentrations ranging from about 0.1% to about 20% w/v of the composition, 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 preferable concentration of hydroxypropyl beta-cyclodextrin is in the range from about 1.0% to about 5** …" Bhowmick at 5:10-18, 6:1-8. "The ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cyclodextrin in the inclusion complex is from about **1:1.65 to about 1:50 by weight**. The amount of hydroxypropyl β-cylcodextrin present in the inclusion complex is sufficient to enhance the physical stability of the olopatadine solution." Bhowmick at 6:18-21.
water	"The solution composition may comprise … **water** to form an aqueous, sterile ophthalmic solution, suspension, or emulsion." Schneider, [0049].

8. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:	See claim 1 above.
at least 0.67 w/v % but no greater than 1.0 w/v	See claim 4 above.

% olopatadine dissolved in the solution;	
2.0 w/v % to 6.0 w/v % PEG having a molecular weight of 300 to 500;	"The compositions of the present invention [which include olopatadine] may contain one or more nonionic, anionic, or cationic polymers as lubricants or as viscosity agents, including but not limited to hydroxypropylmethylcelluloses (HPMCs), methylcelluloses, carboxymethylcelluloses (CMCs), **polyethylene glycols** (PEGS), …" Schneider, [0052]. Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R).
2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone;	See claim 4 above.
at least 0.5 w/v % but no greater than 2.0 w/v % of hydroxypropyl-γ-cyclodextrin, and	"Examples of suitable cyclodextrins for use in the present invention non-exclusively include … 2-hydroxypropyl beta-cyclodextrin; **2-hydroxypropyl gamma-cyclodextrin**; … In a preferred embodiment of the present invention, hydroxypropyl beta-cyclodextrin may be used in concentrations ranging from about 0.1% to about 20% w/v of the composition, 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 preferable concentration of hydroxypropyl beta-cyclodextrin is in the range from about 1.0% to about 5%** …" Bhowmick at 5:10-18, 6:1-8. "The ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cyclodextrin in the inclusion complex is from about **1:1.65 to about 1:50 by weight**. The amount of hydroxypropyl β-cylcodextrin present in the inclusion complex is sufficient to enhance the physical stability of the olopatadine solution." Bhowmick at 6:18-21.
water	See claim 4 above.

12. A method of treating at least one ocular allergy symptom in humans, the method comprising: topically applying to an eye of a human an amount of the solution of claim 4 sufficient to treat the at least one ocular allergy symptom.	"Solution compositions of the invention can be administered **topically to the eye**, for example, to treat allergic conjunctivitis and/or ocular inflammation. In general, the doses used for the above described purposes will vary, but will be in an **effective amount to reduce or eliminate allergic conjunctivitis** and/or ocular inflammation. Generally, 1-2 drops of such compositions will be administered one or more times per day. For example, the composition can be administered 2 to 3 times a day or as directed by an eye care provider." Schneider, [0050].

13. A method as in claim 12 wherein the step of topically applying the solution includes dispensing at least one drop of the solution to the eye.	"Solution compositions of the invention can be administered **topically to the eye**, for example, to treat allergic conjunctivitis and/or ocular inflammation. … Generally, **1-2 drops** of such compositions will be administered one or more times per day." Schneider, [0050].

21. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:	See claim 1 above.
at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution;	See claim 4 above.
2.0 w/v % to 6.0 w/v % PEG having a molecular weight of 300 to 500;	"The compositions of the present invention [which include olopatadine] may contain one or more nonionic, anionic, or cationic polymers as lubricants or as viscosity agents, including but not limited to hydroxypropylmethylcelluloses (HPMCs), methylcelluloses, carboxymethylcelluloses (CMCs),

	polyethylene glycols (PEGS), …" Schneider, [0052]. Castillo, Example 7, Tables 5 and 6 (Formulations L, M, & R).
2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone;	See claim 4 above.
at least 0.5 w/v % but no greater than 2.0 w/v % of hydroxypropyl-γ-cyclodextrin;	"Examples of suitable cyclodextrins for use in the present invention non-exclusively include …2-hydroxypropyl beta-cyclodextrin; **2-hydroxypropyl gamma-cyclodextrin**; … Generally, for solutions meant for ophthalmic administration preferable concentration of hydroxypropyl beta-cyclodextrin is in the range from **about 1.0% to about 5%** …" Bhowmick, 5:10-18, 6:1-8. "The ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cyclodextrin in the inclusion complex is from about **1:1.65 to about 1:50 by weight**. The amount of hydroxypropyl β-cylcodextrin present in the inclusion complex is sufficient to enhance the physical stability of the olopatadine solution." Bhowmick, 6:18-21.
greater than 0.003 w/v % but less than 0.03 w/v % benzalkonium chloride; and	"Topical ophthalmic products may also be packaged in multidose form. Preservatives may thus be required to prevent microbial contamination during use. Suitable preservatives include: **benzalkonium chloride**, … or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from **0.001 to 5.0% w/v**." Schneider, [0051].
water	See claim 4 above.
wherein the pH of the solution is 6.0 to 7.8 and the osmolality of the solution is 200 to 400 mOsm/kg.	"An appropriate buffer system [] may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably, however, the buffer will be chosen to maintain a target **pH within the range of pH 6.0-7.5**." Schneider, [0044] "In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable

	osmolality (generally about 150-450 mOsm, preferably **250-350 mOsm**).” Schneider, [0053].

22. A solution as in claim 21 further comprising at least 0.15 w/v % but no greater than 1.0 w/v % hydroxypropylmethyl cellulose.	“In preferred embodiments of the present invention, **hydroxypropyl methylcellulose** may be used concentrations ranging from about 0.001 % to about 5%, and more preferably in concentrations ranging from **about 0.01 % to about 1 % w/v**.” Bhowmick, 7:10-13.

G. Absence of Secondary Considerations

If Patent Owner presents secondary consideration evidence of nonobviousness in its preliminary response, the Board should refuse consideration of that evidence and institute trial, because “detailed consideration of [a patentee’s] secondary consideration evidence may not be undertaken until [the petitioner] has had an opportunity to test it.” *Amneal Pharms. v. Supernus Pharms*., IPR2013-00368, Paper 8 at 12-13 (PTAB Dec. 17, 2013) (instituting trial despite submission of district court evidence of secondary considerations in preliminary response).

Furthermore, none of the ’154 Patent’s allegedly “surprising” advantages of the claimed formulations would have been unexpected. Statements regarding HP-γ-CD’s allegedly “surprising” preservation effects (Ex. 1001 at 11: 33-38) are dubious due to confounding factors and the lack of clear comparisons. Ex. 1002 ¶ 80. Moreover, because HP-γ-CD’s central cavity is larger than for β-CD derivatives, less interference with BAC’s preservative effects by HP-γ-CD would

have been expected. Ex. 1002 ¶¶ 35, 45, 80. In light of the prior art, it is unsurprising that HP-γ-CD and β-CD derivatives exhibit similar olopatadine-solubilizing abilities. *See, e.g.*, Ex. 1004 at 5:10-30; Ex. 1002 ¶ 81. Finally, a POSA would also not expect HP-γ-CD to interfere with olopatadine efficacy because, as recognized in the art, for poorly soluble drugs, "[w]ith cyclodextrins, it is 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." Ex. 1014 at 149; Ex. 1002 ¶ 82; *cf.* Ex. 1001 at 11:45-50.

The alleged surprising biological activity of the claimed formulations is also not unexpected. First, in view of olopatadine's art-recognized ability to treat allergic late phase reaction symptoms and the known improved efficacy at concentrations higher than 0.67% w/v in treating allergic conjunctivitis, it is entirely unsurprising that higher concentrations provided improved treatment of allergic conjunctivitis late phase reaction. Ex. 1003 ¶ 58. Second, the improved reduction of redness in the early phase seen at higher concentrations would have been expected in view of the identical trend observed in the art for the 0.05 % and 0.1% olopatadine solutions. *Id.*, ¶¶ 59, 62. Third, because redness and ocular itching were known to be mediated through different histamine receptors (H_2 vs. H_1), a POSA would not have had any expectation that inhibition of early onset

redness and itching by olopatadine would be the same. *Id.*, ¶ 60. Finally, the '154 Patent provides no reasons why a POSA would have found it surprising that once a day dosing of 0.67% w/v or higher olopatadine concentrations would achieved enhanced relief from early phase symptoms, when the art already taught use of such concentrations for treatment of allergic conjunctivitis. *Id.*, ¶ 61. At most, these are newly-observed properties of known olopatadine concentrations, which cannot support patentability. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

IX. CONCLUSION

For the foregoing reasons, Petitioners respectfully request that trial be instituted and that claims 1-4, 8, 12, 13, 21, and 22 of the '154 Patent be canceled.

Respectfully submitted,

Dated: August 18, 2016

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) because it contains 13,363 words as determined by the Microsoft® Office Word 2010 word-processing system used to prepare the brief, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a)(1).

/Teresa Stanek Rea/
Teresa Stanek Rea

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, the undersigned certifies that on August 18, 2016, a complete copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,791,154, Power of Attorney, and all supporting exhibits were served via FedEx® on the Patent Owner by serving the correspondence address of record for the '154 Patent:

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